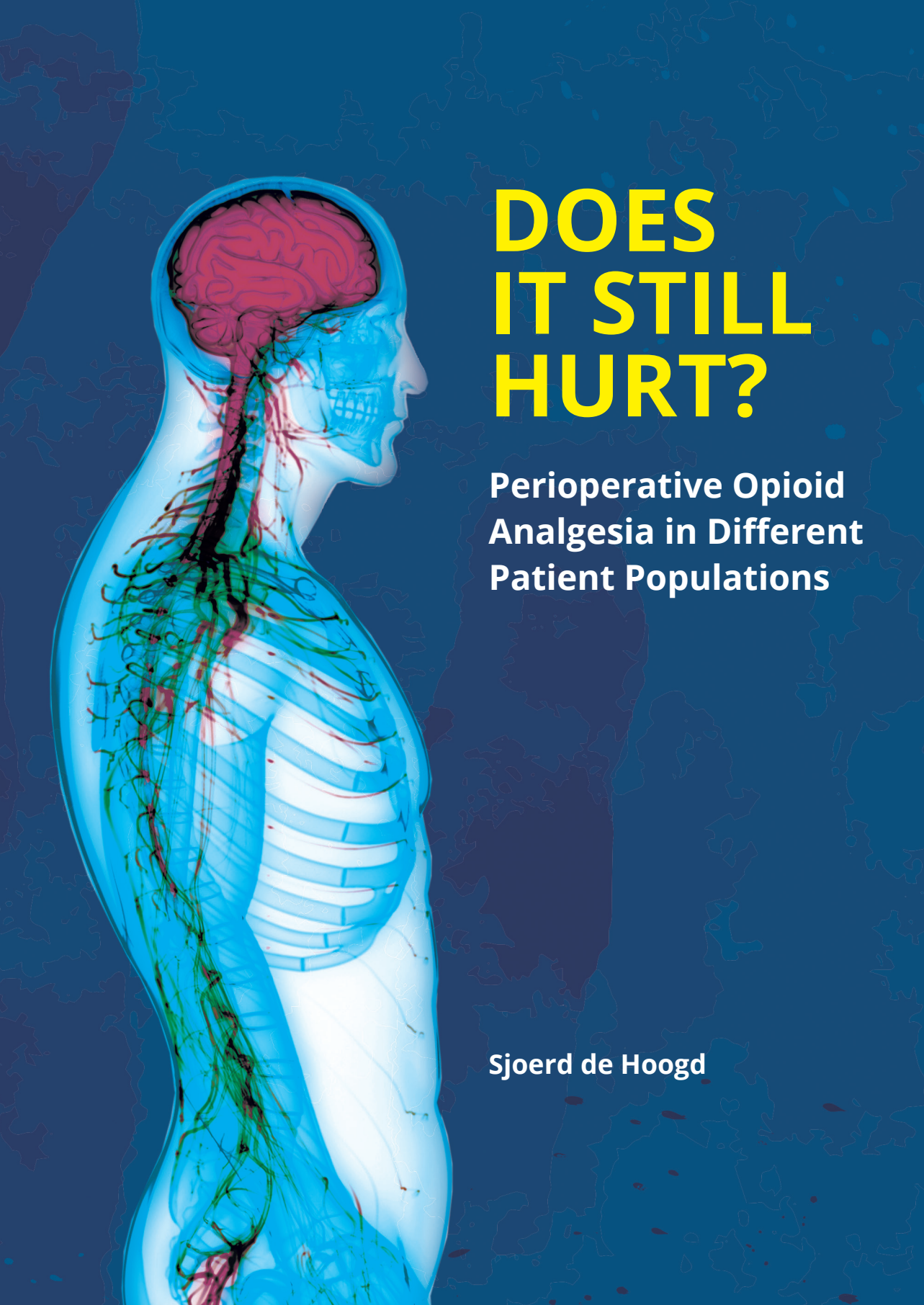
Does it still hurt? Perioperative opioid analgesia in different patient populations

Hoogd, S. de



DOES IT STILL HURT?

Perioperative Opioid Analgesia in Different Patient Populations

Sjoerd de Hoogd

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ISBN: 978-94-6416-771-9
Cover design & Lay-out: Publiss | www.publiss.nl
Print: Ridderprint | www.ridderprint.nl

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Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof. dr. ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 28 oktober 2021
klokke 11.15 uur

door

Sjoerd de Hoogd
geboren te ’s-Gravenhage, Nederland
in 1987

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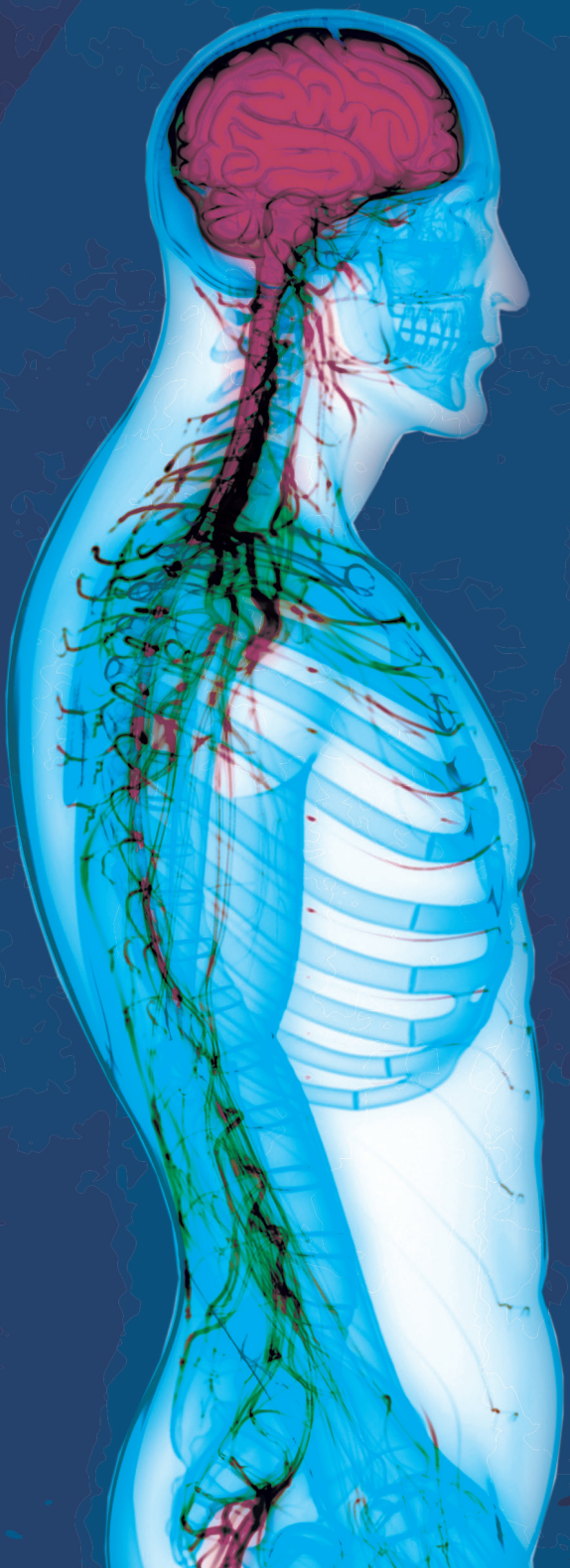
The research described in this thesis was performed at the department of Clinical Pharmacy of the St. Antonius Hospital, Nieuwegein, The Netherlands and the division of Systems Biomedicine and Pharmacology of the Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands. Printing of this thesis was financially supported by: Department of Anaesthesiology, Intensive Care and Pain management, Stichting KNMP fondsen and Stichting Bevordering Klinisch Farmacologisch Onderzoek.

Contents



Section I

General introduction and background

Chapter 1

Introduction

Scope and rationale of the investigations

Pain is an unpleasant and emotional experience, associated with actual or potential tissue damage according to the definition of International Association of the Study of Pain[1]. Acute, as well as chronic postoperative pain, is a multidimensional and complex problem that contains physiological and biopsychosocial aspects[2]. Pain is receiving increasing worldwide attention over the past years. Studies investigating acute postoperative pain report a reduction in incidence over the years, even though overall numbers remain quite high[3]. In the United States, more than 80% of patients that underwent surgery experience acute postoperative pain. The majority of these patients rate the severity of this pain as moderate or severe[4]. Other studies report that at least half of postoperative patients experience adequate pain relief[5]. Postoperative pain can become chronic when it lasts two to three months after surgery and is beyond the healing of injured tissue and the related inflammatory processes[6,7]. An estimated percentage of 10 to 50% of the patients undergoing all types of surgery develop chronic postoperative pain[6,8,9].

Over the last decades it has been suggested that little improvement has been made in postoperative pain management[4]. In the Netherlands, nationwide programs such as the guideline for postoperative pain from the Dutch Society of anesthesiology[10] have been implemented to address postoperative pain, amongst others because pain is a quality indicator in Dutch hospitals[11]. It has been recognized that pain and inadequate pain relief are a heavy burden for the patient, and may have great impact on quality of life and performance of activities of daily living[9,12]. Optimal application and implementation of (inter)national guidelines of pain management and pain relief may decrease morbidity and mortality and increase quality of life in postoperative patients.

Experimental pain studies in animals demonstrated that after surgical incision peripheral and central sensitization occur. A painful stimulus, like surgical incision, activates nociceptors which transduce this 'noxious' information into an electrical signal. This signal is transmitted from the periphery to the central nervous system along ascending peripheral C- and A□-fibers[13]. Complex mechanisms with involvement of C- and A□-fibres have been identified that contribute to acute postoperative pain[14]. C- and A□-fibres terminate in the dorsal horn of the spinal cord. Within the spinal cord, more complex interactions occur between excitatory and inhibitory interneurons and descending inhibitory tracts from higher centres exert their effect. Finally, the pain signal is entering the brain where somatosensory information is processed and pain perception occurs. Besides the ascending tracts from periphery to the brain, descending inhibitory tracts facilitate the modulation

of pain[13]. The functionality of these descending pain modulation in patients can be examined by a pain model using diffuse noxious controls (DNIC). Normally, after a noxious stimulus, peripheral sensitization of the accompanying receptors leads to short-term, transient pain sensitivity. Repetitive activation by noxious stimuli could transform to central sensitization, which amplifies, spreads and extend the periods of pain and has the potency to result in chronic postoperative pain[15]. The main triggers of central sensitization are neuronal, immune, and glial related, involving for example the N-methyl-D-aspartate (NMDA) receptors, glutamate and other neuromodulators[15].

Clinically, several risk factors have been identified for acute postoperative pain and the development of chronic postoperative pain. For acute pain, a large meta-analysis (53 362 patients) identified nine significant risk factors for poor acute pain control after all kind of surgeries[16]. The risk factors identified are younger age, female sex, history of depressive symptoms, use of preoperative analgesia, history of smoking, history of anxiety symptoms, presence of preoperative pain, use of preoperative analgesia and higher body mass index (BMI). Although the severity of acute postoperative pain is important, it appears that the rate at which acute pain resolves is also important[17]. The duration of severe pain in the initial 24 hours postoperatively predicted the chance of developing chronic postoperative pain[18]. A 10% increase in time spent in severe pain was associated with a 30% increase of chronic postoperative pain 12 months after surgery. This makes acute postoperative pain an evident risk factor for the transition of acute to chronic postoperative pain. Other relevant risk factors for chronic postoperative pain can be divided in surgery or patient specific risk factors. Younger age, the female gender, psychosocial factors such as anxiety, preceding pain and genetic susceptibility are patient specific factors that can contribute as a risk factor for chronic postoperative pain[6,7]. Surgery specific risk factors have also been investigated, for example type of surgery, duration of surgery and anaesthetic technique[7]. Because there is a high degree of inter-individual difference in pain response, genetic variation has also been investigated to explain pain variability[19].

Opioids are the cornerstone for postoperative pain management. Intraoperative and postoperative administration of opioids is essential in preventing and managing acute and chronic postoperative pain. Despite the extensive use of opioids, there are still gaps in knowledge about its use, optimal dose or its negative effects especially in different populations such as adult and paediatric patients after cardiac surgery or obese patients.

Opioids in cardiac surgery patients

In adults, cardiac surgery such as coronary artery bypass grafting (CABG) and heart valve replacement are two of the most frequently performed surgeries worldwide[20]. It is known that the risk of postoperative pain in cardiac surgery is high, because of the prolonged duration of surgery and multiple other causes such as intraoperative tissue retraction and dissection, multiple intravascular cannulations, chest tubes left after surgery, and multiple invasive procedures simultaneously[21]. Patients after cardiac surgery with controllable pain, recover faster and have lower risk on cardiovascular complications, pneumonia, and hypercoagulability[22]. In addition to the high incidence of acute postoperative pain, the incidence of chronic postoperative pain is also among the highest compared to other kind of surgeries[9]. Chronic postoperative pain affects even 37% patients in the first 6 months after cardiac surgery, which declines to 17% after two years[23]. Over the last years there is a growing body of literature investigating risk factors for the development of chronic postoperative pain. Younger age, non-elective surgery and female gender have been identified as a risk factors for chronic postoperative pain after cardiac surgery but are impossible to influence[24,25]. Increased acute postoperative pain, anxiety before surgery[24,25] and the use of remifentanil[25] are risk factors that can be managed. Especially the use of remifentanil for intraoperative analgesia is interesting from a pharmacological point of view and is potentially a risk factor that can be eliminated easily. Remifentanil is an ultra-short-acting, hyper potent, μ-opioid receptor agonist[26] which is often used during surgery because of its favourable pharmacokinetic and pharmacodynamic properties[27]. Because remifentanil may affect the NMDA receptor directly or indirectly[28,29], it has been hypothesized that signalling of this NMDA receptor may lead to opioid induced hyperalgesia[30]. The clinical relevance of "remifentanil induced hyperalgesia" is still under debate and therefore more research in this field is warranted.

In children, morphine is the most commonly used drug used for postoperative pain management after cardiac surgery[31]. The pharmacokinetics of morphine has been studied extensively across the paediatric population in all different kind of settings[32], including cardiac surgery[33,34]. Studies investigating the pharmacodynamics of morphine in children are scarce, while it is known that untreated pain after major surgery in neonates and infants results in increased stress hormone levels and prolonged behavioural consequences[35]. To optimize paediatric pain management after cardiac surgery, more insight is needed in the combined pharmacokinetic/pharmacodynamic field of data.

Opioids in obese patients after surgery

Another special patient population that needs increased attention is the (morbidly) obese population. There has been a major increase in prevalence of individuals that are overweight (a BMI above 25 kg/m^2), obese (a BMI above 30 kg/m^2), severely obese (a BMI above 35 kg/m^2) or morbidly obese (a BMI above 40 mg/km^2)[36]. It has been estimated that in 2025, if this rising trend continues, the prevalence of obesity is around 18% for men and 21% for women[36]. With obesity, morbidity and mortality significantly increase[37]. Obese patients are more at risk for all kind of potentially serious health conditions such as cardiovascular disease, diabetes, cancer, osteoarthritis, liver and kidney diseases[38]. For these reasons, obese patients are presenting more frequently for surgical procedures with accompanying complications such as postoperative pain. There is little evidence that obesity itself has impact on postoperative pain[39]. On the contrary, opioids are feared in obese population because of the increased risk for respiratory depression, respiratory failure, and other opioid adverse effects[40,41]. Therefore, knowledge on the extent into which the physiological changes associated with obesity influence the pharmacokinetics of opioids is essential. Morphine is frequently used for postoperative pain management but the pharmacokinetics of morphine and its pharmacologically active metabolites in (morbidly) obese patients has not been studied in detail.

The objective of this thesis

Postoperative pain is a relevant complication and has in potential great impact on patients. The role of opioids in postoperative pain and postoperative pain management, especially in different kind of patient populations, is not thoroughly studied. Therefore, this thesis aimed to contribute to perioperative pain management in different patient populations with the focus on opioid analgesia.

In *section II,* the focus is on adult cardiac surgery patients. In **chapter 2,** we present an overview of the literature on the associations of intraoperative remifentanil administration with acute postoperative pain, hyperalgesia, and chronic postoperative pain. Although studies are diverse and sample sizes are small, there are indications that intraoperative remifentanil may influence the occurrence of acute postoperative hyperalgesia and may result in chronic postoperative pain. To address this issue, a randomised controlled trial investigating the influence of remifentanil on acute and chronic postoperative pain was designed and described in **chapter 3**. In **chapter 4,** we report the outcomes of this randomised controlled trial on acute and chronic postoperative pain 3, 6 and 12 months after surgery. In addition, we investigated the short and long term effects of remifentanil

on experimental pain using the measurement of thermal detection and pain thresholds, which is described in **chapter 5**. To investigate a potential genetic component in this cohort of cardiac surgery patients, **chapter 6** describes the potential influence of two genes that are associated with postoperative pain on acute, chronic and experimental pain.

Section III focuses on children after cardiac surgery. In children, morphine is commonly used for analgesia after cardiac surgery but not much is known about its analgesic efficacy in relation to plasma concentrations. Therefore, in **chapter 7** we report the analysis of the pharmacodynamics of morphine in children after cardiac surgery using repeated Time-to-Event (RTTE) modelling.

In *section IV*, we focus on the obese patient population. As already noted, the obese population is growing over the last decade and with this, obese patients that undergo surgery and experience postoperative pain. First, in **chapter 8**, we present an overview of the literature about the influence of obesity on pharmacokinetic and pharmacodynamic parameters in adults. Second, we present in chapter 9 the analysis of the pharmacokinetics of morphine in obese patients when compared to non-obese healthy volunteers.

In *section V* - **chapter 10**, the results and conclusions of this thesis are summarized and discussed, and future perspectives are presented. In this chapter, perspectives are given concerning postoperative pain management with opioids in different patient populations. Finally, ideas are provided for further pharmacological interventions or studies regarding optimizing postoperative pain management.

Literature

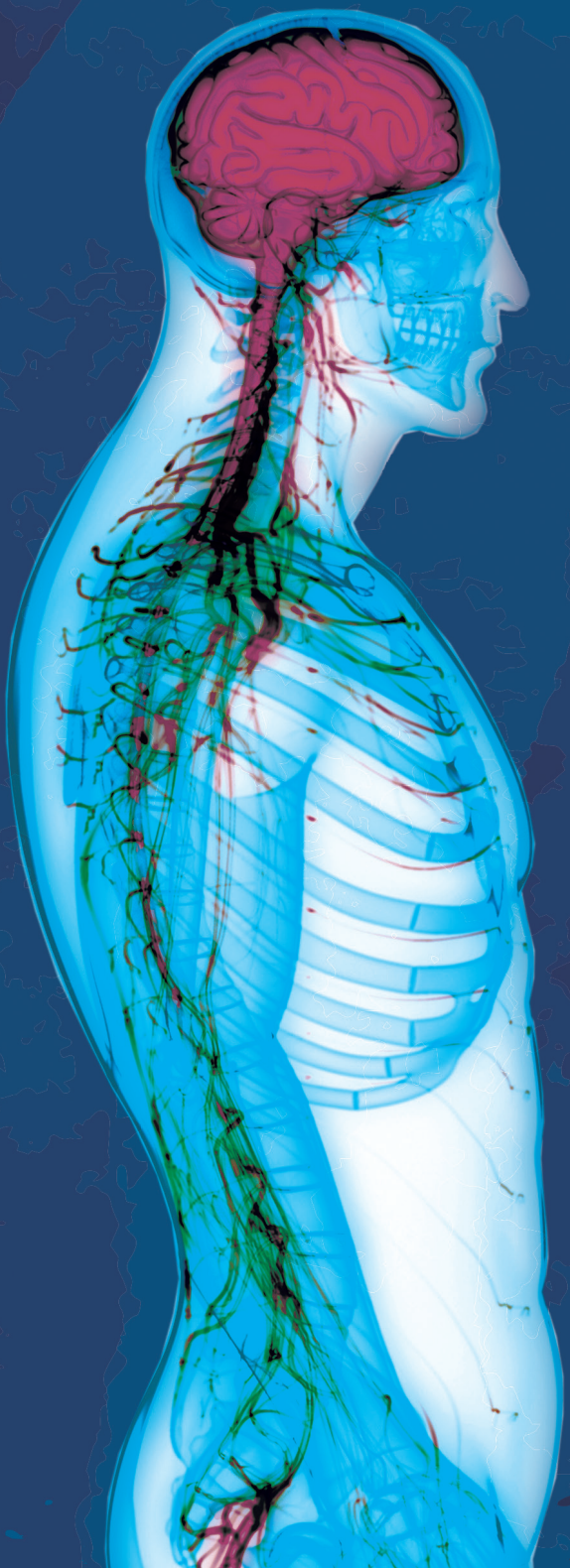
1. Merskey, H. & Bogduk, N. Part III: Pain Terms: A Current List with Definitions and Notes on Usage. in *Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy* 209–214 (1994).
2. Cheatle, M. D. Biopsychosocial Approach to Assessing and Managing Patients with Chronic Pain. *Med. Clin. North Am.* 100, 43–53 (2016).
3. Buvanendran, A. *et al.* The Incidence and Severity of Postoperative Pain following Inpatient Surgery. *Pain Med.* 16, 2277–83 (2015).
4. Gan, T. J., Habib, A. S., Miller, T. E., White, W. & Apfelbaum, J. L. Incidence, patient satisfaction, and perceptions of post-surgical pain: Results from a US national survey. *Curr. Med. Res. Opin.* 30, 149–160 (2014).
5. Apfelbaum, J. L., Chen, C., Mehta, S. S. & Gan, T. J. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth. Analg.* 97, 534–40, table of contents (2003).
6. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
7. Chapman, C. R. & Vierck, C. J. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *J. Pain* 18, 359.e1-359.e38 (2017).
8. Johansen, A., Romundstad, L., Nielsen, C. S., Schirmer, H. & Stubhaug, A. Persistent postsurgical pain in a general population: Prevalence and predictors in the Tromsø study. *Pain* 153, 1390–1396 (2012).
9. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
10. Dutch Society of Anesthesiology. *Guideline: Postoperative Pain*. (2013).
11. Sommer, M. *et al.* The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur. J. Anaesthesiol.* 25, 267–74 (2008).
12. Mongardon, N. *et al.* Assessment of chronic pain after thoracotomy: a 1-year prevalence study. *Clin. J. Pain* 27, 677–681 (2011).
13. Steeds, C. The anatomy and physiology of pain. *Surg.* 31, 49–53 (2013).
14. Pogatzki-Zahn, E. M., Segelcke, D. & Schug, S. A. Postoperative pain—from mechanisms to treatment. *Pain Reports* 2, e588 (2017).
15. Mifflin, K. A. & Kerr, B. J. The transition from acute to chronic pain: Understanding how different biological systems interact. *Canadian Journal of Anesthesia* 61, 112–122 (2014).
16. Yang, M. M. H. *et al.* Preoperative predictors of poor acute postoperative pain control: A systematic review and meta-analysis. *BMJ Open* 9, e025091 (2019).
17. Chapman, C. R., Donaldson, G. W., Davis, J. J. & Bradshaw, D. H. Improving individual measurement of postoperative pain: The pain trajectory. *J. Pain* 12, 257–262 (2011).
18. Fletcher, D. *et al.* Chronic postsurgical pain in Europe: An observational study. *Eur. J. Anaesthesiol.* 32, 725–734 (2015).
19. Young, E. E., Lariviere, W. R. & Belfer, I. Genetic basis of pain variability: recent advances. *J. Med. Genet.* 49, 1–9 (2012).
20. Roger, V. L. *et al.* Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 125, e2–e220 (2012).

21. Mueller, X. M. *et al.* Pain location, distribution, and intensity after cardiac surgery. *Chest* 118, 391–6 (2000).
22. Liu, S. S. & Wu, C. L. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. *Anesth. Analg.* 104, 689–702 (2007).
23. Guimarães-Pereira, L., Reis, P., Abelha, F., Azevedo, L. F. & Castro-Lopes, J. M. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. *Pain* 158, 1869–1885 (2017).
24. Choinière, M. *et al.* Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 186, E213-23 (2014).
25. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
26. Westmoreland, C. L., Hoke, J. F., Sebel, P. S., Hug Jr, C. C. & Muir, K. T. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 79, 893–903 (1993).
27. Thompson, J. P. & Rowbotham, D. J. Remifentanil--an opioid for the 21st century. *Br. J. Anaesth.* 76, 341–343 (1996).
28. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
29. Kim, S. H., Stoicea, N., Soghomonyan, S. & Bergese, S. D. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front. Pharmacol.* 5, 108 (2014).
30. Guntz, E. *et al.* Effects of remifentanil on N-methyl-D-aspartate receptor: an electrophysiologic study in rat spinal cord. *Anesthesiology* 102, 1235–1241 (2005).
31. Zeilmaker-Roest, G. A. *et al.* An international survey of management of pain and sedation after paediatric cardiac surgery. *BMJ Paediatr. open* 1, e000046-2017–000046. eCollection 2017 (2017).
32. Krekels, E. H., Tibboel, D., Danhof, M. & Knibbe, C. A. Prediction of morphine clearance in the paediatric population : how accurate are the available pharmacokinetic models? *Clin. Pharmacokinet.* 51, 695–709 (2012).
33. Elkomy, M. H. *et al.* Pharmacokinetics of Morphine and Its Metabolites in Infants and Young Children After Congenital Heart Surgery. *AAPS J.* 18, 124–133 (2016).
34. Valkenburg, A. J. *et al.* Pharmacodynamics and Pharmacokinetics of Morphine After Cardiac Surgery in Children With and Without Down Syndrome. *Pediatr. Crit. Care Med.* 17, 930–938 (2016).
35. Anand, K. J. & Aynsley-Green, A. Measuring the severity of surgical stress in newborn infants. *J. Pediatr. Surg.* 23, 297–305 (1988).
36. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet (London, England)* 387, 1377–1396 (2016).
37. Global BMI Mortality Collaboration *et al.* Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet (London, England)* 388, 776–86 (2016).
38. Pi-Sunyer, X. The Medical Risks of Obesity. *Postgrad. Med.* 121, 21–33 (2009).

39. Budiansky, A. S., Margarson, M. P. & Eipe, N. Acute pain management in morbid obesity - an evidence based clinical update. *Surg. Obes. Relat. Dis.* 13, 523–532 (2017).

40. Lloret Linares, C. *et al.* Pharmacology of morphine in obese patients: clinical implications. *Clin. Pharmacokinet.* 48, 635–51 (2009).

41. Rose, D. K., Cohen, M. M., Wigglesworth, D. F. & DeBoer, D. P. Critical respiratory events in the postanesthesia care unit. Patient, surgical, and anesthetic factors. *Anesthesiology* 81, 410–418 (1994).



Section II

Opioid analgesia for acute and chronic pain in adult cardiac surgery patients

Chapter 2

Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature

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Clin J Pain. 2016; 32(8):726-735

Abstract

Objective

Remifentanil is an ultra-short acting opioid that is commonly used during both short-term and prolonged surgery. This review investigated associations of intraoperative remifentanil administration with acute postoperative pain, hyperalgesia, and chronic postoperative pain, with emphasis on the perioperative coanaesthetic drug regimen used.

Methods

Medline and Embase databases were searched for randomized studies, evaluating the intraoperative use of remifentanil (>2 h) versus another analgesic or a different dosage of remifentanil, and reporting acute postoperative pain parameters like postoperative pain scores, hyperalgesia, acute opioid tolerance, or analgesics requirements. Furthermore, all studies in which remifentanil was used intraoperatively and parameters for chronic postoperative pain were measured were included (pain levels after a prolonged period of time after surgery).

Results

From the 21 studies that were identified, less than half of the studies found higher acute postoperative pain, higher postoperative analgesic requirements after intraoperative remifentanil use, or both. Coanaesthetics to some extent determined this incidence, with mainly studies using volatile agents reporting increased pain levels. There was less evidence when remifentanil was combined with total intravenous anaesthesia or a combination of anaesthetics. The limited number of studies (n = 4) evaluating chronic pain suggested a potential association with intraoperative use of remifentanil.

Discussion

While studies are divers and sample sizes small, coanaesthetics used in combination with remifentanil may influence the occurrence of postoperative hyperalgesia. No firm conclusions could be made regarding acute and chronic pain, indicating more research with the goal to investigate the effect of volatile or intravenous anaesthetics along with simultaneous remifentanil infusion on acute and chronic postoperative pain is needed.

Introduction

Moderate-to-severe acute postoperative pain is reported in 41% to 86% of the patients undergoing general surgery[1,2]. Acute postoperative pain is also a major risk factor for the development of chronic pain, that is, persistent pain at the surgical site 2 to 3 months after surgery[3–5]. The incidence of chronic postoperative pain varies from 5% to 65% upon different types of surgery and is known to influence health-related outcomes such as quality of life negatively by impairing performance of activities of daily living[6,7]. In view of the relevance of acute and chronic postoperative pain, medical institutions give increasing priority to asses and report patient-reported outcomes related to postoperative pain[8].

Intraoperative and postoperative administration of opioids is vital in preventing and treating postoperative pain. In contrast, the use of opioids may lead to phenomena such as acute opioid tolerance and opioid induced hyperalgesia (OIH)[9–12]. Although OIH was first thought to be associated with all opioids, the strongest association was found with remifentanil[13].

Remifentanil is an ultra-short-acting, hyperpotent, μ-opioid receptor agonist[14] and is often used for short-term and long-term surgery because of its favourable pharmacokinetic and pharmacodynamic properties, including rapid distribution throughout the body, rapid onset, a predictable rapid recovery profile, and dosing reliability[15]. Because remifentanil may directly or indirectly affect the N-methyl-D-aspartate (NMDA) receptor[13,16], it has been hypothesized that signalling of this NMDA receptor may lead to OIH[17]. When remifentanil is used in patients for intraoperative analgesia during surgery, it is coadministered with anaesthetics such as propofol, nitrous oxide, and/or volatile agents. As these anaesthetics may differ in their effect on the NMDA receptor[18,19], it seems of relevance to study the effect of remifentanil on hyperalgesia with respect to the coanaesthetics used[13]. Healthy volunteer studies, in which acute opioid tolerance and OIH has been described substantially, used different pain models and techniques to induce or to measure pain, hyperalgesia and tolerance[20–23]. Concerning hyperalgesia after opioid administration, a larger area of hyperalgesia or a decreased lower mechanical pain threshold has been reported, even though pain scores did not increase[21–25]. The relevance of these findings for clinical patients is unknown because the induced effect in healthy volunteers is restricted to a small region relative to the total body size, whereas patients may experience pain over a much larger area. Moreover, remifentanil infusion in healthy volunteers did not always lead to increased VAS pain scores, which also implies that the clinical implications of these findings for postoperative patients remain unclear[21,24,25].

The purpose of this review is therefore to give an update of the literature concerning the intraoperative use of remifentanil in relation to acute postoperative pain intensity, analgesic consumption, OIH or acute opioid tolerance, and chronic postoperative pain, with emphasis on the intraoperative coanaesthetic drug regimen used.

Materials and Methods

A literature search was performed in Medline (PubMed) and Embase databases using the term "remifentanil", combined with the following terms: "hyperalgesia", "postoperative pain", "opioid induced hyperalgesia", "tolerance" and "chronic pain". The detailed search strategy is available in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/CJP/A333). Abstracts of retrieved citations were reviewed to identify whether inclusion and exclusion criteria were met.

For acute postoperative pain, clinical studies in surgical patients were included if (1) patients were randomized between the intraoperative use of remifentanil and another analgesic or a different dosage of remifentanil; (2) surgical time was longer than 120 minutes (or, if surgical time was not noted, anaesthesia time was >150 min); and (3) acute postoperative pain parameters (if available pain scores, hyperalgesia, acute opioid tolerance, or analgesics requirement) were evaluated. Clinical studies in surgical patients were excluded if (1) surgical or anaesthesia time was not given; (2) no full text was available or language was not English; (3) they were not original articles (e.g. editorials, letters to editors, poster abstracts, commentary); (4) remifentanil was used either preoperatively or postoperatively only or was combined with intraoperative use of intrathecal analgesics; or (5) they included patients younger than 18 years.

For chronic postoperative pain, all studies in which remifentanil was used intraoperatively in adults and pain levels were measured after a prolonged period of time after surgery (e.g. 3, 6 or 12 months postoperatively) were included, implying that studies where remifentanil was combined with intraoperative use of intrathecal analgesics are also reported.

Studies were categorized by the drug regimen used to maintain anaesthesia, that is, volatile agents, total intravenous anaesthesia (TIVA), or a combination of both. Outcomes of postoperative pain levels, analgesic requirements and measurements of hyperalgesia and opioid tolerance are discussed. Strategies to overcome possible remifentanil-induced hyperalgesia, such as the addition of NMDA antagonists, are reviewed elsewhere and are not in the scope of this article[10,12].

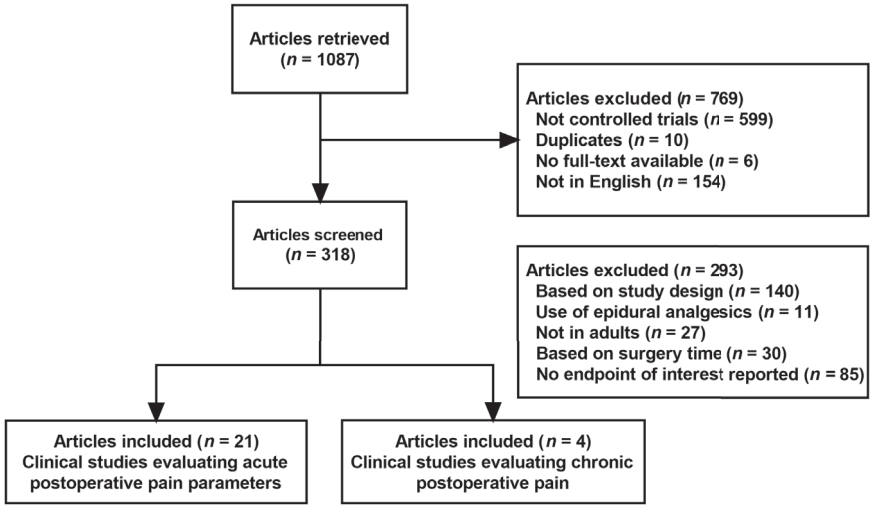

Figure 1. The Consort diagram

On February 6, 2015, the search strategy resulted in 1087 citations from 1993 until that date. Medline searches resulted in 474 articles, of which 431 studies were excluded. The Embase search resulted in 613 articles, which were all excluded. The search results and selection flow chart are reported in Figure 1. The review included 25 studies, 21 randomized studies evaluating the intraoperative use of remifentanil and reporting acute postoperative parameters and four studies evaluating the influence of intraoperative use of remifentanil on chronic postoperative pain.

Definitions

The terms "acute opioid tolerance" and "opioid induced hyperalgesia" originate from animal studies but were later on also used in human studies. Acute opioid tolerance is defined as "the need for a higher dose of the opioid to get the same analgesic effect"[11,26]. The underlying mechanism of acute opioid tolerance is thought to be desensitization of the opioid receptors[11]. Hyperalgesia is defined as "increased pain from a stimulus that normally provokes pain"[27]. It occurs at different locations surrounding the original pain site and has other characteristics than the original pain[11]. Although acute opioid tolerance and OIH have distinct mechanisms, either phenomenon may result in inadequate analgesia in patients treated with opioids[26]. Chronic postoperative pain is defined by the International Association for the Study of Pain (IASP) as pain that develops after surgical

intervention and lasts at least two months, while other causes of pain have been excluded[3,6]. Others have recommended to consider a period of three months rather than the two months suggested by the IASP[28].

Results

Studies evaluating intraoperative remifentanil and acute postoperative pain parameters

Table 1 shows the characteristics of the 21 retrieved clinical studies on acute postoperative pain. In 13 studies, remifentanil was administered together with volatile anaesthetics such as desflurane, isoflurane, sevoflurane, and nitrous oxide. Four studies investigated TIVA in combination with remifentanil. The remaining four studies combined or compared different anaesthetic techniques or compared with or without the combination with remifentanil (Table 1). Study arms or endpoints that were not of interest for this review are not displayed in Table 1. Eight of the 21 studies randomized between a low dose of remifentanil group (0.05 to 0.10 μg/kg/h) and a higher dose (0.15 to 1.0 μg/kg/h). The pain scales used in the different studies varied in score range (0 to 3, 0 to 5, 0 to 10) and methodology (visual, verbal of numerical). The VAS (range, 0 to 10 or 0 to 100 mm) and the (verbal) Numerical Rating Scale (range, 0 to 10) predominated. These scales have been validated for the measurement of acute pain[29].

Postoperative pain intensity

All 21 retrieved studies measured postoperative pain intensity (Table 2). Thirteen studies evaluated remifentanil during maintenance of anaesthesia with volatile agents. Six out of 13 studies randomized between different doses of intraoperative remifentanil (Table 2)[30–35]. A dose-dependent effect on pain scores was shown in 3 studies comparing a low remifentanil dose (0.05 μg/kg/min[30,31] or 0.1 μg/kg/min[32]) with a high dose (0.3 μg/kg/min). No other opioids, besides transition opioids, were used during surgery, and postoperative analgesia was facilitated through a "patient-controlled-analgesia" pump. In all 3 studies, the high dose was associated with higher pain scores. The effect of remifentanil on postoperative pain was prolonged, judged from the fact that patients in the high dose group still had higher pain scores after 3 to 4 hours[32], 12 hours[30,31] or 24 hours[31]. Even though the studies of Lee et al.[30,31] found a significant increase in pain intensity at different time points (Table 2), absolute values for pain intensity were low (i.e. at 24 hours VAS pain scores (mm) of 13.7 ± 4.9 vs. 23.8 ± 6.8 ($p<0.05$))[31]. In contrast to the reports described above, the 3 other studies that compared low-dose remifentanil with a higher dose of remifentanil did not reveal any effect on postoperative pain

intensity 1 hour[34] after surgery, during the first 6 hours after surgery[35], and 48 hours after surgery[33].

Of the 13 studies including volatile anaesthesia to evaluate remifentanil, 7 studies[36–42] compared remifentanil with different comparator arms. The study of Lison et al.[36], did also find a significant difference in pain intensity (0 to 4 pain scale) in the first hour after surgery between the remifentanil and sufentanil groups[36]. The authors of a desflurane-based study compared remifentanil with placebo[37]. Although desflurane has no analgesic features, no other opioids were used in the placebo group. Moreover, no long-acting opioid was used before the end of surgery. Still, pain intensity (100 mm VAS) in the remifentanil arm (0.3 μg/kg/min) was higher after 30 min, and after 6 and 12 hours. Remifentanil was also compared to magnesium sulphate during middle-ear surgery[38]. Pain scores were measured only 15 and 30 minutes after extubation and they were increased in the remifentanil group.

Four studies[39–42] evaluated remifentanil during maintenance of anaesthesia with volatile agents and nitrous oxide (Table 1). Two of these 4 studies found that despite the use of transition opioids before the end of surgery, the postoperative pain intensity for remifentanil was increased compared to sufentanil and adenosine[40,42]. The study of Minkowitz[39] compared fentanyl with remifentanil in combination with isoflurane and nitrous oxide and did not find any effects of remifentanil on postoperative pain intensity. The study of Lee and colleagues randomized between remifentanil (0.17 μg/kg/min) and nitrous oxide (70%) during isoflurane based anaesthesia, in which no significant differences in postoperative pain and postoperative morphine consumption were found[41].

Four studies used TIVA next to remifentanil as maintenance of anaesthesia in patients undergoing cardiac surgery[43–46]. All these studies did not report any increased postoperative pain induced by remifentanil. The study of Rauf et al.[43] randomized between remifentanil and placebo during propofol and fentanyl-based anaesthesia. The difference in pain intensity between groups did not reach significance (p=0.07), probably because the study was not powered on this endpoint[43]. A study on 90 patients comparing remifentanil with placebo during sufentanil and propofol-based anaesthesia found that pain scores at rest were comparable between the groups. However, pain scores during a deep breath were significantly lower in the remifentanil group directly after extubation, and at 8 and 16 hours post-surgery[44]. The study of Richebe et al.[45] compared different dosages after continuous infusion vs. target-controlled infusion of remifentanil.

Table 1. Basic characteristics of clinical studies in surgical patients (n = 21)

	Total (n)	Type of surgery	Anaesthetic Agents	Study arms of interest	n per arm	Maintenance dose remifentanil (μg/kg/min)
Maintenance of anaesthesia with volatile agents.						
Lee et al.[30]	90	Abdominal	DES	Remifentanil (low dose)	30	0.05
				Remifentanil (high dose)	29	0.3
Lee et al.[31]	85	Abdominal	DES	Remifentanil (low dose)	28	0.05
				Remifentanil (high dose)	29	0.3
Guignard et al.[32]	49	Abdominal	DES	Remifentanil (low dose)	25	0.1
				Remifentanil (high dose)	24	0.3
Joly et al.[33]	74	Abdominal	DES	Remifentanil (low dose)	25	0.05
				Remifentanil (high dose)	25	0.4
Song et al.[34]	75	Abdominal	DES	Remifentanil (low dose)	25	0.1
				Remifentanil (high dose)	25	0.3
Treskatch et al.[35]	48	Abdominal	SEV	Remifentanil (low dose)	15	0.08
				Remifentanil (high dose)	17	0.2
Lison et al.[36]	113	Cardiac	ISO	Remifentanil	57	1.0
				Sufentanil	56	0.02
Lee et al.[37]	75	Abdominal	DES	Remifentanil	25	0.3
				Saline	25	-
Ryu et al.[38]	80	Middle ear	SEV	Remifentanil	40	0.15
				Magnesiumsulphate	40	31.5 mg/kg/min
Minkowitz et al.[39]	210	Major*	ISO, N_2O	Remifentanil	139	0.5
				Fentanyl	71	1.0 μg/kg/hr
Fukunaga et al.[40]	62	Major*	DES, N_2O	Remifentanil	31	0.05-0.5
				Adenosine	31	50-500
Lee et al.[41]	60	Abdominal	ISO	Remifentanil	30	0.05
				N_2O	30	0.5

	Total (n)	Type of surgery	Anaesthetic Agents	Study arms of interest	n per arm	Maintenance dose remifentanil (µg/kg/min)
Derrode et al.[42]	30	Abdominal	DES, N_2O	Remifentanil	15	0.15
				Sufentanil	15	0.01
Maintenance of anaesthesia with TIVA						
Rauf et al.[43]	20	Cardiac	Prop, FENT	Remifentanil	10	0.1
				Saline	10	-
Lahtinen et al.[44]	90	Cardiac	Prop,SUF	Remifentanil	45	0.3
				Saline	45	-
Maddali et al.[46]	176	Cardiac	Prop	Remifentanil	59	1,00
				Fentanyl	58	0.025-0.15
Richebe et al.[45]	38	Cardiac	Prop	Remifentanil (low dose)	19	7 ng/ml*
				Remifentanil (high dose)	19	0.3
Maintenance of anaesthesia using a combination of volatile and intravenous agents						
Yeom et al.[47]	60	Spinal fusion	SEV, N_2O	Remifentanil	20	0.03
				Saline	20	-
			Prop	Remifentanil	20	0.16
Shin et al.[48]	186	Breast cancer	SEV	Remifentanil (low dose)	46	1 ng/ml†
				Remifentanil (high dose)	50	4 ng/ml†
			Prop	Remifentanil (low dose)	42	1 ng/ml†
				Remifentanil (high dose)	48	4 ng/ml†
Jo et al.[49]	60	Gyn-aecological	Prop, N_2O	Remifentanil	20	3-4 ng/ml†
				Saline	20	-
Gaszynski et al.[50]	57	Abdominal	Prop, N_2O	Remifentanil	20	0.25-1.5
				Fentanyl	15	0.025-0.15
				Alfentanil	22	1.0-1.5

* Surgery not specified. † target concentration with target-controlled infusion.
DES indicates desflurane; FEN, fentanyl; ISO, isoflurane; N_2O, nitrous oxide; Prop, propofol; SEV, sevoflurane; SUF, sufentanil; TIVA, total intravenous anaesthesia.

Table 2. Outcome of clinical studies in surgical patients (n = 21)

Study	End Points	Results
Maintenance of anaesthesia with volatile agents.		
Lee et al.[30]	Pain intensity after 1, 6, 12 and 24 h (100 mm VAS)	High dose remifentanil (HR) study arm had higher VAS scores at 1. 6 and 12 h after surgery compared to low dose (LR). (p<0.05)
	PCA (morphine/ketorolac/ ramosetron) use over 24 h (ml)	HR vs. LR: 60.0 ± 2.3 vs. 58.3 ± 2.6, p<0.05
	Time to first analgesic requirement (min)	HR vs. LR: 28.3 ± 8.3 vs. 37.5 ± 10.7, p<0.05
Lee et al.[31]	Pain intensity after 1, 6, 12 and 24 h (100 mm VAS)	Postoperative pain scores were significantly greater in the HR group at all time points compared to low dose (LR). (P<0.05)
	PCA (morphine/ketorolac/ ramosetron) use over 24 h (ml)	HR vs. LR: 51.4 ± 4.2 vs. 41.4 ± 6.2, p<0.05
	Time to first analgesic requirement (min)	HR vs. LR: 20.9 ± 8.6 vs. 30.2 ± 9.8, p<0.05
Guignard et al.[32]	Pain intensity until 24 h after surgery (0-10 VRS, 0-10 VAS)	15, 30 en 45 min after extubation VRS for pain were greater in the HR group. VAS pain scores were higher 3 and 4 hr after extubation in the HR group.
	Total morphine consumption at 24 hr after surgery (mg)	HR vs. LR: 59(43 to 71) vs. 32 (19 to 59), p<0.01
	Time to requesting additional morphine.	The high-dose remifentanil group required morphine significantly earlier. (p<0.05)
Joly et al.[33]	Pain intensity during 48 h after surgery (100 mm VAS, VRS)	No statistically significant differences in pain among groups.
	Total morphine consumption over 48 h (mg)	HR vs. LR: 86 (59 to 109) vs. 68(50 to 91), p<0.05
	Time to first analgesic requirement (min)	HR vs. LR: 24 (20 to 33) vs. 35 (28 to 46), NS
Song et al.[34]	Pain intensity (0-10 VAS) 1 hr after surgery.	HR vs. LR: 60.1 ± 20.3 vs. 58.0 ± 12.2, NS
	Analgesic consumption (ketorolac) the first hour after surgery (mg)	HR vs. LR: 27.0 ± 6.1 vs. 25.8 ± 6.9, NS
	PCA (morphine) use over 24 h (ml)	HR vs. LR: 60.1 ± 2.3 vs. 58.5 ±2.9, NS
	Time to first analgesic requirement (min)	HR vs. LR: 32. 2 ± 10.3 vs. 36.2 ± 11.9, NS
Treskatch et al.[35]	Pain intensity 0-6 hr after surgery (0-3 BPS, 0-4 VRS, 0-10 NRS)	No significant difference in postoperative pain intensity between groups.
	Total morphine consumption 6 h after surgery(mg)	HR vs. LR: 28 ± 5 vs. 30 ± 4, NS
	Time to first analgesic requirement (min)	HR vs. LR: 17 (10 to 21) vs. 12 (7 to 27), NS

Study	End Points	Results
Lison et al.[36]	Pain intensity (0-4 Pain scale) during first 3 h after weaning	Postoperative pain scores during the first hour of weaning were higher in the remifentanil group. (0.38 ± 0.42 vs. 0.24 ± 0.40, p<0.05)
Lee et al.[37]	Pain intensity after 30 min, 6, 12, 24 and 36 h (100 mm VAS)	Postoperative pain intensity was higher at 30 min, 6 h and 12 h in the remifentanil group compared to saline group. (P<0.05)
	PCA (morphine/ketorolac/ ramosetron) use over 36 h (ml)	Remi vs. saline: 88.88 ± 1.66 vs. 87.72 ± 1.49, p<0.01
	Time to first analgesic requirement (min)	Remi vs. saline: 34.0 ± 8.7 vs. 61.4 ± 5.3, p<0.01
Ryu et al.[38]	Pain intensity (0-100 mm VAS) the first 30 min after extubation	Only 15 and 30 min after extubation, higher pain scores were measured in the remifentanil group. (15 min: 53.5 (23.6) vs. 41.7 (19.2), p<0.05, 30 min: 53.5 (24.2) vs. 34.3 (17.8), p<0.05)
	The use of rescue analgesics (%)	Remi vs. Magnesium: 58% vs. 33%, P<0.05
Minkowitz et al.[39]	Pain intensity during 48 h after surgery (0-3 pain scale)	Groups were similar with respect to pain severity ratings at all postoperative times (until 48 h).
	Total morphine consumption 24 and 48 h after surgery	Total morphine consumption was not significantly different in both groups.
Fukunaga et al.[40]	Pain intensity after cough and deep breath until 48 h after surgery (0-10 VRNS)	Pain intensity 15 min after surgery in the remifentanil group was increased (9.0 ± 1.7 vs. 3.6 ± 3.3, p<0.001), this continued over the following 48 h. (p<0.01)
	Total morphine consumption over 48 h (mg)	Total morphine consumption was increased in the remifentanil group after 15 min (NS), 2 h (24 ± 8 vs. 7 ± 6, p<0.001) and 48 h (92 ± 35 vs. 53 ± 26, p<0.001)
Lee et al.[41]	Pain intensity at rest and movement 24 h after surgery. (0-10 VAS)	There was no difference pain scores during 24 h after surgery. (NS)
	Total morphine consumption the first 24 h	No significant differences between groups.
Derrode et al.[42]	Pain intensity until 12 h after surgery (0-10 VAS)	The remifentanil group had higher VAS scores the first 2 h after extubation.
	Total morphine consumption at 24 h after surgery (mg)	Remi vs. Sufentanil: 56 (29) vs. 37 (20), p<0.05
	Time to first analgesic requirement (min)	Remi vs. Sufentanil: 11 (1-29) vs. 55 (2-240), p<0.001
Maintenance of anaesthesia with TIVA		
Rauf et al.[43]	Pain intensity during the first hour after surgery (0-10 VAS)	Remi vs. Saline: 5 (2–9) vs. 3 (0–6), NS
	Morphine consumption during the first hour after surgery (mg)	Remi vs. Saline: 8.2 vs. 3.3, p<0.05
	Total morphine consumption 12 h after surgery (mg)	Remi vs. Saline: 27.1 (8.7) vs. 24 (6.6), NS

Study	End Points	Results
Lahtinen et al.[44]	Pain intensity at rest and after cough during 40 h (100 mm VAS)	The remifentanil group showed lower pain scores during deep breath immediately after extubation and 8 and 16 h after extubation. (P=0.02)
	Time to first analgesic requirement (min)	Remi vs. Saline: 9 (0-525) vs. 8.8 (0-170) . NS
	Total oxycodon consumption 48 h after surgery (mg)	Remi vs. Saline: 98 (29-166) vs. 99 (42-219). NS
Maddali et al.[46]	Pain intensity during 12 h (100 mm VAS)	No significant differences in pain intensity the first 12 h after surgery.
	The use of rescue analgesia (%)	Remi vs. fentanyl: 76.1% vs. 76.2%, NS
Richebe et al.[45]	Pain intensity at rest and movement during 44 h. (0-10 VAS and VRS)	No significance difference in VRS and VAS at rest and cough at different time points.
	Total morphine consumption after 48 h (mg)	HR vs. LR: 33 (31) vs. 31 (17), NS
Maintenance of anaesthesia using a combination of volatile and intravenous agents		
Yeom et al.[47]	Pain intensity at rest during 48 h (0-10 NRS)	Pain intensity did not differ significantly between groups the first 48 h postoperatively
	Total fentanyl consumption 48 h after surgery (μg)	No significant difference were found in PCA fentanyl requirements 48 h after surgery.
Shin et al.[48]	Pain intensity (0-10 VAS) during 24 h	The VAS scores during 24 h after surgery were higher in the high remifentanil-sevoflurane group than the other 3 groups. ($p<0.001$)
	Total morphine consumption after 24 h (mg)	Morphine consumption was higher in the high remifentanil - sevoflurane group vs. other groups. (38.6 ± 14.9 vs. 31.5 ± 3.7 vs. 31.7 ± 8.3 vs. 30.1 ± 6.1, $p<0.001$)
Jo et al.[49]	Pain intensity at rest and after cough and fentanyl use over 48 h (100 mm VAS)	Only 2 h after surgery pain intensity was lower in patients at rest in the remifentanil group. (36.5 ± 14.6 vs. 26.5 ± 9.3, $p=0.002$)
	Total fentanyl consumption 24 h after surgery (μg)	Remi vs. Saline: 756.5 ± 502.4 vs. 651.6 ± 367.5, NS
	Fentanyl titration dose (μg)	Remi vs. Saline: 227.5 ± 88.1 vs. 133.8 ± 87.8 , $p=0.001$
Gaszynski et al.[50]	Pain intensity during 6 h (0-5 verbal scale)	Significantly more patients in the remifentanil group reported disturbing pain. (25% vs. 13.3% vs. 4.5%, $p<0.05$)
	Analgesic consumption the first 6 h postoperatively	More analgesics were used in the remifentanil group. ($p<0.05$)

NRS indicates Numerical Rating Scale; NS, not significant; PCA, patient-controlled analgesia; VAS, Visual Analogue Scale; VRS, Verbal Rating scale

No difference was found in postoperative pain scores. Lastly, the study of Maddalli et al.[46] randomized between high dose remifentanil (1.0 μg/kg/min) and fentanyl (0.025 to 0.15 μg/kg/min) during cardiac surgery. After surgery, the fentanyl group continued with a reduced dose of fentanyl, whereas the remifentanil group received a bolus of fentanyl (1.0 μg/kg) at the end of surgery. No differences in pain intensity were measured during the first 12 hour after surgery.

Finally, four studies evaluated remifentanil using different anaesthetic regimens, or combined TIVA with volatile anaesthetics (Table 1)[47–50]. The study of Yeom et al.[47] compared three regimens: sevoflurane/nitrous oxide, sevoflurane/remifentanil/nitrous oxide, and propofol/remifentanil. No significant differences were seen in postoperative pain intensity after surgery. It is noteworthy that the remifentanil dosage was low in both groups (resp. 0.03 μg/kg/min and 0.16 μg/kg/min) compared to previously discussed studies[30–32]. Shin et al.[48], compared similarly low dosages of remifentanil (0.06 versus 0.15 μg/kg/min) when combined with sevoflurane or propofol (Table 1). Highest pain scores 24 hours after surgery were found in the highest remifentanil dose in the sevoflurane group[48]. The study of Jo et al.[49] combined propofol with nitrous oxide and randomized between remifentanil and placebo. This study found lower pain scores at rest in de remifentanil group. The placebo group received analgesics during postoperative phase only. Yet another study that maintained anaesthesia with propofol and nitrous oxide, found more disturbing pain, but less "small pain" in the remifentanil group versus the fentanyl and alfentanil groups[50].

Analgesic consumption

Of the 21 retrieved studies, 20 studies measured postoperative analgesic consumption, use of rescue analgesics, and/or time to first analgesic requirement. The most common endpoint with respect to postoperative analgesic consumption was total analgesic consumption over 24 hours.

Four out of 6 studies with volatile anaesthetics evaluated different doses of remifentanil and reported a significantly higher volume used of the patient-controlled analgesia pump over the first 24 postoperative hours in the (high dose) remifentanil group, even though relative differences were small[30–32,37]. When remifentanil was compared to another drug, that is, adenosine, magnesium sulfate, or sufentanil, the administration of remifentanil was also associated with increased requirements of postoperative analgesics (Table 2)[38,40,42]. In four studies with volatile anaesthetics, no significant difference was found between groups in total analgesic consumption[34,35,39,41].

When time to first analgesic requirement was used as an endpoint, results were also inconclusive. Five studies found a significant difference between the study arms, in which the time of the first analgesic requirement varies from 9 to 55 minutes in the (high dose) remifentanil group compared to the low-dose remifentanil group or comparative group[30–32,37,42]. Three other studies did not find any effect of remifentanil on time to first analgesic requirement[33–35].

One of four TIVA studies reported a significantly higher morphine consumption during the first hour after surgery in the remifentanil group[43]. The difference was, however, no longer significant at 12 hours. Patients in both groups received a 15 μg/kg bolus of fentanyl at induction of anaesthesia and additional boluses of fentanyl during surgery. The total fentanyl consumption in both groups was not reported. Although a statistical difference between postoperative analgesic consumption was found, the absolute morphine consumption was low (8.2 vs. 3.3 mg, $p<0.05$)**.** The other 3 studies that used TIVA reported no increase in total postoperative analgesic use in the remifentanil-treated patients[44–46]. To maintain anaesthesia two of these studies used long-acting opioids (e.g., sufentanil and fentanyl) next to propofol[43,44].

Concerning studies in which remifentanil was combined with a combination of volatile and intravenous agents, the study of Shin et al.[48] found higher morphine consumption after 24 hours in the high-dose remifentanil-sevoflurane group compared to the low-dose remifentanil-sevoflurane group or the remifentanil-propofol group. Two studies combining remifentanil with propofol/nitrous oxide found a higher titration dose[49] and a higher analgesic consumption 6 hours after surgery[50] in the remifentanil group. No differences in analgesic consumption were found between groups in the study of Yeom et al.[47]

OIH or acute opioid tolerance measured with Quantative Sensory Testing (QST)

In total, 5 of the 21 retrieved studies aimed for an objective quantification of sensation using QST, thereby exposing patients to pressure, thermal, and electrical stimuli. Four studies were performed with volatile anaesthetics[30,31,33,34] and one with intravenous agents[45]. None of these studies had acute opioid tolerance as endpoint. All 5 studies found a significantly enlarged area of hyperalgesia or significant decreased sensory threshold in patients receiving (high dose) remifentanil.

Joly et al.[33] studied two dosages of remifentanil (0.05 vs. 0.40 μg/kg/min) and did not find a difference in pain levels using the VAS between the two groups. However, measuring the area of hyperalgesia with QST, they found that the

area of hyperalgesia near the incision was significantly enlarged, and tactile pain thresholds adjacent to the incision were significantly decreased both at 24 and 48 hours after surgery in the high-dose remifentanil group. In contrast, tactile and pressure pain thresholds measured on the forearm did not differ between groups or between the time points before and after surgery.

In the studies of Song et al.[34] and Richebe et al.[45], the authors compared two different dosages of remifentanil. No dose-dependent effect of remifentanil was found on pain levels or analgesic requirements. Again, measured with QST, the tactile pain threshold was increased and the area of hyperalgesia near the incision, was significantly increased up to four days after surgery[34,45].

Moreover, two studies collected, in addition to standard postoperative parameters, hyperalgesia thresholds near the incision before and 24 hours after surgery. Both studies reported a significantly lower hyperalgesia threshold 24 hours after surgery in the high-dose (0.3 μg/kg/min) remifentanil group, indicating prolonged sensory changes after exposure to high-dose remifentanil[30,31].

Studies evaluating intraoperative remifentanil and long-term effects on pain parameters

Four studies addressed chronic postoperative pain and its possible association with the intraoperative use of remifentanil. Although all studies evaluated long-term effects of remifentanil on pain parameters, they varied in type of surgery, the sample size, and the study design as shown in Table 3.

The study of Salangros[51] compared low-dose remifentanil plus preoperative epidural analgesics with high-dose remifentanil plus postsurgical epidural analgesics after cardiac surgery. The incidence of chronic thoracic pain was significant higher in the high-dose remifentanil group after three months (50% vs. 16.7%), 6 months (55% vs. 16.7%), and at the end of the study (55% vs. 11.1%; median follow-up 9.5 months). However, the timing of the epidural block was different in both groups, which may have influenced the outcome[52].

The follow-up study in 90 cardiac patients compared the prevalence of chronic thoracic pain after 12 months upon the intraoperative use of remifentanil combined with fentanyl versus fentanyl alone[53]. Remifentanil was a risk factor for the development of chronic pain at 12 months (odds ratio 8.9, 95% confidence interval: 1.6 to 49.0) and a higher dose of remifentanil was more correlated with chronic pain than a lower dose. A point of concern is that remifentanil was given concomitantly with fentanyl, but despite this, a dose dependent relation was found.

Table 3: Clinical studies in surgical patients with effects of remifentanil on chronic postoperative pain (n = 4)

Study	Total (n)	Type of surgery	Study design	Outcome
Salengros et al.[51]	38	Thoracotomy*	RCT	High dose remifentanil without epidural analgesia had high incidence of CPP compered to low-dose with epidural analgesia.
Van Gulik et al.[53]	90	Cardiac	Prospective follow-up	Use of remifentanil was associated in a dose related manner with CPP.
Song et al.[54]	366	Lung and oesophageal cancer	RCT	Increased incidence of CPP in remifentanil-sevoflurane group vs the remifentanil-propofol group.
Cho et al.[55]	175	Breast cancer	Retrospective cohort	Increased incidence of CPP in remifentanil-sevoflurane group vs the remifentanil-propofol group.

* Type of surgery not specified.

CPP indicates chronic postoperative pain; RCT, randomized controlled trial.

In a prospective study, intrathecal analgesics were combined with sevoflurane (volatile group) or propofol and remifentanil (TIVA group)[54]. Acute pain intensity after surgery did not differ between both groups. However, chronic thoracic pain was significantly lower in the TIVA group after three months (38% vs. 57%, p=0.001) and 6 months (34% vs. 51%, p=0.002) compared with the sevoflurane group. Still, determining the precise effect of remifentanil is problematic, because the total dose of remifentanil was not reported and patients received epidural analgesia during and after surgery in both arms.

Cho et al.[55] analysed in a retrospective study the influence of sevoflurane or propofol on remifentanil-based anaesthesia during breast surgery. Both groups received an equal amount of remifentanil during surgery, but the combination of remifentanil with a volatile agent was associated with a higher incidence of chronic postoperative pain. The combination of sevoflurane and remifentanil was significantly associated with a 1.5 times greater prevalence of chronic pain compared with the propofol and remifentanil combination.

Discussion

This review provides an update of the literature on intraoperative remifentanil in relation to postoperative pain intensity, analgesic consumption, OIH or acute opioid tolerance, and chronic postoperative pain. Although other recent reviews focus on opiates and acute postoperative pain[13,16], this review focuses

on administered coanaesthetics and evaluates the association between remifentanil and chronic postoperative pain. Overall, there are indications that intraoperative remifentanil used in combination with coanaesthetics may cause acute postoperative hyperalgesia, however, no firm conclusions could be made regarding postoperative acute pain intensity, opioid consumptions and chronic pain.

Several studies investigated the influence of remifentanil on pain parameters in a (placebo) controlled study design, without the use of other opioids and administered together with inhalational anaesthetics[30,31,37,40]. Studies with this design showed increased postoperative pain levels and analgesic consumption. In contrast, in all four TIVA studies, the administration of remifentanil did not attenuate the postoperative pain intensity. With focus on different anaesthetics techniques, the study of Shin et al.[48] is of special interest. This study compared remifentanil administered with different strategies for maintenance of anaesthesia (i.e. propofol vs. sevoflurane) and also found an increase in postoperative pain during 24 hours after surgery in the high-dose remifentanil-sevoflurane group, but not in the low-dose remifentanil-sevoflurane and remifentanil-propofol groups[48]. However, this effect was not replicated in another study with the same groups, except that nitrous oxide was added to the maintenance anaesthesia with sevoflurane[47].

A possible explanation for the findings described above may be that propofol and nitrous oxide antagonize the NMDA receptors, which results in less central sensitization, thereby attenuating the development of hyperalgesia or tolerance to opioids[18,19]. This is in line with the finding that the glutamergic system is instrumental in both opioid tolerance and OIH[56]. Volatile anaesthetics such as desflurane, sevoflurane, and isoflurane have poor analgesic properties and have a minor impact on NMDA receptors relative to the impact of nitrous oxide[57]. More specifically, a study comparing remifentanil-propofol-based anaesthesia with and without the addition of nitrous oxide found that the addition of nitrous oxide did not influence postoperative pain and cumulative morphine consumption but did reduce remifentanil induced hyperalgesia[58]. It cannot be excluded, however, that these results on the influence of coanaesthetics are explained by other unidentified variables. Most of the studies that used volatile anaesthetics concerned abdominal surgery, whereas TIVA studies concerned cardiac surgery. Postoperatively, cardiac surgery patients are sedated longer compared with abdominal surgery patients. As such, on recovery from anaesthesia, the effect of remifentanil may have worn off during sedation, which may potentially explain the absence of increased pain scores in the remifentanil groups when combined

with TIVA for cardiac surgery. It is unknown whether sensitization occurs during sedation and whether pain perception on the long term is affected. In contrast, remifentanil stands out among other opioids for its pharmacological effects and possible side effects, either directly or indirectly, on the NMDA receptor[59,60].

Another possible cause for acute postoperative pain induced by remifentanil may be the extremely short half-life of remifentanil. Upon cessation of remifentanil infusion and in the absence of transition analgesics, postoperative parameters such as pain scores and analgesic consumption may be prone to increase[30,31,37,40]. This hypothesis is, however, disputed by the results of studies in which patients receiving long-acting opioids before the end of surgery still reported an effect of remifentanil on postoperative pain or analgesic requirements[32,40]. Finally, results of studies using QST suggested that remifentanil may cause hyperalgesia. However, although areas of hyperalgesia were increased, there was not always an increase in pain scores, indicating that these findings may not be clinically relevant. It seems that pain scales are not always sensitive enough to measure the existence of hyperalgesia or are incapable of measuring hyperalgesia when no actual painful stimulus is given. As such, the clinical relevance of increased postoperative hyperalgesia measured with QST as a cause of acute postoperative pain or increased analgesic consumption is therefore still not known[61]. Even though there seems some evidence that remifentanil leads to higher acute postoperative pain levels, postoperative analgesic requirements, or both, study designs are divers and sample sizes small. Evidence regarding the association of intraoperative remifentanil and acute postoperative pain levels and analgesic requirements are conflicting. The frequency of pain measurements varied from a single measurement after awaking from anaesthesia to hourly or 12-hourly measurements. Postoperative pain management protocols varied considerably, depending on type of surgery, hospital, and country from which the study originates. Postoperative pain levels and/or analgesic consumption were not always the primary endpoint of the studies. A large number of retrieved articles were excluded because remifentanil was administered in both study arms and in the same dose. The number of excluded articles of language other than English is also a form of bias. Moreover, postoperative pain and the postoperative use of analgesics were often not measured. Nonetheless, a broad overview of articles is given that specifically focus on the intraoperative use of remifentanil. In addition, the exclusion criteria used narrowed the scope of this review to adults undergoing prolonged surgery. In our opinion, this group of patients is the most relevant since remifentanil is used extensively during general anesthesia[62,63]. The focus on prolonged surgery is chosen due to the implied that patients received higher

amounts of remifentanil and underwent more invasive and painful surgeries. Therefore, our conclusions cannot be extended to less invasive surgeries, with a lower total dose of remifentanil, even though studies are available that have found higher postoperative pain levels and analgesic requirements upon short procedures[64–66].

Future studies with the goal to investigate the synergic or confounding effect of volatile or intravenous anaesthetics along with the simultaneous infusion of remifentanil and the effect on management of postoperative pain and analgesic consumption are needed. Ideally, the follow-up time is minimally 3 months to be able to determine the long-term clinical relevance of potential acute tolerance or OIH. In general, it would be worthwhile to identify the influence of the intraoperative use of opioids on chronic postoperative pain, as was initiated recently for cardiac surgery[67]. The available studies addressing postoperative chronic pain are divers in study design, yet cautiously indicate that the use of remifentanil may have adverse consequences on the long term, for which it would be worthwhile to study the possible clinical relevance. Only a few chronic pain studies so far included outcomes such as opioid-related side effects, ability to mobilize, and psychical recovery, emotional functioning, and participant disposition. Standardized outcomes like these have been recommended to standardize research in the field of chronic postoperative pain[68,69].

In conclusion, although studies are divers and sample sizes small, there are indications intraoperative remifentanil used in combination with coanaesthetics may influence the occurrence of acute postoperative hyperalgesia and may result in chronic postoperative pain. The current research is inconclusive to make firm clinical recommendations, especially when volatile agents are used; still there seems to be some evidence of a physiological effect. To determine the clinical relevance of these findings, more research on the influence of coanaesthetics and remifentanil on acute pain and chronic postoperative pain are needed.

Acknowledgments

The authors thank Ko Hagoort, MA, Department of Pediatric Surgery, Erasmus MC—Sophia Children's Hospital, Rotterdam, The Netherlands; for text editing.

Literature

1. Apfelbaum, J. L., Chen, C., Mehta, S. S. & Gan, and T. J. Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. *Anesth. Analg.* 97, 534–540 (2003).
2. Sommer, M. *et al.* The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur. J. Anaesthesiol.* 25, 267–74 (2008).
3. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
4. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
5. Choinière, M. *et al.* Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 186, E213-23 (2014).
6. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
7. Mongardon, N. *et al.* Assessment of chronic pain after thoracotomy: a 1-year prevalence study. *Clin. J. Pain* 27, 677–81 (2011).
8. Goldstein, E., Farquhar, M., Crofton, C., Darby, C. & Garfinkel, S. Measuring hospital care from the patients' perspective: an overview of the CAHPS Hospital Survey development process. *Health Serv. Res.* 40, 1977–1995 (2005).
9. Angst, M. S. & Clark, J. D. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 104, 570–587 (2006).
10. Koppert, W. & Schmelz, M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract. Res. Anaesthesiol.* 21, 65–83 (2007).
11. Raffa, R. B. & Pergolizzi Jr, J. V. Opioid-induced hyperalgesia: is it clinically relevant for the treatment of pain patients? *Pain Manag. Nurs.* 14, e67-83 (2013).
12. Rivosecchi, R. M. *et al.* An evidence based systematic review of remifentanil associated opioid-induced hyperalgesia. *Expert Opin. Drug Saf.* 13, 587–603 (2014).
13. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
14. Westmoreland, C. L., Hoke, J. F., Sebel, P. S., Hug Jr, C. C. & Muir, K. T. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 79, 893–903 (1993).
15. Thompson, J. P. & Rowbotham, D. J. Remifentanil--an opioid for the 21st century. *Br. J. Anaesth.* 76, 341–343 (1996).
16. Kim, S. H., Stoicea, N., Soghomonyan, S. & Bergese, S. D. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front. Pharmacol.* 5, 108 (2014).
17. Guntz, E. *et al.* Effects of remifentanil on N-methyl-D-aspartate receptor: an electrophysiologic study in rat spinal cord. *Anesthesiology* 102, 1235–1241 (2005).
18. Jevtovic-Todorovic, V. *et al.* Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nat. Med.* 4, 460–463 (1998).
19. Grasshoff, C. & Gillessen, T. Effects of propofol on N-methyl-D-aspartate receptor-mediated calcium increase in cultured rat cerebrocortical neurons. *Eur. J. Anaesthesiol.* 22, 467–470 (2005).

20. Martucci, K. T., Eisenach, J. C., Tong, C. & Coghill, R. C. Opioid-independent mechanisms supporting offset analgesia and temporal sharpening of nociceptive information. *Pain* 153, 1232–1243 (2012).
21. Chu, L. F. *et al.* Modulation of remifentanil-induced postinfusion hyperalgesia by the β-blocker propranolol in humans. *Pain* 153, 974–981 (2012).
22. Angst, M. S., Koppert, W., Pahl, I., Clark, D. J. & Schmelz, M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. *Pain* 106, 49–57 (2003).
23. Luginbühl, M. *et al.* Modulation of remifentanil-induced analgesia, hyperalgesia, and tolerance by small-dose ketamine in humans. *Anesth. Analg.* 96, 726–32, table of contents (2003).
24. Lenz, H. *et al.* Effects of COX inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans. *Pain* 152, 1289–1297 (2011).
25. Chu, L. F., Dairmont, J., Zamora, A. K., Young, C. A. & Angst, M. S. The endogenous opioid system is not involved in modulation of opioid-induced hyperalgesia. *J. pain* 12, 108–15 (2011).
26. Chu, L. F., Angst, M. S. & Clark, D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin. J. Pain* 24, 479–496 (2008).
27. Pasero, C. & McCaffery, M. Opioid-induced hyperalgesia. *J. Perianesth. Nurs.* 27, 46–50 (2012).
28. Haroutiunian, S., Nikolajsen, L., Finnerup, N. B. & Jensen, T. S. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 154, 95–102 (2013).
29. Williamson, A. & Hoggart, B. Pain: a review of three commonly used pain rating scales. *J. Clin. Nurs.* 14, 798–804 (2005).
30. Lee, C., Kim, Y.-D. & Kim, J.-N. Antihyperalgesic effects of dexmedetomidine on high-dose remifentanil-induced hyperalgesia. *Korean J. Anesthesiol.* 64, 301–7 (2013).
31. Lee, C., Lee, H.-W. & Kim, J.-N. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean J. Anesthesiol.* 64, 19–24 (2013).
32. Guignard, B. *et al.* Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 93, 409–17 (2000).
33. Joly, V. *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 103, 147–55 (2005).
34. Song, Y.-K. *et al.* Interaction between postoperative shivering and hyperalgesia caused by high-dose remifentanil. *Korean J. Anesthesiol.* 66, 44–51 (2014).
35. Treskatsch, S., Klambeck, M., Mousa, S. A., Kopf, A. & Schäfer, M. Influence of high-dose intraoperative remifentanil with or without amantadine on postoperative pain intensity and morphine consumption in major abdominal surgery patients: a randomised trial. *Eur. J. Anaesthesiol.* 31, 41–9 (2014).
36. Lison, S., Schill, M. & Conzen, P. Fast-track cardiac anesthesia: efficacy and safety of remifentanil versus sufentanil. *J. Cardiothorac. Vasc. Anesth.* 21, 35–40 (2007).
37. Lee, C., Song, Y.-K., Jeong, H.-M. & Park, S.-N. The effects of magnesium sulfate infiltration on perioperative opioid consumption and opioid-induced hyperalgesia in patients undergoing robot-assisted laparoscopic prostatectomy with remifentanil-based anesthesia. *Korean J. Anesthesiol.* 61, 244–50 (2011).

38. Ryu, J.-H., Sohn, I.-S. & Do, S.-H. Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate. *Br. J. Anaesth.* 103, 490–5 (2009).
39. Minkowitz, H. S. Postoperative pain management in patients undergoing major surgery after remifentanil vs. fentanyl anesthesia. Multicentre Investigator Group. *Can. J. Anaesth.* 47, 522–8 (2000).
40. Fukunaga, A. F., Alexander, G. E. & Stark, C. W. Characterization of the analgesic actions of adenosine: comparison of adenosine and remifentanil infusions in patients undergoing major surgical procedures. *Pain* 101, 129–38 (2003).
41. Lee, L. H. Y., Irwin, M. G. & Lui, S.-K. Intraoperative remifentanil infusion does not increase postoperative opioid consumption compared with 70% nitrous oxide. *Anesthesiology* 102, 398–402 (2005).
42. Derrode, N., Lebrun, F., Levron, J.-C., Chauvin, M. & Debaene, B. Influence of peroperative opioid on postoperative pain after major abdominal surgery: sufentanil TCI versus remifentanil TCI. A randomized, controlled study. *Br. J. Anaesth.* 91, 842–9 (2003).
43. Rauf, K., Vohra, A., Fernandez-Jimenez, P., O'Keeffe, N. & Forrest, M. Remifentanil infusion in association with fentanyl-propofol anaesthesia in patients undergoing cardiac surgery: effects on morphine requirement and postoperative analgesia. *Br. J. Anaesth.* 95, 611–5 (2005).
44. Lahtinen, P., Kokki, H. & Hynynen, M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 105, 794–800 (2006).
45. Richebé, P. *et al.* Target-controlled dosing of remifentanil during cardiac surgery reduces postoperative hyperalgesia. *J. Cardiothorac. Vasc. Anesth.* 25, 917–25 (2011).
46. Maddali, M. M., Kurian, E. & Fahr, J. Extubation time, hemodynamic stability, and postoperative pain control in patients undergoing coronary artery bypass surgery: an evaluation of fentanyl, remifentanil, and nonsteroidal antiinflammatory drugs with propofol for perioperative and postoperativ. *J. Clin. Anesth.* 18, 605–10 (2006).
47. Yeom, J. H., Kim, K. H., Chon, M.-S., Byun, J. & Cho, S. Y. Remifentanil used as adjuvant in general anesthesia for spinal fusion does not exhibit acute opioid tolerance. *Korean J. Anesthesiol.* 63, 103–7 (2012).
48. Shin, S.-W. *et al.* Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. *Br. J. Anaesth.* 105, 661–7 (2010).
49. Jo, H. R. *et al.* Remifentanil-induced pronociceptive effect and its prevention with pregabalin. *Korean J. Anesthesiol.* 60, 198–204 (2011).
50. Gaszynski, T. M., Strzelczyk, J. M. & Gaszynski, W. P. Post-anesthesia Recovery after Infusion of Propofol with Remifentanil or Alfentanil or Fentanyl in Morbidly Obese Patients. *Obes. Surg.* 14, 498–503 (2004).
51. Salengros, J.-C. *et al.* Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J. Cardiothorac. Vasc. Anesth.* 24, 608–16 (2010).
52. Bong, C. L., Samuel, M., Ng, J. M. & Ip-Yam, C. Effects of preemptive epidural analgesia on post-thoracotomy pain. *J. Cardiothorac. Vasc. Anesth.* 19, 786–793 (2005).

53. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
54. Song, J. G. *et al.* Incidence of post-thoracotomy pain: a comparison between total intravenous anaesthesia and inhalation anaesthesia. *Eur. J. Cardiothorac. Surg.* 41, 1078–1082 (2012).
55. Cho, A. R. *et al.* The effects of anesthetics on chronic pain after breast cancer surgery. *Anesth. Analg.* 116, 685–693 (2013).
56. Wilder-Smith, O. H. & Arendt-Nielsen, L. Postoperative hyperalgesia: its clinical importance and relevance. *Anesthesiology* 104, 601–607 (2006).
57. Petrenko, A. B., Yamakura, T., Sakimura, K. & Baba, H. Defining the role of NMDA receptors in anesthesia: Are we there yet? *Eur. J. Pharmacol.* 723C, 29–37 (2013).
58. Echevarria, G. *et al.* Nitrous oxide (N(2)O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. *Br. J. Anaesth.* 107, 959–965 (2011).
59. Yuan, Y. *et al.* Glycogen synthase kinase-3beta contributes to remifentanil-induced postoperative hyperalgesia via regulating N-methyl-D-aspartate receptor trafficking. *Anesth. Analg.* 116, 473–481 (2013).
60. Li, Y. *et al.* Inhibition of glycogen synthase kinase-3beta prevents remifentanil-induced hyperalgesia via regulating the expression and function of spinal N-methyl-D-aspartate receptors in vivo and vitro. *PLoS One* 8, e77790 (2013).
61. Werner, M. U. Vanguard research in opioid-induced hyperalgesia - but guard the basics. *Pain* 153, 943–944 (2012).
62. Komatsu, R. *et al.* Remifentanil for general anaesthesia: a systematic review. *Anaesthesia* 62, 1266–1280 (2007).
63. Uchida, K. *et al.* Impact of remifentanil introduction on practice patterns in general anesthesia. *J. Anesth.* 25, 864–871 (2011).
64. Ozkose, Z., Yalcin Cok, O., Tuncer, B., Tufekcioglu, S. & Yardim, S. Comparison of hemodynamics, recovery profile, and early postoperative pain control and costs of remifentanil versus alfentanil-based total intravenous anesthesia (TIVA). *J. Clin. Anesth.* 14, 161–168 (2002).
65. Alper, I., Erhan, E., Ugur, G. & Ozyar, B. Remifentanil versus alfentanil in total intravenous anaesthesia for day case surgery. *Eur. J. Anaesthesiol.* 20, 61–64 (2003).
66. Mukherjee, K., Seavell, C., Rawlings, E. & Weiss, A. A comparison of total intravenous with balanced anaesthesia for middle ear surgery: effects on postoperative nausea and vomiting, pain, and conditions of surgery. *Anaesthesia* 58, 176–180 (2003).
67. de Hoogd, S. *et al.* Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials* 15, 466 (2014).
68. VanDenKerkhof, E. G., Peters, M. L. & Bruce, J. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. *Clin. J. Pain* 29, 2–8 (2013).
69. Turk, D. C. *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 106, 337–345 (2003).

Chapter 3

Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomised controlled trial

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Trials. 2014; 27(15):466

Abstract

Background

Chronic thoracic pain after cardiac surgery is prevalent (11 to 56%) and may affect patients' physical and mental health status. Despite its favourable pharmacokinetic and pharmacodynamic properties, high doses of remifentanil administered during surgery are reported to cause acute postoperative pain and increased requirements for analgesics. Recently, an association between remifentanil use and the incidence of chronic thoracic pain in the long term was also reported. Our objective is to investigate the influence of the intraoperative remifentanil on chronic postoperative pain in a prospective randomised controlled trial.

Methods/Design

In this prospective, randomised, single-blind clinical trial, all patients (n = 126) between 18 and 85 years undergoing cardiac surgery via sternotomy receive a continuous infusion of propofol together with intermittent intravenous fentanyl at predetermined times perioperatively. Patients are randomised to receive either an additional continuous infusion of remifentanil (0.15 μg/kgIBW/min) or additional fentanyl (200 to 500 μg) as needed during surgery.

The primary end point is the prevalence of chronic thoracic pain 12 months after surgery. Secondary end points include acute postoperative pain; postoperative analgesic use; chronic thoracic pain 3 and 6 months after surgery; quality of life (SF-12) at 3, 6 and 12 months after surgery; work productivity; and use of health care. In addition, thermal detection and pain thresholds are measured preoperatively, 3 days after surgery and 12 months after surgery using quantitative sensory testing (QST). Finally, the influence of several genetic variances on the different outcomes will be measured.

Discussion

Chronic thoracic pain is prevalent after cardiac surgery, and research is needed to minimize the risk of chronic persistent postoperative pain, which is an invalidating, long-term complication of surgery. The objective of this trial is to determine the influence of perioperative remifentanil on long-term pain outcomes for cardiac patients in a prospective randomised trial. The results may be used to optimize perioperative analgesia techniques and, thereby, improve quality of life after cardiac surgery.

Background

Remifentanil is a pain-relieving drug frequently used during surgery due to its favourable pharmacokinetic and pharmacodynamic properties. It is characterized by rapid onset, predictable rapid recovery profile and dosing reliability[1]. Its use is associated with a shorter length of hospital stay and duration of mechanical ventilation after cardiac surgery and a cardioprotective effect in coronary artery bypass graft (CABG) surgery patients[2,3]. On the other hand, high doses of remifentanil administered during surgery have been reported to cause acute postoperative pain and opioid-induced hyperalgesia[4]. Acute postoperative pain, in turn, is a major risk factor for the development of chronic pain[5–7]. Studies report incidences of chronic thoracic pain after cardiac surgery via sternotomy varying from 11% to 56%, depending on the definition and the study population[8–12]. These patients reported significantly lower physical and mental health status compared to patients without chronic thoracic pain[8,11,13,14].

Little is known about a possible association between the intraoperative use of remifentanil and the development of chronic pain. A dose-dependent relationship was shown in 90 cardiac patients one year after surgery[15]. Also a randomised study designed to evaluate allodynia after thoracotomy and the occurrence of chronic thoracic pain suggested that there might be an association between the use of high dose remifentanil and increased prevalence of chronic thoracic pain[16]. More recently, a retrospective study found that the combination of remifentanil and sevoflurane was less favourable in terms of chronic pain compared to a propofol and remifentanil combination. Patients with chronic pain had received a significantly higher dose of remifentanil, but significance was not reached in multivariate analysis[17].

In our hospital, about 60% of cardiac surgery patients receive remifentanil next to fentanyl intraoperatively, depending on the anaesthetist's preference[15]. We wonder whether the possible development of hyperalgesia and chronic thoracic pain, with the negative impact on quality of life and cost efficacy, carries the risk of overcoming the advantages of remifentanil.

So far, however, no prospective randomised controlled trials designed to evaluate the influence of intraoperative remifentanil on the incidence of chronic thoracic pain are available. The current prospective randomised trial is designed to investigate the influence of perioperative additional remifentanil or additional fentanyl on the development of chronic thoracic pain at 3, 6 and 12 months after surgery. In addition, changes in thermal detection thresholds and pain thresholds and the influence of genetic variances will be investigated.

Methods/Design

Study design

This study is a prospective, randomised, single-blind clinical trial carried out in the St. Antonius Hospital, Nieuwegein, the Netherlands (Figure 1). The study population consists of adult cardiac patients undergoing elective coronary artery bypass (CABG) surgery and/or valve replacement surgery via sternotomy. Patients are blinded for treatment and are randomly assigned to the remifentanil or fentanyl group. The study was approved by the local Ethics Committee of this hospital (Verenigde Commissies Mensgebonden Onderzoek (VCMO) R13.013). The study was registered on the Clinical Trials register on 13 December 2013 (ClinicalTrials.gov number NCT02031016). The research coordinator will obtain written informed consent from each participant.

Eligibility

The following inclusion criteria are being applied: (1) patients undergoing cardiac surgery via sternotomy (a CABG and/or valve replacement); and (2) age between 18 and 85 years; (3) weight between 45 and 140 kg. Exclusion criteria are: (1) pregnancy or breastfeeding; (2) language barrier; (3) history of drug abuse; (4) neurologic condition such as peripheral neuropathy and fibromyalgia; (5) known remifentanil, fentanyl, morphine or paracetamol allergy; (6) a body mass index (BMI) above 35 kg/m2 (7) prior cardiac surgery (re-operations); and (8) patients with chronic pain conditions.

Interventions

Intraoperative analgesic protocol

Anaesthesia will be induced with midazolam (2.5 to 5.0 mg) followed by a propofol bolus (1 to 2 mg/kg), fentanyl (250 to 500 μg) and pancuronium (0.05-2 mg/kg). After tracheal intubation, patients will be ventilated to normocapnia with oxygen enriched air (50 to 100% oxygen). No nitrous oxide will be used. Sevoflurane will be used as needed. Both groups receive a continuous infusion of propofol (starting dose 200 to 300 mg/hour) and intermittent intravenous fentanyl at predetermined times (that is, before incision, at sternotomy, at aorta cannulation and at opening of the pericardium). Patients in the remifentanil group will receive a continuous infusion of remifentanil (starting infusion dose 0.15 μg/kg ideal body weight (IBW)/min) on top of this propofol-fentanyl aesthetic regimen. Patients in the fentanyl group will receive additional boluses of fentanyl 200 to 500 μg as needed instead of the remifentanil infusion.

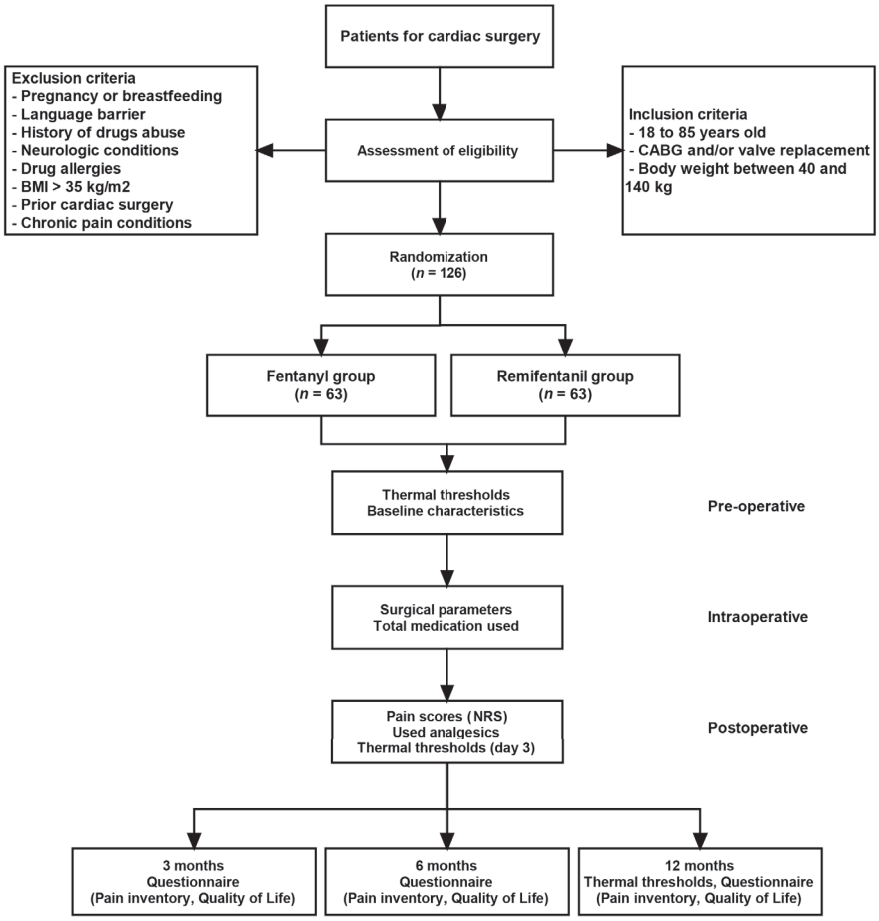

Figure 1. Flowchart of the study outline.

Patients in both groups will receive 5 to 10 mg of intravenous morphine 30 minutes before the anticipated end of surgery. After surgery, patients will either go to the Intensive Care Unit (ICU) or to the Post-Anaesthesia Care Unit (PACU).

Quantitative sensory testing

One day before surgery, three days after surgery and one year after surgery quantitative sensory testing (QST) will be performed. Cold and warm detection thresholds and pain thresholds will be measured, using the 'method of limits' with the Thermal Sensory Analyser (TSA) II 2001 (Medoc Advanced Medical Systems, U.S.)[18,19]. The threshold values will be corrected for age, gender and reaction time.

Before the first test session, patients will be asked to practice testing at least twice. A test-retest variability of less than 20% is required before formal pain testing begins. The TSA II has been used extensively to determine warm/cold detection limits and warm/cold pain thresholds.

Postoperative treatment

Patients in both groups will receive the same postoperative treatment. In both the ICU and the PACU, a pain management protocol is in place as part of standard care, consisting of a continuous infusion of morphine (starting dose of 2 mg/hour), which is adapted depending on Numerical Rating Scale (NRS) pain scores, as well as paracetamol four times a day (1 g oral/intravenous)[20]. Any perioperative fentanyl or remifentanil is discontinued at arrival at the ICU or PACU. NRS scores are assessed three times a day and administered medication is registered as part of standard care. On the general postoperative wards, the pain protocol consists of 2.5 to 10 mg morphine (oral/intravenous) on demand and paracetamol four times a day (1 g oral).

Follow-up

After discharge from the hospital, patients will be asked to complete questionnaires 3, 6 and 12 months after surgery. This questionnaire contains questions about pain (perception, location, intensity) based on the Brief Pain Inventory[21] and was described previously[5]. In addition, quality of life (QoL) is measured with the short form (SF)-12 health status instrument, and work productivity and use of health care resources are measured. One year after cardiac surgery, pain thresholds are measured, using the same QST protocol.

Primary endpoint and secondary endpoints

The primary endpoint is the percentage of patients with chronic thoracic pain (NRS >0) one year after cardiac surgery. Secondary endpoints are mean daily acute postoperative NRS scores (0 to 10) and analgesic consumption until discharge from the hospital. Also chronic pain (NRS), Quality of Life, analgesic consumption, work productivity, and use of health care 3, 6 and 12 months after surgery are assessed. In addition, warm/cold detection and pain thresholds (absolute and relative to preoperative values (baseline)) using quantitative sensory testing (QST) are considered. The length of ICU, PACU and hospital stay will be calculated.

In addition to primary and secondary endpoints, an exploratory screening of different genes in this population will be investigated. The possible influence of different genetic variances that are involved in pain sensitivity (for example,

GTP-cyclohydrolase 1 (GCH-1), WDFY family member 4 (WDFY4), Zinc Finger gene Family (ZNF), Melanocortin 1 Receptor (MC1R)) and the pharmacokinetics and pharmacodynamics of opiates (for example, glucuronosyl transferase (UGT), Multidrug Resistance-associated Protein (MRP), mu-opioid receptor gene 1 (*OPRM1*), Catechol-O-methyltransferase (*COMT*)) will be explored.

Data analysis

Statistical analyses will be done with The SPSS statistical package (version 22.0 for Windows; SPSS, Chicago, IL). Patient demographics, baseline characteristics and clinical observations are compared between patients receiving remifentanil versus fentanyl during cardiac surgery. Nonparametric data will be expressed as median (range) and analysed by chi-square. Parametric data will be expressed as mean ± SD and analysed by Student's t-tests or ranks tests. The effect of intraoperative use of remifentanil on chronic pain one year after cardiac surgery is analysed using univariate logistic regression analysis. If baseline characteristics are not balanced, multivariable techniques will be applied. To evaluate the effect of remifentanil versus fentanyl during cardiac surgery on pain thresholds, paired t-tests will be used.

To estimate the effect of the genotype on the outcome variables, each gene is examined to determine the appropriate model. The gene variants will be coded based on the observed distribution. The outcome parameters are compared between genotypes by a linear mixed model analysis based on the maximum likelihood ratio with the patient genotype status as fixed factors and the time point of outcome parameters as repeated measurement.

Sample size calculations

In a previous study of 90 patients on chronic thoracic pain after cardiac surgery, 15 of the 52 patients who received remifentanil developed chronic thoracic pain (29%) versus three of the 38 patients who did not receive remifentanil (8%); resulting in an odds ratio of 4.7[15]. Rounding numbers, the sample size calculation is made on the assumption that in this prospective study, approximately 30% of the patients receiving remifentanil will develop chronic thoracic pain and that approximately 10% of the patients receiving fentanyl will develop chronic thoracic pain. The sample size is calculated with a power of 0.80 and an alpha of 0.05; two sided. A total number of 117 patients are needed. According to previous reports, mortality thirty days after cardiac surgery is approximately 2 to 13.3%[22,23]. In a previous study, 8.4% died within one year after surgery[15]. Therefore, the total number of patients needed in this trial is 117 * 1.08 = 126; 63 patients in each arm.

Discussion

This is the first randomised trial that prospectively evaluates the influence of intraoperative remifentanil on the incidence of chronic thoracic pain. Studies in healthy volunteers indicate that remifentanil increases the occurrence of secondary hyperalgesia in experimental pain models[24–28]. Other studies have described higher pain levels or analgesic requirements in the acute phase after surgery upon intraoperative use of remifentanil[4,29,30]. The clinical long-term relevance of these mostly short-term increases in pain scores, analgesic requirements or secondary hyperalgesia is unknown.

The putative biological mechanism by which remifentanil would cause chronic pain is unclear. Opioid-induced hyperalgesia is well described in animal studies but the occurrence in patients is still under debate[31]. Animal studies suggest that remifentanil influences the N-methyl-D-aspartate (NDMA) currents by affecting opioid receptors[32,33]. Modulation of these NDMA currents could lead to central sensitization and consequently possibly to chronic postoperative pain.

Ideally, the study design should be double blind and contain no other opioid besides remifentanil. As a study arm without opioids during surgery is obviously unethical, fentanyl was selected for the other arm. The current design, where intermittent fentanyl at predetermined times is combined with continuous propofol as the basis for standardized Total Intravenous Anaesthesia (TIVA) in both arms, is based on the design of a previous study investigating risk factors for chronic thoracic pain in our hospital[15]. With one arm randomised to an additional remifentanil infusion and one arm randomised to additional intermittent fentanyl as needed, these two study groups can both be considered the standard of care in our hospital. Given the familiarity with the two study arms, we do not expect unintentional effects from the nonblinding of anaesthesiologists and ward nurses. It is emphasized that the patient is kept blinded for the treatment group, which is of particular relevance since it is the patient who determines the primary endpoint, that is, chronic thoracic pain one year after surgery. Another potential design that was considered was a group receiving remifentanil only with another group receiving fentanyl only. While the remifentanil-only group, in particular, cannot be considered a standard of care treatment in our hospital, we underline that when the current design was used in a previous nonrandomised study, a difference in the prevalence of chronic thoracic pain was detected[15].

In the current study, all patients will be evaluated for their sensory detection and pain thresholds using QST preoperatively, three days and 1 year after surgery. This randomised trial in which chronic thoracic pain after cardiac surgery is studied

in the remifentanil and control arm is not only an opportunity to investigate the influence of remifentanil on sensory thresholds, but also to explore the influence of cardiac surgery and chronic pain on sensory modalities. Ideally, for this purpose, a pain battery with more than one stimulus (for example, electricity and pressure) should be used; however, in our opinion, use of a large number of pain thresholds measurements is not feasible in patients prior to and three days after invasive cardiac surgery.

The results of this randomised trial may be used to optimize intraoperative analgesia techniques and thereby improve the quality of life of patients after cardiac surgery.

Literature

1. Derrode, N., Lebrun, F., Levron, J.-C., Chauvin, M. & Debaene, B. Influence of peroperative opioid on postoperative pain after major abdominal surgery: sufentanil TCI versus remifentanil TCI. A randomized, controlled study. *Br. J. Anaesth.* 91, 842–9 (2003).
2. Wong, G. T., Huang, Z., Ji, S. & Irwin, M. G. Remifentanil reduces the release of biochemical markers of myocardial damage after coronary artery bypass surgery: a randomized trial. *J. Cardiothorac. Vasc. Anesth.* 24, 790–796 (2010).
3. Greco, M. *et al.* Remifentanil in cardiac surgery: a meta-analysis of randomized controlled trials. *J. Cardiothorac. Vasc. Anesth.* 26, 110–6 (2012).
4. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
5. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
6. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
7. Choinière, M. *et al.* Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 186, E213-23 (2014).
8. Eisenberg, E., Pultorak, Y., Pud, D. & Bar-El, Y. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). *Pain* 92, 11–17 (2001).
9. Kalso, E., Mennander, S., Tasmuth, T. & Nilsson, E. Chronic post-sternotomy pain. *Acta Anaesthesiol. Scand.* 45, 935–939 (2001).
10. Lahtinen, P., Kokki, H. & Hynynen, M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 105, 794–800 (2006).
11. Gjeilo, K. H., Klepstad, P., Wahba, A., Lydersen, S. & Stenseth, R. Chronic pain after cardiac surgery: a prospective study. *Acta Anaesthesiol. Scand.* 54, 70–78 (2010).
12. Meyerson, J., Thelin, S., Gordh, T. & Karlsten, R. The incidence of chronic post-sternotomy pain after cardiac surgery--a prospective study. *Acta Anaesthesiol. Scand.* 45, 940–4 (2001).
13. Bruce, J. *et al.* The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. *Pain* 104, 265–273 (2003).
14. Taillefer, M. C. *et al.* Prevalence, characteristics, and predictors of chronic nonanginal postoperative pain after a cardiac operation: a cross-sectional study. *J. Thorac. Cardiovasc. Surg.* 131, 1274–1280 (2006).
15. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
16. Salengros, J.-C. *et al.* Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J. Cardiothorac. Vasc. Anesth.* 24, 608–16 (2010).
17. Cho, A. R. *et al.* The effects of anesthetics on chronic pain after breast cancer surgery. *Anesth. Analg.* 116, 685–693 (2013).

18. Rolke, R. *et al.* Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 123, 231–243 (2006).
19. Rolke, R. *et al.* Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur. J. Pain* 10, 77–88 (2006).
20. Ahlers, S. J. *et al.* Efficacy of an intravenous bolus of morphine 2.5 versus morphine 7.5 mg for procedural pain relief in postoperative cardiothoracic patients in the intensive care unit: a randomised double-blind controlled trial. *Anaesth. Intensive Care* 40, 417–426 (2012).
21. Cleeland, C. S. & Ryan, K. M. Pain assessment: global use of the Brief Pain Inventory. *Ann. Acad. Med. Singapore* 23, 129–38 (1994).
22. Edwards, F. H. *et al.* Prediction of operative mortality after valve replacement surgery. *J. Am. Coll. Cardiol.* 37, 885–892 (2001).
23. Noordzij, P. G. *et al.* Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology* 112, 1105–1115 (2010).
24. Angst, M. S., Koppert, W., Pahl, I., Clark, D. J. & Schmelz, M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. *Pain* 106, 49–57 (2003).
25. Koppert, W. *et al.* Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans. *Pain* 106, 91–9 (2003).
26. Koppert, W. *et al.* Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. *Anesthesiology* 99, 152–9 (2003).
27. Lenz, H. *et al.* Effects of COX inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans. *Pain* 152, 1289–1297 (2011).
28. Tröster, A. *et al.* Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. *Anesthesiology* 105, 1016–23 (2006).
29. Kim, S. H., Stoicea, N., Soghomonyan, S. & Bergese, S. D. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front. Pharmacol.* 5, 108 (2014).
30. Rivosecchi, R. M. *et al.* An evidence based systematic review of remifentanil associated opioid-induced hyperalgesia. *Expert Opin. Drug Saf.* 13, 587–603 (2014).
31. Raffa, R. B. & Pergolizzi Jr, J. V. Opioid-induced hyperalgesia: is it clinically relevant for the treatment of pain patients? *Pain Manag. Nurs.* 14, e67-83 (2013).
32. Guntz, E. *et al.* Effects of remifentanil on N-methyl-D-aspartate receptor: an electrophysiologic study in rat spinal cord. *Anesthesiology* 102, 1235–1241 (2005).
33. Zhao, M. & Joo, D. T. Enhancement of spinal N-methyl-D-aspartate receptor function by remifentanil action at delta-opioid receptors as a mechanism for acute opioid-induced hyperalgesia or tolerance. *Anesthesiology* 109, 308–17 (2008).

Chapter 4

Randomised controlled trial on the influence of intra-operative remifentanil versus fentanyl on acute and chronic pain after cardiac surgery

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Pain Pract. 2018;18(4):443-451

Abstract

Background

Remifentanil has been associated with increased acute and potentially chronic postoperative pain. The objective of this prospective randomised controlled trial was to investigate the influence of intraoperative remifentanil on acute and chronic postoperative pain after cardiac surgery.

Methods

Patients (n = 126) receiving standardized anaesthesia with propofol and intermittent intravenous fentanyl at predetermined times for cardiac surgery were randomised to receive intra-operatively either a continuous remifentanil infusion or additional intermittent intraoperative fentanyl as needed. Primary endpoint was chronic thoracic pain at 12 months after surgery, secondary endpoints were pain at 3 and 6 months after surgery and analgesic requirements and pain levels in the first 72 hours.

Results

There was no significant difference in incidence of chronic thoracic pain between the remifentanil and fentanyl groups, respectively 20% vs. 18%; p=0.817. At 3 months, however, significantly more patients in the remifentanil group reported chronic thoracic pain (51% vs. 33 %, p=0.047). This effect was more pronounced in younger patients and patients receiving a higher dose of remifentanil (both $p<0.05$). The first 24 and 48 hours postoperatively, morphine consumption in the remifentanil group was significantly higher than in the fentanyl group (34.3 mg (interquartile range (IQR) 25.3 to 48.2) vs. 30.2 mg (IQR 19.2 to 38.1); p=0.028 and 46.8 mg (IQR 33.8 to 59.2) vs. 39.0 mg (IQR 6.2 to 51.4); p=0.047, respectively).

Conclusions

Intraoperative use of remifentanil during cardiac surgery does not impact chronic postoperative pain one year after surgery. Nevertheless, remifentanil increases analgesic requirements and thoracic pain until three months after surgery and its use is therefore less favourable during cardiac surgery.

Introduction

Opioids are part of the multimodal anaesthesia regimen for the management of pain during and after surgery. One of these opioids, remifentanil, is often used because of its favourable pharmacokinetic and pharmacodynamic properties, including fast onset and offset of action, predictable rapid recovery profile independent on infusion duration, and metabolism independent of kidney or liver function[1,2]. Recently, however, opioids, and in particular remifentanil, have been associated with opioid-induced hyperalgesia (OIH) or acute opioid tolerance[1,3]. Concerning remifentanil, its ultra-short half-life, resulting in abrupt analgesic offset after cessation of the infusion, is thought to contribute to high postoperative pain levels[1]. Still, the clinical impact of these higher levels on the short term but particularly on the long term, is not clear[4–6].

In recent years, more attention has been focused on the risk of chronic pain after surgery[7,8]. The International Association for the Study of Pain defines chronic postoperative pain as pain that develops after surgical intervention and lasts at least two months while other causes of pain have been excluded[9]. Specifically for cardiac surgery, where the incidence of chronic postoperative pain is relatively high[10], intraoperative use of remifentanil has been associated with chronic thoracic pain[11,12]. In a randomised study designed to evaluate the occurrence of chronic thoracic pain after cardiac surgery remifentanil was combined with epidural anaesthesia. The incidence of chronic pain in the high-dose remifentanil group was significantly higher than in the low-dose group[12]. In another observational study in 90 cardiac surgery patients, intraoperative remifentanil was predictive for chronic thoracic pain in a dose-dependent manner[11]. However, this study was not designed to investigate the role of remifentanil in chronic pain after surgery.

Therefore, we performed a prospective randomised controlled trial investigating the influence of intraoperative remifentanil administration during cardiac surgery on the development chronic thoracic pain after surgery. For this purpose, we randomised between two standard care regimes in our hospital and collected data on chronic postoperative pain and quality of life 3, 6 and 12 months after surgery. In addition, acute pain was evaluated by collecting pain scores and morphine consumption over the first 72 postoperative hours.

Materials and Methods

Design and patients

This study is a prospective, randomised, single-blind clinical trial of which the study protocol has been published previously[13]. The study was approved by the local

research ethics committee and registered at ClinicalTrials.gov (NCT02031016). Patients were included from February until November 2014. Written informed consent was obtained from all subjects. Eligible patients were randomly assigned 1:1 (using computerized random numbers) to either the remifentanil or the fentanyl study arm and blinded for treatment group allocation. Inclusion criteria were: (1) patients undergoing cardiac surgery via sternotomy (a coronary artery bypass graft and/or valve replacement); and (2) age between 18 and 85 years; and (3) weight between 45 and 140 kg. Exclusion criteria were: (1) pregnancy or breastfeeding; (2) language barrier; (3) history of drug abuse; (4) neurologic condition such as peripheral neuropathy and fibromyalgia; (5) known remifentanil, fentanyl, morphine or paracetamol allergy; (6) a body mass index (BMI) above 35 kg/m^2; (7) prior cardiac surgery (reoperations); or (8) chronic pain condition.

Intraoperative anaesthesia and analgesia

Premedication and induction of anaesthesia was standardized in all patients. Both groups then received a continuous infusion of propofol (starting dose 200 to 300 mg/h) and intermittent intravenous fentanyl (500 μg) at predetermined times (i.e. before incision, at sternotomy, at aorta cannulation and at opening of the pericardium). At the discretion of the attending anaesthesiologist, the dose of fentanyl could be reduced to a minimum of 200 μg depending on patient characteristics (e.g. old age, haemodynamics, low body weight, ejection fraction). Patients in the remifentanil group received a continuous infusion of remifentanil (starting dose 0.15 μg/kg ideal body weight (IBW)/min) in addition to the propofol and predetermined fentanyl anaesthetic regimen. Remifentanil starting dose could be adjusted at the discretion of the anaesthesiologist. Patients in the fentanyl group received additional boluses of fentanyl if predetermined fentanyl doses were insufficient. The attending anaesthesiologist decided, based on patient characteristics (e.g. sweating, haemodynamics, body weight, ejection fraction), if extra fentanyl (200 to 500 μg) was indicated. As needed, the attending anaesthesiologist could also give a reduced additional bolus. In both groups, sevoflurane was used as needed, and no nitrous oxide was used. In both groups, patients received 5 or 10 mg of intravenous morphine (depending on hemodynamic status) 30 minutes before the anticipated end of surgery.

Postoperative pain measurement and analgesia

After surgery, patients were first admitted either to the Intensive Care Unit (ICU) or to the Post-Anaesthesia Care Unit (PACU). These units as well as the general postoperative ward use the same standardized postoperative treatment[14,15]. Numeric Rating Scale (NRS) pain scores (0-10) were collected at least three times

a day by the nursing staff on the ICU/PACU or ward. Immediately after surgery, 1 g of paracetamol oral or intravenous 4 times a day was given together with a continuous infusion of morphine (starting dose 2 mg/h), which was adapted individually on the guidance of the patient's NRS pain scores. A pain titration protocol was used, with a targeted NRS value of <4. Analgesics were increased after patients reported NRS of ≥4 and decreased when a NRS score of 0 or 1 was reported.[15] The continuous infusion of morphine was stopped upon transfer to the general postoperative ward and replaced by 2.5 to 10 mg of (intravenous) morphine on demand. Paracetamol (1 g oral or intravenous) four times a day was continued until discharge. On the ward, patients could receive oxycodone or tramadol orally, which was calculated to morphine equivalents. Consumption of opioids was calculated per 24 hours until 72 hours after surgery.

Study endpoints

Primary endpoint of this study was chronic postoperative pain, which was evaluated at 12 months after cardiac surgery. Chronic thoracic pain was defined as sternal and/or thoracic pain (NRS score >0) which the patient identified as related to surgery, and which was different from angina[16]. Chronic thoracic pain was measured with a questionnaire based on the Brief Pain Inventory[17], and described previously[16]. The questionnaire was sent by regular mail or email. Secondary outcomes were chronic pain at 3 and 6 months after surgery, opioid consumption during the first 72 hours after surgery, and health-related quality of life at 3, 6 and 12 months after surgery. Quality of life was measured with the physical composite score (PCS) and the mental composite score (MCS) of the short form (SF)-12 health status instrument, both ranging from 0 to 100, with higher scores representing higher levels of functioning[18]. Dutch age- and sex-standardized population norms are available elsewhere[19].

Statistical Analysis

The planned statistical analyses have been described previously[13]. We determined that a sample size of 126 patients would provide a power of 80% to detect a 20% absolute reduction in the primary outcome from a baseline risk of 30%, at a two-sided alpha level of 0.05[11]. All analyses were performed according to the intention-to-treat principle. We used the chi-square test or Fisher's exact test to analyse categorical variables and Student's *t*-test or the Mann-Whitney test for continuous variables. The Kolmogorov-Smirnov test together with visual inspection of the histograms were used to assess whether the variables were normally distributed. Odds Ratios (OR) and 95% confidence intervals were calculated to quantify risk. Imbalance (if any) in the baseline characteristics was approached from a

clinician's and literature perspective and statistically tested through assessment of the impact on the coefficient of the treatment allocation in a multivariable logistic regression analysis. Post hoc, we have also explored (1) potential effect modification by testing the significance of an interaction term with age in our multivariable logistic regression model and (2) a potential dose-related effect of remifentanil by replacing the dichotomous treatment allocation variable by a categorical variable (fentanyl, low-dose remifentanil, high-dose remifentanil). A sensitivity analysis was conducted by exclusion of patients with missing data at any of the intermediate follow-up time points. The statistical analyses were conducted with the SPSS statistical package (version 24.0 for Windows; SPSS, Chicago, IL, U.S.A.). All statistical tests were two-sided and used a significance level of 0.05.

Results

Figure 1 shows the randomization and flow of patients in the trial; of the 555 patients screened for eligibility, 128 patients signed informed consent, of which 2 were excluded later on because of the exclusion criteria (1 patient's surgical procedure was altered to a non-invasive approach and one patient appeared to have had prior cardiac surgery). Table 1 describes the characteristics of the remaining 126 patients available for analysis. A total of 122 (96.8%) patients filled in the questionnaire 12 months after the study; two patients died, contact was lost with the other two patients. All analyses for the primary outcome were based on the data from these 122 patients.

Outcomes

The primary outcome, chronic thoracic pain 12 months after surgery, was not significantly different between the remifentanil and fentanyl group, respectively (20% vs. 18%, p=0.819; Odds Ratio (OR) 0.9; 95% confidence interval (CI) 0.4 to 2.2) (Table 2). Regarding physical and mental composite scores of quality of life one year after surgery (secondary outcome), no differences between the remifentanil and fentanyl groups, respectively, were found (PCS 57.0 (interquartile range (IQR) 53.3 to 59.6) vs. 56.9 (IQR 51.2 to 58.8); p=0.459, MCS 55.2 (IQR 50.7 to 58.1) vs. 55.7 (IQR 52.2 to 58.6); p=0.596) (Table 2).

In the group of 23 patients who reported pain 12 months after surgery, pain levels were not significantly different between remifentanil and fentanyl groups, respectively, on an average (4.0 (IQR 2.0 to 4.0) vs. 3.0 (IQR 1.3 to 5.8); p=0.708), good (2.0 (IQR 1.0 to 4.0) vs. (0.0 (IQR 0.0 to 3.0); p=0.113), and bad day (5.0 (IQR

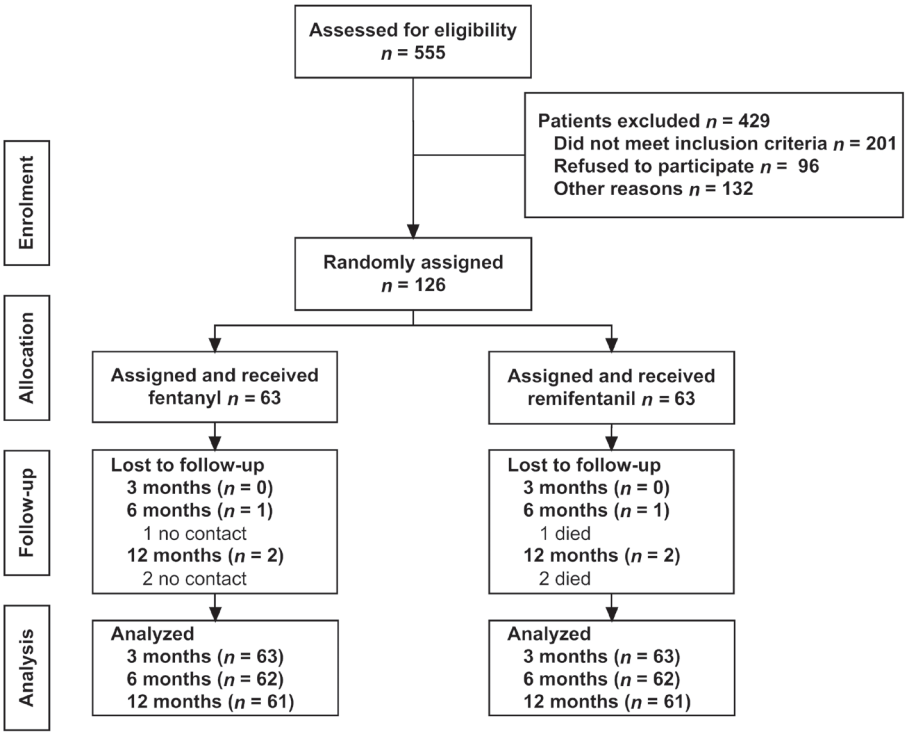

Figure 1. Consort diagram with the flow of the patients in the study.

2.0 to 7.0) vs. 3.5 (IQR 1.3 to 5.8); p=0.226). Type of pain was comparable between the remifentanil and fentanyl groups, respectively, and was mostly described as sharp pain (36.4% vs. 41.7%) or pressure pain (36.4% vs. 33.3%). Pain was mostly localized around the site of incision in both the remifentanil group and the fentanyl group, respectively 63.6% vs. 41.7%, p=0.524. No significant differences were found between pain characteristics at different time points (see Table S1 in the Supplementary Appendix).

Figure 2 shows the percentage of patients reporting thoracic pain after 3, 6 and 12 months. The number of patients reporting thoracic pain after 3 months was significantly higher in the remifentanil compared to the fentanyl group, respectively (51% vs. 33%, p=0.047; OR 2.1; 95% CI 1.0 to 4.2). The effect was not different at 6 months (32% vs. 27%, p=0.556; OR 0.8; 95% CI 0.4 to 1.7).

During the first 24 and 48 hours after surgery, the median consumption of opioids in the remifentanil group was significantly higher than in the fentanyl group, respectively (34.3 mg (IQR 25.3 to 48.2) vs. 30.2 mg (IQR 19.2 to 38.1); p=0.028

Table 1. Characteristics of patients in the remifentanil and fentanyl group

	Fentanyl n = 63	**Remifentanil n = 63**
Male gender	57 (90%)	58 (92%)
Age (years)	66 (7.6)	62 (9.0)
BMI (kg/m^2)	28.0 (3.1)	27.5 (3.6)
Preoperative NRS score	0 (0 to 0)	0 (0 to 0)
Preoperative Quality of Life score		
PCS	49.3 (43.3 to 53.1)	47.6 (39.6 to 54.3)
MCS	51.3 (46.1 to 57.2)	50.4 (46.8 to 54.3)
Type of surgery		
CABG	51 (81%)	49 (78%)
Valve	9 (14%)	7 (11%)
Combination	3 (5%)	7 (11%)
euroSCORE	3 (2 to 4)	2 (0 to 4)
Duration of anaesthesia (min)	218.6 (49.0)	233.4 (72.1)
Duration of surgery (min)	187.4 (46.7)	198.1 (70.8)
Mechanical ventilation (h)	10.8 (4.5)	13.3 (23.8)
Intraoperative use of analgesics/sedatives		
Sevoflurane		
Minutes	32.8 (23.1)	32.4 (24.8)
MAC	0.34 (0.1)	0.33 (0.1)
End tidal	0.69 (0.3)	0.67 (0.3)
Propofol (mg/kg)	13.1 (4.4)	13.3 (6.9)
Fentanyl (µg/kg)	26.1 (9.0)	21.8 (7.8)
Remifentanil (µg/kg)	NA	25.1 (8.9)
Patients admitted to PACU	35 (56%)	41 (65%)
Length of hospital stay (days)	5.0 (3.0 to 7.0)	5.0 (3.0 to 7.0)
Length of stay in the ICU/PACU (h)	19.5 (16.7 to 22.4)	19.6 (16.2 to 21.4)

Continuous data are presented as means (standard deviation) or medians (interquartile range), and categorical data are presented as number (%).

BMI, Body Mass Index; CABG, Coronary artery bypass grafting; MAC; minimum alveolar concentration, NRS, Numerical Rating Scale ; IQR, interquartile range; PCS, physical composite score; MCS, mental composite score.

and 46.8 mg (IQR 33.8-59.2) vs. 39.0 mg (IQR 26.2-51.4); p=0.047) (Figure 3). This cumulative difference in opioid consumption was not significantly different at 72 hours after surgery (48.3 mg (IQR 34.7 to 62.2) vs. 43.0 mg (IQR 27.9 to 76.3); p=0.162). This difference in opioid consumption led to no significant difference (p>0.05) in pain scores (NRS) the first 72 hours after surgery (see Table S2 in the Supplementary Appendix). There was no significant difference between the amount of morphine given at the anticipated end of surgery (10.0 mg (IQR 10.0 to 10.0) vs. 10.0 (IQR 10.0 to 10.0); p=0.953).

Table 2. Chronic thoracic pain and quality of life at 3, 6 and 12 months

	Fentanyl	Remifentanil	OR (95% CI)	P-value
Chronic thoracic pain (n, %)				
3 months (n = 126)	21 (33%)	32 (51%)	2.1 (1.0 to 4.2)	0.047
6 months (n = 124)	20 (32%)	17 (27%)	0.8 (0.4 to 1.7)	0.556
12 months (n = 122)	12 (20%)	11 (18%)	0.9 (0.4 to 2.2)	0.817
Quality of life (median, IQR)				
3 months (n = 126)				
PCS	55.0 (46.9 to 58.6)	55.2 (48.9 to 58.8)		0.971
MCS	51.4 (48.2 to 55.4)	53.6 (48.4 to 57.3)		0.325
6 months (n = 124)				
PCS	56.0 (50.1 to 58.3)	55.9 (48.6 to 58.8)		0.901
MCS	53.2 (49.5 to 57.6)	54.3 (48.9 to 57.4)		1.0
12 months (n = 122)				
PCS	56.9 (51.2 to 58.8)	57.0 (53.3 to 59.6)		0.459
MCS	55.7 (52.2 to 58.6)	55.2 (50.7 to 58.1)		0.596

Continuous data are expressed as mean (standard deviation) or median (interquartile range), and categorical data are expressed as number (%).

95% CI: 95% confidence interval; IQR, interquartile range; NRS, Numeric Rating Scale; MCS, mental composite score, PCS, physical composite score; OR; Odds ratio

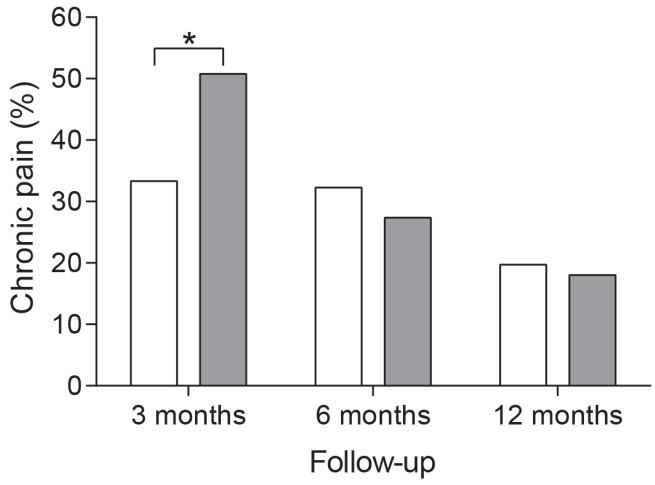

Figure 2. Chronic postoperative pain reported 3, 6, and 12 months after surgery in the fentanyl group (solid black) compared to the remifentanil group (grey). *p = 0.047

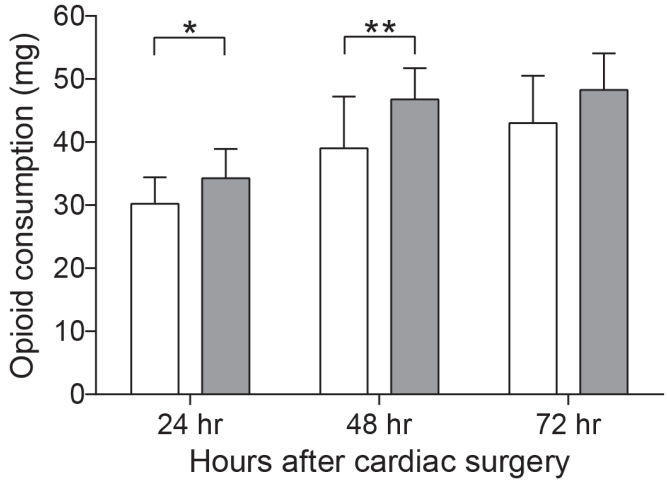

Figure 3. Cumulative opioid consumption 24, 48, and 72 hours postoperatively in the fentanyl group (solid black) compared to the remifentanil group (grey). *p = 0.028; **p = 0.047.

Because there was a 4-year difference in mean age (66 years vs. 62 years, p=0.007) between the two study arms, we explored the impact of imbalanced age in a multivariable logistic regression analysis. In that analysis, age altered the coefficient of treatment allocation by more than 10%, resulting in an adjusted OR of 0.6 (95%CI 0.2 to 1.7; p=0.362). In a post hoc analysis, effect modification by age was not significant 12 months after surgery. No significant difference of chronic pain 12 months after surgery was found between patients < 65 years of age (adjusted OR 1.1; 95%CI 0.3 to 3.7; p=0.920) and patients ≥ 65 years of age (adjusted OR 0.4; 95%CI 0.1 to 2.1; p=0.281). No dose-related effect of remifentanil on chronic pain 12 months after surgery was found.

Regarding the secondary endpoints, age was found as an effect modifier through an interaction term (p=0.038). This resulted in a significant effect of remifentanil on chronic thoracic pain after 3 months for patients < 65 years of age (adjusted OR 4.0; 95% CI 1.3 to 12.2; p=0.016) and no effect in patients ≥ 65 years of age (adjusted OR 0.9; 95% CI 0.3 to 2.5; p=0.856). This effect of age was absent 6 months after surgery. A dose-related effect of remifentanil on pain after 3 months with ORs of 1.3 (95% 0.5 to 3.1) and 3.3 (95% 1.4 to 8.1) was also observed for a cumulative dose of < 1875 μg and ≥ 1875 μg, respectively. This dose-related effect was absent for the outcome of chronic pain 6 months after surgery. The

sensitivity analysis excluding patients with missing data at any of the time points resulted in very similar results compared to the original analyses (see Table S3 in the Supplementary Appendix).

Discussion

This randomised single-blind controlled trial showed that the use of remifentanil during cardiac surgery does not lead to an increased incidence of chronic thoracic pain 12 months after surgery. Considering the short-term effects, remifentanil was associated with a small, but significant, increase in postoperative opioid consumption during the first 48 hours after cardiac surgery. In addition, more patients in the remifentanil group developed chronic thoracic pain at the site of surgery after three months and this effect proved to be age dependent and dose related.

To start, this study shows no significant increase in chronic thoracic pain 12 months postoperatively for remifentanil compared to fentanyl, even though a significant difference in reported thoracic pain was observed three months after surgery (see Figure 2). The latter suggests alteration of pain sensitivity caused by remifentanil. Our finding that chronic pain was especially observed in patients receiving a higher dose of remifentanil further supports this. A dose-dependent relationship is also in line with previous reports[11,20,21].

A few other studies have suggested an effect of remifentanil on chronic pain. Salengros et al.[12] concluded that high-dose remifentanil plus postsurgical epidural analgesics resulted in higher incidences of chronic pain after cardiac surgery compared to preoperative epidural analgesics and low-dose remifentanil during surgery. In another study, remifentanil proved a risk factor for the development of chronic pain at 12 months in a dose-dependent manner[11]. In contrast to our study, these studies were not designed to measure the effect of remifentanil on chronic postoperative pain and/or postoperative analgesics.

Generally stated, the mechanisms of post procedural pain and chronic postsurgical pain are complex and poorly understood. Nerve injury or inflammatory reactions after surgery causing central sensitization are suggested as causes of postsurgical pain[22]. Modulation or increased activity of NDMA receptors have been hypothesized to lead to inflammatory and neuropathic pain states[23], and possibly activation and exacerbation of hyperalgesia[24]. It is known that remifentanil affects the NMDA receptor directly or indirectly[23,25], which as such could influence the development of acute and chronic pain. This effect of remifentanil on the NMDA

receptor could explain the higher morphine consumption directly postoperative and the higher incidence of chronic thoracic pain after 3 months in the remifentanil group. In addition, age-related alterations of NMDA receptors[26,27] and decreased neuroplasticity in the elderly could explain the relatively lower sensitivity to the effects of remifentanil at higher age, found in this study. This finding requires further exploration as this subgroup analysis was not predefined.

In this study we quantified acute postoperative pain on the basis of the need for postoperative opioids in the first 72 hours, as was done in previous studies[3,4,28,29]. All patients received, besides a morphine loading dose on the operating room at the end of surgery, a continuous morphine infusion which was subsequently adapted on the guidance of individual pain scores. The ICU and PACU in our hospital was the setting for this study, with a pain management protocol that has been in place for years[14] allowing for randomised controlled trials and related studies[15,30,31]. In this setting, patients receiving intraoperative remifentanil received significantly more morphine after 48 hours after surgery compared to patients receiving intraoperative fentanyl, which implies that patients in the remifentanil group requested for more pain relief. While the difference between the groups is statistically significant, the absolute difference is very small and most likely not of clinical consequence as there are no safety issues involved with these amounts of morphine. Still, other studies have also reported an association between the administration of intraoperative remifentanil and an increase in consumption of postoperative analgesics during the first 24 or 48 postoperative hours[20,21,32–34]. Compared to these reports, our study is the first randomised controlled trial that also investigates and report chronic thoracic pain.

In times of cost containment in healthcare remifentanil has, due to its favourable pharmacokinetic profile, received special interest in fast-track cardiac surgery. The use of remifentanil potentially reduces time of mechanical ventilation and length of hospital stay[35]. However, when reviewed from a patient point of view, the advantages of remifentanil are questionable. In addition to worse pain outcomes, postoperative cognitive dysfunction and recovery after fast track surgery were not improved when remifentanil was compared to long-acting sufentanil[36,37]. In light of these results, clinicians should outweigh the proposed benefits of remifentanil against the suggested negative impact for the patients, such as the impact on postoperative pain, knowing that several alternatives for remifentanil are available and that a lower dose of remifentanil decreases the risk for development of chronic pain the first couple of months. Cardiac surgery is major surgery with a high incidence of chronic postoperative pain; therefore, remifentanil may not be the ideal opioid for this kind of surgery.

Some limitations of our study should be addressed. First, as pointed out in our study protocol[13], ideally, the study design should be double blind and contain no other opioid besides remifentanil. However, since patients themselves report postoperative pain scores, which in turn guide morphine administration, we felt that with blinding the patients only, adequate blinding for the main endpoint was already preserved. Moreover, a double-blind double dummy trial is not only labour intensive but also expensive. In addition, a study arm without opioids is obviously unethical, and therefore we chose a design described before[11]. In this design, we decided not to compare fentanyl with a study arm with only short-acting remifentanil since it was expected that high doses remifentanil would be needed in this painful and extended procedure. In our study, increased analgesic consumption in the remifentanil group is found, which is in accordance to other studies with different control groups[20,21,38], although in those reports it cannot be excluded that results are subject to selection bias. Last, sample size calculation was based on a reduction of the primary outcome from 30% to 10%, based on a previous observational study[11]. In our present study, the incidence of chronic postoperative pain was around 20% in both study arms, suggesting that other factors besides remifentanil might have been responsible for the increased risk for thoracic pain in the observational study. It might be possible that the calculated sample size for primary outcome may provide insufficient statistical power to detect clinically relevant differences on secondary outcome parameters such as pain scores.

In conclusion, remifentanil administration during cardiac surgery does not impact chronic postoperative pain one year after surgery. In the shorter term, remifentanil increases the need for opioid consumption postoperatively and leads to higher incidence of chronic thoracic pain three months after surgery. This negative impact on the shorter-term makes that remifentanil is less favourable for prolonged surgery such as cardiac surgery.

Acknowledgements

The authors thank Ko Hagoort, MA, Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, for text editing and Richard Sandifort, BSc, Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands, for support in data entry.

Literature

1. Angst, M. S. Intraoperative Use of Remifentanil for TIVA: Postoperative Pain, Acute Tolerance, and Opioid-Induced Hyperalgesia. *J. Cardiothorac. Vasc. Anesth.* 29 Suppl 1, S16-22 (2015).
2. Miller, T. E. & Gan, T. J. Total intravenous anesthesia and anesthetic outcomes. *J. Cardiothorac. Vasc. Anesth.* 29 Suppl 1, S11-5 (2015).
3. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
4. De Hoogd, S. *et al.* Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. *Clin. J. Pain* 32, 726–735 (2016).
5. Yu, E. H., Tran, D. H., Lam, S. W. & Irwin, M. G. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia* 71, 1347–1362 (2016).
6. Wilder-Smith, O. H. & Arendt-Nielsen, L. Postoperative hyperalgesia: its clinical importance and relevance. *Anesthesiology* 104, 601–607 (2006).
7. Mansfield, K. E., Sim, J., Jordan, J. L. & Jordan, K. P. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. *Pain* 157, 55–64 (2016).
8. Reddi, D. Preventing chronic postoperative pain. *Anaesthesia* 71 Suppl 1, 64–71 (2016).
9. Macrae, W. A. & Davies, H. T. O. Chronic postsurgical pain. *Crombie IK, Lint. S, Croft P, Von Korff M, LeResche L, Ed. Epidemiol. pain. Seattle IASP Press* (1999).
10. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
11. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
12. Salengros, J.-C. *et al.* Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J. Cardiothorac. Vasc. Anesth.* 24, 608–16 (2010).
13. de Hoogd, S. *et al.* Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials* 15, 466 (2014).
14. van Gulik, L. *et al.* Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. *Eur. J. Anaesthesiol.* 27, 900–905 (2010).
15. Ahlers, S. J. *et al.* Efficacy of an intravenous bolus of morphine 2.5 versus morphine 7.5 mg for procedural pain relief in postoperative cardiothoracic patients in the intensive care unit: a randomised double-blind controlled trial. *Anaesth. Intensive Care* 40, 417–426 (2012).
16. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
17. Cleeland, C. S. & Ryan, K. M. Pain assessment: global use of the Brief Pain Inventory. *Ann. Acad. Med. Singapore* 23, 129–38 (1994).
18. Ware Jr, J., Kosinski, M. & Keller, S. D. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med. Care* 34, 220–233 (1996).

19. Mols, F., Pelle, A. J. & Kupper, N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual. Life Res.* 18, 403–414 (2009).
20. Guignard, B. *et al.* Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 93, 409–17 (2000).
21. Lee, C., Kim, Y.-D. & Kim, J.-N. Antihyperalgesic effects of dexmedetomidine on high-dose remifentanil-induced hyperalgesia. *Korean J. Anesthesiol.* 64, 301–7 (2013).
22. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
23. Li, Y. *et al.* Inhibition of glycogen synthase kinase-3beta prevents remifentanil-induced hyperalgesia via regulating the expression and function of spinal N-methyl-D-aspartate receptors in vivo and vitro. *PLoS One* 8, e77790 (2013).
24. Voscopoulos, C. & Lema, M. When does acute pain become chronic? *Br. J. Anaesth.* 105 Suppl, i69-85 (2010).
25. Yuan, Y. *et al.* Glycogen synthase kinase-3beta contributes to remifentanil-induced postoperative hyperalgesia via regulating N-methyl-D-aspartate receptor trafficking. *Anesth. Analg.* 116, 473–481 (2013).
26. Cohen, S. A. & Muller, W. E. Age-related alterations of NMDA-receptor properties in the mouse forebrain: partial restoration by chronic phosphatidylserine treatment. *Brain Res.* 584, 174–180 (1992).
27. Wang, C. & Jensen, F. E. Age dependence of NMDA receptor involvement in epileptiform activity in rat hippocampal slices. *Epilepsy Res.* 23, 105–113 (1996).
28. Kim, S. H., Stoicea, N., Soghomonyan, S. & Bergese, S. D. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front. Pharmacol.* 5, 108 (2014).
29. Rivosecchi, R. M. *et al.* An evidence based systematic review of remifentanil associated opioid-induced hyperalgesia. *Expert Opin. Drug Saf.* 13, 587–603 (2014).
30. Ahlers, S. J. *et al.* The Val158Met polymorphism of the COMT gene is associated with increased pain sensitivity in morphine-treated patients undergoing a painful procedure after cardiac surgery. *Br. J. Clin. Pharmacol.* 75, 1506–1515 (2013).
31. Ahlers, S. J. *et al.* Morphine Glucuronidation and Elimination in Intensive Care Patients: A Comparison with Healthy Volunteers. *Anesth. Analg.* 121, 1261–1273 (2015).
32. Lee, C., Lee, H.-W. & Kim, J.-N. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean J. Anesthesiol.* 64, 19–24 (2013).
33. Fukunaga, A. F., Alexander, G. E. & Stark, C. W. Characterization of the analgesic actions of adenosine: comparison of adenosine and remifentanil infusions in patients undergoing major surgical procedures. *Pain* 101, 129–38 (2003).
34. Lee, C., Song, Y.-K., Jeong, H.-M. & Park, S.-N. The effects of magnesium sulfate infiltration on perioperative opioid consumption and opioid-induced hyperalgesia in patients undergoing robot-assisted laparoscopic prostatectomy with remifentanil-based anesthesia. *Korean J. Anesthesiol.* 61, 244–50 (2011).
35. Greco, M. *et al.* Remifentanil in cardiac surgery: a meta-analysis of randomized controlled trials. *J. Cardiothorac. Vasc. Anesth.* 26, 110–6 (2012).

36. Rasmussen, L. A. *et al.* Ultrashort acting remifentanil is not superior to long-acting sufentanil in preserving cognitive function-a randomized study. *J. Clin. Anesth.* 33, 127–134 (2016).
37. Bhavsar, R., Ryhammer, P. K., Greisen, J., Rasmussen, L. A. & Jakobsen, C. J. Remifentanil Compared With Sufentanil Does Not Enhance Fast-Track Possibilities in Cardiac Surgery-A Randomized Study. *J. Cardiothorac. Vasc. Anesth.* 30, 1212–1220 (2016).
38. Joly, V. *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 103, 147–55 (2005).

Supplemental Material

Table S1. Characteristics of chronic pain

			Fentanyl	Remifentanil	p-value
Pain levels (NRS) (median, IQR)	3 months (n = 51)	Average day (0 to 10)	3.0 (3.0 to 6.0)	3.0 (2.0 to 4.8)	0.520
		Good day (0 to 10)	1.0 (0.0 to 3.0)	1.0 (1.0 to 3.0)	0.802
		Bad day (0 to 10)	5.0 (3.0 to 6.0)	3.5 (2.0 to 5.0)	0.393
	6 months (n = 37)	Average day (0 to 10)	2.0 (1.0 to 4.0)	3.0 (2.0 to 4.5)	0.344
		Good day (0 to 10)	1.0 (0.0 to 1.8)	1.0 (0.0 to 2.5)	0.898
		Bad day (0 to 10)	3.5 (2.0 to 4.8)	4.0 (2.0 to 6.5)	0.200
	12 months (n = 23)	Average day (0 to 10)	3.0 (1.3 to 5.8)	4.0 (2.0 to 4.0)	0.708
		Good day (0 to 10)	0.0 (0.0 to 3.0)	2.0 (1.0 to 4.0)	0.113
		Bad day (0 to 10)	3.5 (1.3 to 5.8)	5.0 (2.0 to 7.0)	0.226
Type of pain (n, %)	3 months (n = 53)	Sharp pain	9 (42.9)	12 (37.5)	
		Burning pain	2 (9.5)	4 (12.5)	
		Pressure pain	2 (9.5)	5 (15.6)	
		Other kind of pain	8 (38.1)	11 (34.4)	0.897
	6 months (n = 35)	Sharp pain	3 (16.7)	6 (35.3)	
		Burning pain	2 (11.1)	1 (5.9)	
		Pressure pain	2 (11.1)	5 (29.4)	
		Other kind of pain	11 (61.1)	5 (29.4)	0.184
	12 months (n = 23)	Sharp pain	5 (41.7)	4 (36.4)	
		Burning pain	1 (8.3)	1 (9.1)	
		Pressure pain	4 (33.3)	4 (36,4)	
		Other kind of pain	2 (16.7)	2 (18.2)	0.995
Localization of pain (n, %)	3 months (n = 52)	Diffuse	3 (14.3)	5 (16.1)	
		Around incision site	10 (47.6)	20 (64.5)	
		Other	8 (38.1)	6 (19.4)	0.320
	6 months (n = 36)	Diffuse	0 (0.0)	4 (25.0)	
		Around incision site	13 (65.0)	8 (50.0)	
		Other	7 (35.0)	4 (25.0)	0.060
	12 months (n = 23)	Diffuse	6 (50.0)	3 (33.3)	
		Around incision site	5 (41.7)	7 (63.6)	
		Other	1 (8.3)	1 (9.3)	0.524

Continuous data are expressed as mean (standard deviation) or median (interquartile range), and categorical data are expressed as number (%). IQR, interquartile range; NRS, Numeric Rating Scale.

Table S2. Acute postoperative pain levels.

		n	Fentanyl	Remifentanil	p-value
Postoperative pain (NRS) (median, IQR)	0-12 h	121	1.7 (1.0 to 2.5)	1.5 (1.0 to 2.6)	0.691
	12-48 h	124	2.5 (1.9 to 3.5)	2.7 (1.5 to 3.6)	0.529
	48-60 h	115	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	0.921
	60-72 h	122	2.0 (1.4 to 3.0)	2.0 (1.0 to 2.9)	0.351
	72-84 h	107	2.0 (1.0 to 3.0)	2.0 (0.8 to 3.0)	0.960
	84-96 h	86	2.0 (1.0 to 2.8)	1.5 (0.5 to 2.3)	0.167

Continuous data are expressed as median (interquartile range)

IQR, interquartile range; NRS, numerical rating scale;

Table S3. Sensitivity analyses (n = 121)

			Fentanyl	Remifentanil	RR (95% CI)	p-value
Chronic thoracic pain (n, %)	3 months		19 (32%)	31 (51%)	2.2 (1.1 to 4.7)	0.032
	6 months		20 (33%)	17 (28%)	0.8 (0.4 to 1.7)	0.514
	12 months		12 (20%)	11 (18%)	0.9 (0.4 to 2.2)	0.783
Quality of life (median, IQR)	3 months	PCS	55.0 (47.1 to 58.5)	55.4 (49.3 to 58.8)	-	0.762
		MCS	51.4 (48.4 to 55.6)	54.0 (48.7 to 57.4)	-	0.268
	6 months	PCS	56.0 (50.4 to 58.1)	55.9 (48.5 to 58.8)	-	0.961
		MCS	53.2 (49.3 to 57.5)	54.4 (49.3 to 57.4)	-	0.870
	12 months	PCS	56.9 (51.8 to 58.8)	57.0 (53.3 to 59.6)	-	0.554
		MCS	55.7 (52.6 to 58.8)	55.2 (50.7 to 58.2)	-	0.490
Cumulative opioid consumption (mg) (median, IQR)	24 h after surgery		29.4 (19.1 to 38.0)	35.8 (25.7 to 42.4)	-	0.017
	48 h after surgery		37.3 (25.4 to 55.4)	47.1 (34.3 to 59.3)	-	0.032
	72 h after surgery		42.0 (26.9 to 64.1)	48.9 (34.8 to 63.6)	-	0.107

Data are expressed as number (%).
95% CI: 95% confidence interval; IQR, interquartile range; MCS, mental composite score, PCS, physical composite score; NRS, Numeric Rating Scale; RR: relative risk

Chapter 5

Short- and long-term impact of remifentanil on thermal detection and pain thresholds after cardiac surgery: a randomised controlled trial

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Eur J Anaesthesiol. 2019;36(1):32-39

Abstract

Background: The clinical relevance of the suggested hyperalgesic effects of remifentanil is still unclear, especially in the long term.

Objective: The current study evaluated the impact of remifentanil on thermal thresholds 3 days and 12 months after surgery, measured with Quantative Sensory Testing.

Design: A prospective, single-blind, randomised controlled trial.

Setting: A tertiary care teaching hospital in The Netherlands, from 2014 to 2016.

Patients: A total of 126 patients aged between 18 and 85 years, undergoing cardiothoracic surgery via sternotomy (coronary artery bypass grafts and/or valve replacement) were included. Exclusion criteria were BMI above 35 kg/m^2, history of cardiac surgery, chronic pain conditions, neurological conditions, allergy to opioids or paracetamol, language barrier and pregnancy.

Intervention(s): Patients were allocated randomly to receive intra-operatively either a continuous remifentanil infusion or intermittent intra-operative fentanyl as needed in addition to standardised anaesthesia with propofol and intermittent intravenous fentanyl at predetermined time points.

Main outcome measures: Warm and cold detection and pain thresholds 3 days and 12 months after surgery. In addition, the use of remifentanil, presence of postoperative chronic pain, age, opioid consumption and pre-operative quality of life were tested as a predictor for altered pain sensitivity 12 months after surgery.

Results: Both warm and cold detection, and pain thresholds, were not significantly different between the remifentanil and fentanyl groups 3 days and 12 months after surgery ($p>0.05$). No significant predictors for altered pain sensitivity were identified.

Conclusions: Earlier reports of increased pain sensitivity one year after the use of remifentanil could not be confirmed in this randomised study using Quantitative Sensory Testing. This indicates that remifentanil plays a minor role in the development of chronic thoracic pain. Still, the relatively high incidence of chronic thoracic pain and its accompanying impact on quality of life remain challenging problems.

Introduction

Chronic postsurgical pain – defined as the persistence of pain at least 3 months after a surgical procedure – has been reported to occur in 25 to 55% of patients after cardiac surgery[1–4]. It is known to have a negative impact on quality of life (QoL) and daily activities, contributing to increasing public health costs and lost productivity[5–7]. Chronic postsurgical pain is considered to be mostly neuropathic and associated with sensory abnormalities[8]. Altered pain sensitivity in clinical patients can be identified using quantitative sensory testing (QST)[9,10] by exposing patients to external stimuli and thereby mapping their pain and detection thresholds[11]. Studies report a predictive value of increased pain sensitivity measured with QST for the development of acute postoperative pain[12] in contrast to no predictive value of response to analgesic treatment[13]. Lundblat et al.[14] showed that pre-operative lower electrical pain threshold predicted higher pain intensity 18 months after total knee replacement. A recent cohort study revealed that lower pain pressure thresholds with heightened widespread pain sensitivity before surgery were associated with significantly higher pain severity at 12 months after total hip replacement[15].

Evidence is growing for opioid-induced hyperalgesia being another external factor besides surgery itself that could influence pain perception[16]. Remifentanil is a fast-acting opioid and favoured for its pharmacokinetic profile, but is also associated with postoperative hyperalgesia[16–18]. A retrospective study in cardiac patients suggested that remifentanil use was associated with chronic postoperative pain 12 months after surgery[19]. A recent randomised controlled trial performed (REFLECT trial) showed no significant difference in the incidence of chronic thoracic pain one year after surgery between patients receiving either intraoperative remifentanil or fentanyl (11 (17.5%) vs. 12 (19.7%), p=0.817)[20]. However, a significant difference was found at 3-months follow-up, when patients treated with remifentanil reported postoperative pain significantly more often compared with the control group (32 (50.8%) vs. 21 (33.3%), p=0.049). These patients also consumed significantly more opioids compared to the remifentanil group 48 hours directly after surgery (p=0.047)[20].

As part of the REFLECT trial, thermal detection and pain thresholds were measured before surgery, and 3 days after and 12 months after the surgery. This study aims to investigate the effect of remifentanil on these thermal detection and pain thresholds, and to identify whether altered thresholds predict the development of chronic postsurgical pain after cardiac surgery.

Methods

The prospective and randomised controlled REFLECT trial was approved by the local research ethics committee (VCMO St. Antonius Hospital, Chairperson V. Deneer, ref: R13.013) on 8 August 2013, and registered with EudraCT (ref: 2013-000201-23). Written informed consent was obtained from all patients before the cardiothoracic surgical procedure.

Patients aged 18 to 85 years were eligible if they were scheduled for elective cardiac surgery via sternotomy (coronary artery bypass grafting and/or valve replacement). Exclusion criteria were: pregnancy or breastfeeding; language barrier; history of drug abuse; neurological conditions such as peripheral neuropathy or fibromyalgia; known remifentanil, fentanyl, morphine or paracetamol allergy; BMI above 35 kg/m^2; prior cardiac surgery (re-operations); and chronic pain condition. Patients with a BMI above 35 kg/m^2 were excluded because altered sensory thresholds have been reported compared with nonobese patients[21].

The study protocol has been published previously[22]. All patients were scheduled for cardiac surgery with a classical full sternotomy approach, so no minimally invasive surgery was performed. After standardized induction protocol, both groups received a continuous infusion of propofol (starting dose 200 to 300 mg/h) and intermittent intravenous fentanyl (200 to 500 µg) at predetermined times (before incision, at sternotomy, at aorta cannulation and at opening of the pericardium). Patients were allocated randomly to either a remifentanil or a fentanyl study arm and were blinded to treatment group allocation. The remifentanil arm received a continuous remifentanil infusion based on ideal body weight 0.15 µg/kg/min. The fentanyl arm received additional fentanyl boluses (200 to 500 µg) as needed.

Thirty minutes before the anticipated end of surgery, each patient received a fixed dose of intravenous morphine of 10 mg, or, when indicated 5 mg. Immediately after surgery, paracetamol (1 g orally or intravenously) was given four times a day together with a continuous infusion of morphine (starting dose 2 mg/h), which was adapted individually on the guidance of the patient's numerical rating scale (NRS) pain scores according to the standard pain protocol of the hospital with a target NRS value of less than 4[23]. On the ward, the continuous infusion of morphine was replaced by 2.5 to 10 mg of intravenous morphine as needed as per protocol.

One day before surgery, three days after surgery and 12 months after surgery, patients underwent Quantitative Sensory Testing (QST) in a quiet room pre-operatively and on the ward postoperatively. Thermal detection and pain thresholds were assessed with the Thermal Sensory Analyser (TSA; Type II Medoc

Ltd. Advanced Medical Systems, Ramat Yishai, Israel) using previously published protocols[24,25]. The thermode (30×30mm) stimulating surface was placed on the volar side of the nondominant forearm. The applied temperature ranged from 0 to 50 ºC, which is safe and nondamaging to the skin. First, the subject's visual motor reaction time was measured with open-source software (http://delphiforfun.org/Programs/Reaction_times.htm). Next, detection and pain thresholds for cold and heat were determined with the method of limits[26]. The detection thresholds for cold and heat were examined by gradually decreasing or increasing, respectively, the baseline temperature of 32°C at a rate of 1°C/s. The subject was instructed to press the button as soon as the cold or heat stimulus was felt, after which the temperature normalised to baseline temperature. Then, the subject was instructed to press the button if the thermode started to feel painful – either for cold or heat. For the determination of pain thresholds, the temperature was reversed at a rate of to press the button as soon as the cold or heat stimulus was felt, after which the temperature normalized to baseline temperature. Then, the subject was instructed to press the button if the thermode started to feel painful – either for cold or heat. For the determination of pain thresholds, the temperature was reversed at a rate of 10.0°C/s after the button was pressed. A minimum of two tests served as rehearsals. Detection and pain thresholds were calculated as the means of the four following tests. If the button was not pressed before 0 or 50°C was reached, the test was automatically terminated. In this case, the pain thresholds were set at 0 and 50°C, respectively. All QST tests in this study were performed by the same researcher.

Postoperatively, a nurse on the ICU/Post Anaesthesia Care Unit or the ward recorded pain scores using the visual analogue scale three times daily and opioid consumption during the first 72 h. After discharge from the hospital, subjects were asked to complete a questionnaire 3, 6 and 12 months after surgery. This questionnaire has been described previously[27] and is based on the Brief Pain Inventory[28] containing questions about pain (perception, location, intensity). In addition, QoL was self-reported with the short form-12 health status instrument at the same time points.

Statistical analysis

Continuous data are presented as median (interquartile range) and analysed using the Mann-Whitney *U* test, or as mean ± SD and analysed using Student's *t* test, where appropriate. Normal distribution of the variables was assessed with the Kolmogorov-Smirnov test and histograms. Categorical data were compared between treatment groups using χ^2 tests. Independent of treatment group, the

QST outcomes and reaction times at the follow-up time points were compared with baseline using the Wilcoxon signed-rank test. In a multivariate analysis of the QST data, the following independent variables were included for warm and cold detection and pain thresholds: treatment condition (remifentanil vs. fentanyl), baseline QST measurement, age, opioid consumption first 72 h, chronic pain 12 months after surgery, pre-operative QoL. Reaction time was only included in the analysis of the reaction time-dependent thresholds for detection of heat and cold. A robust regression analysis with MM estimation was used to account for the fact that the model residuals were not normally distributed. The weight function was the Tukey bisquare estimator. *P* values (two-sided) of less than 0.05 were considered statistically significant. Data were analysed in IBM SPSS Statistics version 24 (Chicago, Illinois, USA) and R-statistics version 3.0.1 (Vienna, Austria).

Power

A sample size calculation was performed for the primary endpoint, chronic thoracic pain and based on the findings of a previous stud[19]. This study found, 1 year after cardiac surgery, an incidence of chronic pain of approximately 10% in the fentanyl study arm and 30% in the remifentanil arm. This resulted in a total number of patients of 117, with a power of 0.80 and a two-sided significance level of 0.05. Taking into account a mortality rate of 8% one year after surgery[19], the total number of patients is 126; which results in 63 subjects per arm.

Results

A total of 555 patients were screened for eligibility; 201 patients did not meet the inclusion criteria, 96 patients refused to participate and 132 patients were excluded for other reasons (n = 127 logistic reasons and n = 5 unknown). In total, 126 patients were included (Figure 1).

Detection thresholds and pain thresholds were measured in all 126 subjects one day before surgery. After surgery, 124 subjects were tested (two had been transferred to other hospitals). One year after surgery, QST measurements were taken in 112 subjects. Two patients had died, other patients were not able to visit the hospital again or contact was lost (Figure 1).

An overview of patient characteristics is shown in Table 1. More details on the primary outcome of the study can be found in the original article[20].

Three days after surgery, no significant differences in detection thresholds were found between the groups (cold median ºC (IQR): 30.2 (29.6 to 30.7), vs. 29.8 (28.6

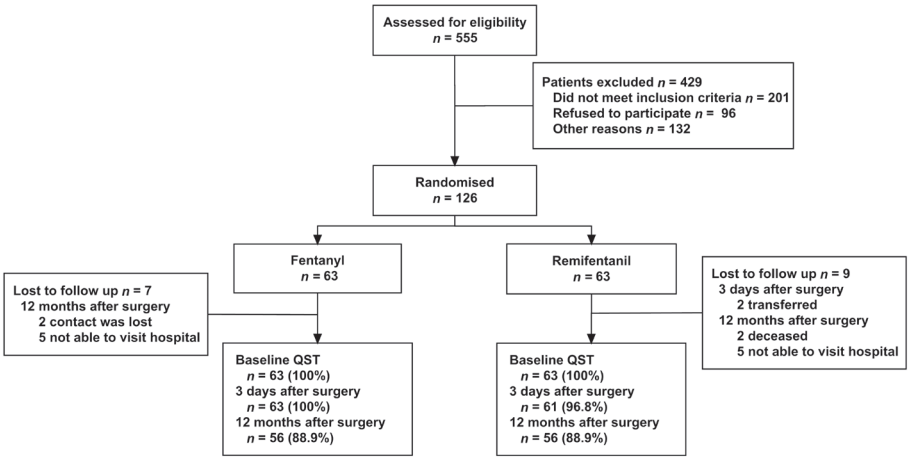

Figure 1. Flowchart of the study

to 30.7) p=0.320; warm: 35.2 (34.6 to 36.5) vs. 35.7 (34.6 to 36.9), p=0.31). Pain thresholds were not significantly different between groups (heat pain median: 47.0 (44.2 to 48.6) vs. 46.8 (43.7 to 49.0), p=0.87; cold pain: 10.1 (2.8 to 18.4) vs. 8.6 (1.3 to 20.1), p=0.86). Twelve months after surgery, no significant differences in detection and pain thresholds were found between the groups (warm detection: 35.2 (34.5 to 36.3) vs. 35.3 (34.5 to 36.9), p=0.91; cold detection: 30.4 (29.4 to 30.7) vs. 30.3 (29.5 to 30.7), p=0.70; heat pain: 47.7 (45.4 to 49.2) vs. 48.1 (45.7 to 49.4), p=0.88; cold pain: 6.6 (1.7 to 18.3) vs. 4.8 (1.6 to 13.5), p=0.65). (Figure 2)

Independent of group allocation, three days after surgery pain thresholds for heat and cold (median ºC (IQR)) were lower than baseline values (heat: 46.9 (43.8 to 48.7) vs. 48.1 (46.4 to 49.1), p<0.001; cold: 9.5 (1.8 to 19.2) vs. 5.6 (1.5 to 15.3); p=0.002). This could not be explained by the reaction time, as this was significantly higher 3 days postsurgery compared to baseline (0.308±0.1 vs. 0.380±0.1; p<0.001). Pain thresholds returned back to baseline levels 12 months after surgery (heat baseline: 48.1 (46.4 to 49.1) vs. 12 months: 48.0 (45.7 to 49.3), p=0.782; cold baseline: 5.7 (1.5 to 15.2) vs. 12 months: 4.9 (1.7 to 15.5), p=0.588) (Supplemental data content Table S1, http://links.lww.com/EJA/A173). Twelve months after surgery, detection thresholds for heat and cold (median ºC (IQR)) were lower than baseline values (warm: 35.2 (34.5 to 36.4) vs. 35.8 (34.7 to 37.3); p=0.047; Cold: 30.4 (29.4 to 30.7) vs. 29.9 (28.9 to 30.6); p=0.045) (Supplemental data content Table S1, http://links.lww.com/EJA/A173).

Table 1. Patient and perioperative characteristics

	Fentanyl (n = 63)	Remifentanil (n = 63)	p-value
Male gender	57 (90%)	58 (92%)	0.752
Age (years)	66 (7.6)	62 (9.0)	0.007
BMI (kg/m^2)	28.0 (3.1)	27.5 (3.6)	0.471
Preoperative NRS	0 (0 to 0)	0 (0 to 0)	0.765
Preoperative Quality of Life			
PCS	49.3 (43.3 to 53.1)	47.6 (39.6 to 54.3)	0.666
MCS	51.3 (46.1 to 57.2)	50.4 (46.8 to 54.3)	0.212
Type of surgery			0.389
CABG	51 (81.0)	49 (77.8)	
Valve	9 (14.3)	7 (11.1)	
Combination	3 (4.8)	7 (11.1)	
EuroSCORE*	3 (2 to 4)	2 (0 to 4)	0.035
Intraoperative characteristics			
Duration of general anaesthesia (min)	218.6 (49.0)	233.4 (72.1)	0.179
Duration of surgery (min)	187.4 (46.7)	198.1 (70.8)	0.317
Cross to clamp time (min)	51.4 (21.3)	59.6 (32.5)	0.095
Propofol (mg/kg)	12.0 (9.7 to 16.6)	12.6 (9.5 to 15.4)	0.913
Fentanyl (µg/kg)	26.1 (19.4 to 31.4)	19.4(15.4 to 27.2)	0.003
Remifentanil (µg/kg)	NA	22.9 (18.1 to 30.9)	NA

Continuous data are presented as mean±SD or median (interquartile range), and categorical data are presented as number (%).

BMI, Body Mass Index; CABG, Coronary artery bypass grafting; EuroSCORE: European System for Cardiac Operative Risk Evaluation;, NRS, Numerical Rating Scale;; PCS, physical composite score; MCS, mental composite score,

Regression estimates for the four QST modalities measured 12 months after surgery are shown in Table 2. In the model, treatment condition (remifentanil or fentanyl), presence of chronic pain 12 months after surgery, age, opioid consumption and pre-operative QoL were not significantly associated with altered pain sensitivity measured with QST. Baseline values were associated with the follow-up values for cold detection and pain thresholds 12 months after surgery. The regression estimates for detection and pain thresholds measured 3 days after surgery also revealed no significant predictors for altered pain sensitivity. For all four modalities, baseline measurements showed significant correlation with the measurement 3 days after surgery after adjustment for other variables (Supplemental data content Table S2, http://links.lww.com/EJA/A173).

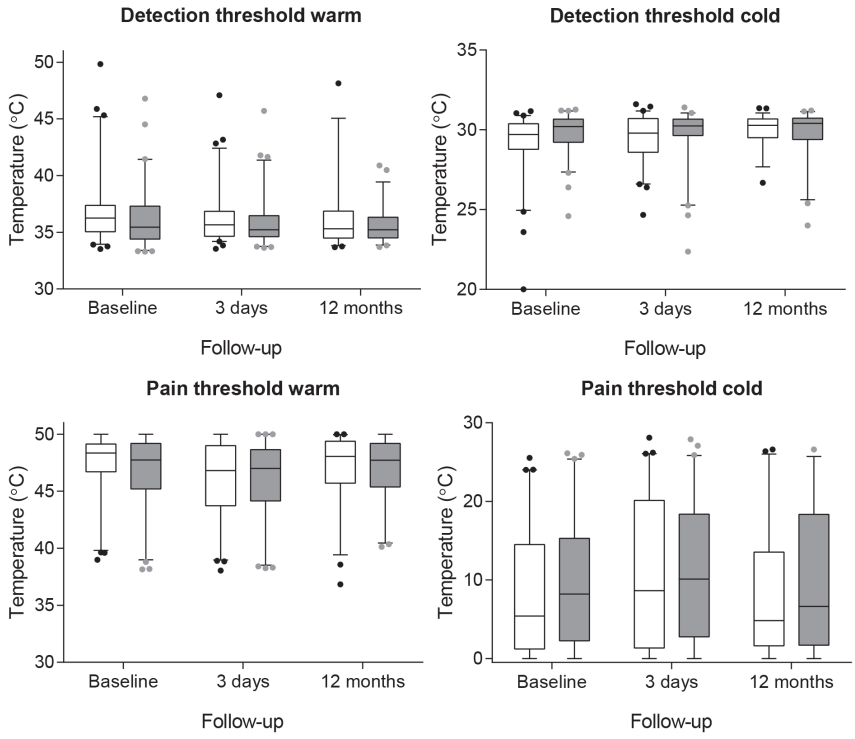

Figure 2. Detection and pain thresholds at baseline (n = 126), 3 days after surgery (n = 124) and 12 months after surgery (n = 121). Whiskers represent the 5th to 95th percentiles. Black, fentanyl group; grey, remifentanil group.

Discussion

Several studies of widely different design found that remifentanil use during surgery correlated with more postoperative pain and higher opioid consumption in the short term[16,18]. The aim of this study was to determine whether the intra-operative use of remifentanil would have any effect on thermal detection and pain thresholds in the short and longer term after surgery. Statistical analysis showed no significant differences in detection and pain thresholds in patients treated with remifentanil or fentanyl three days and one year after cardiac surgery. In a regression analysis, no other significant predictors for altered pain sensitivity one year after surgery were present.

The primary analysis of the REFLECT trial showed that patients receiving remifentanil during cardiac surgery needed more opioids after surgery to reach adequately low pain scores. In addition, three months after surgery, these patients

reported also more pain related to the surgery, a difference that was not found 1 year after surgery[20]. These potential short-term effects of remifentanil did not result in the significant difference in pain and detection thresholds three days after surgery. In line with the reported pain scores, one year after surgery sensory thresholds were also not significantly different between the two groups.

Regarding the effect of remifentanil on QST modalities directly after surgery, one study showed an increase in pain sensitivity to tactile stimuli in the high-dose remifentanil group during two days after surgery[29]. Another study found a decrease in pressure pain tolerance thresholds directly after eye surgery in the high-dose remifentanil group, whereas thermal thresholds showed no effect[30]. In the present study, thermal pain thresholds three days after surgery had significantly decreased from baseline values in both treatment groups. This could indicate higher sensitivity for heat and cold sensation three days after the surgery, despite the administration of analgesics. A confounding factor is that patients in the remifentanil group received more opioids in the first 48 hours compared to the fentanyl group. However, patients in both groups had received opioids and decreased thresholds were found in both groups. One year after surgery, pain thresholds had returned to baseline values. No significant differences in detection and pain thresholds were found between the remifentanil and fentanyl groups.

To our knowledge, no data is available regarding the intra-operative use of remifentanil and its effect on hyperalgesia measured with QST in the longer term. Despite being another concept than hyperalgesia, with different definition and mechanism, one study measured allodynia (i.e. pain due to a stimulus that does not usually provoke pain) one month after remifentanil administration. In 38 cardiac surgery patients, an increased area of mechanical allodynia around the incisional site was found in the patient receiving high dose remifentanil plus postsurgical epidural analgesics[31]. This study illustrates that remifentanil use during surgery can have impact on sensory thresholds in the longer term. Our study focussed only secondary hyperalgesia, which is thought to derive from central sensitization to pain[32]. No differences in thermal thresholds were found before and 12 months after surgery. As patients in the remifentanil group directly after surgery had an increased need for opioids and report more thoracic pain three months after surgery, it was encouraging to find that after 12 months there were no significant differences in patient-reported outcomes or in sensory thresholds. This implies that the clinical relevance of remifentanil induced (secondary) hyperalgesia on sensory perception on the longer term is minimal or possibly self-limiting.

Table 2. Robust Regression Estimates of Remifentanil, With Adjustment for Different Covariates: Detection and Pain Thresholds 12 months after surgery

Modality	Estimate	95% CI limits	p-value
Detection threshold for cold			
Intercept	25.6	23.8 to 27.5	<0.001
Remifentanil	0.01	-0.26 to 0.27	0.955
Baseline detection threshold cold (°C)	0.15	0.12 to 0.18	<0.001
Age (years)	0.00	-0.02 to 0.01	0.667
Opioid consumption first 72 h (mg)	0.00	-0.01 to 0.01	0.897
Chronic pain after 1 year	0.09	-0.27 to 0.46	0.612
QoL pre-operative	0.01	-0.03 to 0.04	0.737
Reaction time (s)	0.44	-1.26 to 2.13	0.611
Detection threshold for heat			
Intercept	26.5	20.6 to 32.3	<0.001
Remifentanil	0.36	-0.16 to 0.88	0.178
Baseline detection threshold heat (°C)	0.23	0.09 to 0.38	0.002
Age (years)	-0.001	-0.03 to 0.03	0.932
Opioid consumption first 72 h (mg)	0.01	0.00 to 0.02	0.259
Chronic pain after 1 year	0.30	-0.40 to 0.99	0.401
QoL pre-operative	0.003	-0.04 to 0.05	0.897
Reaction time (s)	-0.09	-3.96 to 3.78	0.964
Pain threshold for cold			
Intercept	-0.23	-10.6 to 10.1	0.965
Remifentanil	-1.06	-3.70 to 1.58	0.427
Baseline pain threshold cold (°C)	0.82	0.57 to 1.07	<0.001
Age (years)	-0.01	-0.16 to 0.13	0.853
Opioid consumption first 72 h (mg)	-0.01	-0.06 to 0.03	0.591
Chronic pain after 1 year	0.56	-2.78 to 3.90	0.741
QoL pre-operative	0.07	-0.09 to 0.24	0.363
Pain threshold for heat			
Intercept	22.9	8.50 to 37.3	0.002
Remifentanil	-0.11	-0.92 to 0.70	0.791
Baseline pain threshold heat (°C)	0.53	0.22-0.84	0.001
Age (years)	0.01	-0.05 to 0.06	0.746
Opioid consumption first 72 h (mg)	0.004	-0.01 to 1.02	0.615
Chronic pain after 1 year	-0.25	-1.51 to 1.02	0.702
QoL pre-operative	-0.02	0.07 to 0.03	0.422

95% CI, 95% confidence interval; QoL, Quality of Life questionnaire.

The possible mechanisms of remifentanil-induced hyperalgesia are still controversial. The ultra-short half-life of remifentanil together with inadequate and timely administration long-acting analgesics could be an explanation for the

increase in pain scores and in the use of postoperative opioids after the use of remifentanil. However, in our and other studies in which long-acting opioids were administered in a timely manner for bridging the possible opioid gap, increases in pain parameters directly after surgery have been reported[17,18]. This suggests that there are more potential causes of hyperalgesia.

On a molecular level, it has been suggested that changes in neuroplasticity in the peripheral and central nervous system may lead to central sensitization of nociceptive pathways, resulting in reduced nociceptive thresholds[33]. Although multiple mechanisms are postulated, the N-methyl-D-aspartate (NMDA) receptor appears to play a key role in the development of opioid induced hyperalgesia. This receptor is involved in neuroplasticity, long-term potentiation and affected by remifentanil through multiple pathways[34–36]. It is unknown what the mechanism is regarding a prolonged remifentanil effect, but animal data showed a potential role of protein kinase C zeta (PRCKZ), which appears to plays a role in the development of prolonged remifentanil-induced hyperalgesia. PRCKZ is involve in long-term potentiation and pain memory, and peaks two days after cessation of remifentanil infusion and returns to baseline level after 7 days. Blockade of this substance reversed postinfusion hyperalgesia induced by remifentanil[37]. The involvement of the NMDA receptor and its role in neuroplasticity could possibly explain the transient negative impact of remifentanil 3 months after surgery. This is only hypothesizing, and more research is needed to identify the complex pathways that are involved in the acute and prolonged effects of remifentanil.

The reported incidence of chronic thoracic pain one year after surgery in this study is 18.9% overall and not significantly different between study groups. Previous studies have reported 1-year incidences around 25%[2–4]. Pharmacologic interventions for preventing chronic pain are still not convincing, with a modest effect of ketamine as most promising[38]. Other drugs, for example pregabalin, seem to have no added value[39]. QST is widely used to diagnose and monitor chronic and neuropathic pain disorders[11]. However, in clinical routine practice, QST is not that well established in relation to postoperative pain since results are conflicting or not that convincing and measurements are time-consuming. As mentioned earlier, some studies report a predictive value of preoperative QST measurements, while others find no such association[40,41]. Our study shows no distinctive added value of measuring thermal detection and pain thresholds for evaluating chronic postsurgical pain in patients 1 year after cardiac surgery. In addition to thermal thresholds, other methods have been used to study chronic postoperative pain. Measurement of diffuse inhibitory noxious control (DNIC) gives a dynamic view of the pain processing system[42]. Patients with impaired

conditioned pain modulation or DNIC were found to have a greater likelihood of developing chronic postoperative pain[11,43]. Pre-operative DNIC explained around 25% of the variability in chronic postoperative pain intensity, while the numbers of static thresholds were below 6%. It is possible that the use of multiple modalities of QST, such as pressure, electrical thresholds or measuring DNIC, provides more information, but the more extensive and time-consuming, the more difficult the use of QST protocols in daily practice. In addition, static QST thresholds such as detection and pain thresholds appear to have sufficient test-retest reliability[44]. Our study measured thermal detection and pain thresholds three days and 12 months after surgery and was performed to assess the potential of QST for application in clinical practice. After all, it takes only 16-18 min per measurement. Still, gathering pieces of evidence of the complicated puzzle of postoperative pain management adds to the final goal of reducing incidences of short-term and chronic postoperative pains. Recently, it has been suggested that patients with peripheral neuropathic pain can be divided into subgroups based on sensory profiles, potentially increasing the response to pharmacological treatment[45]. Whether QST also can play a role in the management of postoperative pain is a field for future research.

Limitations

First, the ideal study design should be double-blind and contain no other opioid besides remifentanil. Patients in the remifentanil group received also fentanyl during surgery as this was standard care in our hospital and it is not, in our opinion, in patients' best interest to use high-dose remifentanil as single analgesic during this prolonged procedure because of the risk of increased immediate postoperative pain. Of note, an earlier observational study using the same regimens suggested remifentanil was predictive for chronic thoracic pain 1 year after the study[19]. However, it has to be taken into account that patients in the remifentanil group received also fentanyl during surgery and the possibility that fentanyl contribute to the outcome of the study cannot be excluded.

Second, the design of this study is single-blind. In our opinion, blinding only patients to study treatment was enough to ensure a valid outcome of the primary and secondary outcomes since patients self-reported pain scores and were in control of QST measurements.

Third, the QST-battery was limited to thermal stimuli while multiple modalities (e.g. electrical, pressure) can give more information about pain perception of the individual patient. Conclusions can be drawn only for the development of

secondary hyperalgesia 1 year after remifentanil administration measured with thermal thresholds. For instance, no data are available about mechanical or electrical tests around the wound.

Conclusion

Despite the unfavourable effects of remifentanil vs. fentanyl on chronic thoracic pain after 3 months, it is positive that no significant effect of remifentanil on thermal pain sensitivity and chronic thoracic pain was found 1 year after cardiac surgery. Additional predictors of altered pain sensitivity could not be identified. Again, this study contributes to the body of literature that concludes that chronic postoperative pain is multimodal while it remains difficult to predict which patients are at risk to develop chronic postoperative pain. However, this study showed again a high incidence of chronic thoracic pain after cardiac surgery, which is known to have considerable impact on the QoL. Investing in the prevention and early detection of chronic postsurgical pain logically is the next step.

Acknowledgements

The authors thank Ko Hagoort, MA, Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, for text editing and Richard Sandifort, BSc, Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands, for support in data entry.

Literature

1. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
2. Bruce, J. *et al.* The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. *Pain* 104, 265–273 (2003).
3. Ho, S. C., Royse, C. F., Royse, A. G., Penberthy, A. & McRae, R. Persistent pain after cardiac surgery: an audit of high thoracic epidural and primary opioid analgesia therapies. *Anesth. Analg.* 95, 820–3, table of contents (2002).
4. Meyerson, J., Thelin, S., Gordh, T. & Karlsten, R. The incidence of chronic post-sternotomy pain after cardiac surgery--a prospective study. *Acta Anaesthesiol. Scand.* 45, 940–4 (2001).
5. Berger, A., Dukes, E. M. & Oster, G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J. Pain* 5, 143–149 (2004).
6. Leadley, R. M. *et al.* Healthy aging in relation to chronic pain and quality of life in Europe. *Pain Pract.* 14, 547–558 (2014).
7. Andrew, R., Derry, S., Taylor, R. S., Straube, S. & Phillips, C. J. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Pract.* 14, 79–94 (2014).
8. Haroutiunian, S., Nikolajsen, L., Finnerup, N. B. & Jensen, T. S. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 154, 95–102 (2013).
9. Rolke, R. *et al.* Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* 123, 231–243 (2006).
10. Zaslansky, R. & Yarnitsky, D. Clinical applications of quantitative sensory testing (QST). *J. Neurol. Sci.* 153, 215–238 (1998).
11. Arendt-Nielsen, L. & Yarnitsky, D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J. Pain* 10, 556–572 (2009).
12. Werner, M. U., Mjobo, H. N., Nielsen, P. R. & Rudin, A. Prediction of postoperative pain: a systematic review of predictive experimental pain studies. *Anesthesiology* 112, 1494–1502 (2010).
13. Grosen, K., Fischer, I. W., Olesen, A. E. & Drewes, A. M. Can quantitative sensory testing predict responses to analgesic treatment? *Eur. J. Pain* 17, 1267–1280 (2013).
14. Lundblad, H., Kreicbergs, A. & Jansson, K. A. Prediction of persistent pain after total knee replacement for osteoarthritis. *J. bone Jt. surgery.British Vol.* 90, 166–171 (2008).
15. Wylde, V. *et al.* Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. *Pain* 156, 47–54 (2015).
16. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
17. Yu, E. H., Tran, D. H., Lam, S. W. & Irwin, M. G. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia* 71, 1347–1362 (2016).
18. De Hoogd, S. *et al.* Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. *Clin. J. Pain* 32, 726–735 (2016).

19. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
20. de Hoogd, S. *et al.* Randomized Controlled Trial on the Influence of Intraoperative Remifentanil versus Fentanyl on Acute and Chronic Pain after Cardiac Surgery. *Pain Pract.* 18, 443–451 (2018).
21. Torensma, B., Thomassen, I., van Velzen, M. & In 't Veld, B. A. Pain Experience and Perception in the Obese Subject Systematic Review (Revised Version). *Obes. Surg.* 26, 631–639 (2016).
22. de Hoogd, S. *et al.* Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials* 15, 466 (2014).
23. Ahlers, S. J. *et al.* Efficacy of an intravenous bolus of morphine 2.5 versus morphine 7.5 mg for procedural pain relief in postoperative cardiothoracic patients in the intensive care unit: a randomised double-blind controlled trial. *Anaesth. Intensive Care* 40, 417–426 (2012).
24. van den Bosch, G. E., van Dijk, M., Tibboel, D. & Valkenburg, A. J. Thermal quantitative sensory testing in healthy Dutch children and adolescents standardized test paradigm and Dutch reference values. *BMC Pediatr.* 17, 77 (2017).
25. Valkenburg, A. J. *et al.* Long-Term Effects of Neonatal Morphine Infusion on Pain Sensitivity: Follow-Up of a Randomized Controlled Trial. *J. Pain* 16, 926–933 (2015).
26. Rolke, R. *et al.* Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur. J. Pain* 10, 77–88 (2006).
27. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
28. Cleeland, C. S. & Ryan, K. M. Pain assessment: global use of the Brief Pain Inventory. *Ann. Acad. Med. Singapore* 23, 129–38 (1994).
29. Joly, V. *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 103, 147–55 (2005).
30. Schmidt, S., Bethge, C., Forster, M. H. & Schafer, M. Enhanced postoperative sensitivity to painful pressure stimulation after intraoperative high dose remifentanil in patients without significant surgical site pain. *Clin. J. Pain* 23, 605–611 (2007).
31. Salengros, J.-C. *et al.* Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J. Cardiothorac. Vasc. Anesth.* 24, 608–16 (2010).
32. Jensen, T. S. & Finnerup, N. B. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *The Lancet.Neurology* 13, 924–935 (2014).
33. Lee, M., Silverman, S. M., Hansen, H., Patel, V. B. & Manchikanti, L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 14, 145–161 (2011).
34. Li, Y. *et al.* Inhibition of glycogen synthase kinase-3beta prevents remifentanil-induced hyperalgesia via regulating the expression and function of spinal N-methyl-D-aspartate receptors in vivo and vitro. *PLoS One* 8, e77790 (2013).
35. Yuan, Y. *et al.* Glycogen synthase kinase-3beta contributes to remifentanil-induced postoperative hyperalgesia via regulating N-methyl-D-aspartate receptor trafficking. *Anesth. Analg.* 116, 473–481 (2013).

36. Arout, C. A., Edens, E., Petrakis, I. L. & Sofuoglu, M. Targeting Opioid-Induced Hyperalgesia in Clinical Treatment: Neurobiological Considerations. *CNS Drugs* 29, 465–486 (2015).
37. Zhao, Q. *et al.* Involvement of Spinal PKMzeta Expression and Phosphorylation in Remifentanil-Induced Long-Term Hyperalgesia in Rats. *Cell. Mol. Neurobiol.* 37, 643–653 (2017).
38. Chaparro, L. E., Smith, S. A., Moore, R. A., Wiffen, P. J. & Gilron, I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane database Syst. Rev.* (7):CD0083, CD008307 (2013).
39. Martinez, V., Pichard, X. & Fletcher, D. Perioperative pregabalin administration does not prevent chronic postoperative pain: systematic review with a meta-analysis of randomized trials. *Pain* 158, 775–783 (2017).
40. Granot, M. Can we predict persistent postoperative pain by testing preoperative experimental pain? *Curr. Opin. Anaesthesiol.* 22, 425–430 (2009).
41. Marcuzzi, A., Dean, C. M., Wrigley, P. J., Chakiath, R. J. & Hush, J. M. Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. *J. Pain Res.* 9, 599–607 (2016).
42. Yarnitsky, D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr. Opin. Anaesthesiol.* 23, 611–615 (2010).
43. Yarnitsky, D. *et al.* Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* 138, 22–28 (2008).
44. Nothnagel, H. *et al.* How stable are quantitative sensory testing measurements over time? Report on 10-week reliability and agreement of results in healthy volunteers. *J. Pain Res.* 10, 2067–2078 (2017).
45. Baron, R. *et al.* Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain* 158, 261–272 (2017).

Supplemental Material

Table S1. Median thermal thresholds independent of intervention group

		Baseline (n = 126)	3 days (n = 122)	12 months (n = 112)
Detection threshold (°C)	Heat	35.8 (34.7 to 37.3)	35.5 (34.6 to 36.6)	35.2 (34.5 to 36.4)*
	Cold	29.9 (28.9 to 30.6)	30.0 (28.9 to 30.7)	30.4 (29.4 to 30.7)*
Pain threshold (°C)	Heat	48.1 (46.4 to 49.1)	46.9 (43.8 to 48.7)*	48.0 (45.7 to 49.3)
	Cold	5.7 (1.5 to 15.2)	9.5 (1.8 to 19.2)*	4.9 (1.7 to 15.5)

* indicates $p<0.05$ compared to baseline
Values are presented as median (IQR). P-values based on Wilcoxon signed rank test

Table S2. Robust Regression Estimates of Treatment Condition, With Adjustment for Different Covariates: Detection and Pain Thresholds 3 days after surgery

Modality	Estimate	95% CI limits	p-value
Detection threshold for cold			
Intercept	24.9	22.3 to 27.5	<0.001
Remifentanil	-0.17	-0.33 to 0.66	0.499
Baseline detection threshold cold (°C)	0.22	0.17 to 0.27	<0.001
Age (years)	-0.02	-0.05 to 0.01	0.135
Opioid consumption first 72 hrs (mg)	0.00	0.00 to 0.00	0.724
Chronic pain after 1 year	0.00	0.00 to 0.00	0.537
QoL pre-operative	0.01	-0.03 to 0.04	0.778
Reaction time (s)	-0.66	-2.4 to 1.1	0.451
Detection threshold for heat			
Intercept	29.2	24.5 to 34.0	<0.001
Remifentanil	-0.06	-0.58 to 0.46	0.822
Baseline detection threshold heat (°C)	0.15	0.03 to 0.26	0.016
Age (years)	0.01	-0.02 to 0.03	0.689
Opioid consumption first 72 h (mg)	0.01	-0.0 to 0.01	0.065
Chronic pain after 1 year	0.00	0.0 to 0.0	0.308
QoL pre-operative	-0.01	-0.06 to 0.03	0.569
Reaction time (s)	2.2	0.13 to 4.3	0.038
Pain threshold for cold			
Intercept	1.3	-11.9 to 14.5	0.846
Remifentanil	-0.6	-3.2 to 2.1	0.675
Baseline pain threshold cold (°C)	0.8	0.56-0.95	<0.001
Age (years)	0.07	-0.07 to 0.21	0.345
Opioid consumption first 72 h (mg)	0.03	-0.0 to 0.07	0.134
Chronic pain after 1 year	0.00	0.00 to 0.00	0.619
QoL pre-operative	-0.07	-0.22 to 0.88	0.386
Pain threshold for heat			
Intercept	18.7	4.5 to 32.9	0.011
Remifentanil	0.12	-1.0 to 1.2	0.842
Baseline pain threshold heat (°C)	0.68	0.4 to 1.0	<0.001
Age (years)	-0.04	-0.09 to -0.01	0.151
Opioid consumption first 72 h (mg)	-0.003	-0.02 to -0.01	0.619
Chronic pain after 1 year	0.00	0.00 to 0.00	0.168
QoL pre-operative	-0.04	-0.1 to 0.03	0.259

95% CI, 95% confidence interval; QoL, Quality of Life questionnaire.

Chapter 6

OPRM1 and *COMT* polymorphisms: implications on postoperative acute, chronic and experimental pain after cardiac surgery

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Pharmacogenomics 2020;21(3):181-193
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Abstract

Aim

Investigate the potential role of *OPRM1* (mu-opioid receptor) and *COMT* (catechol-O-methyltransferase enzyme) polymorphisms in postoperative acute, chronic and experimental thermal pain.

Methods

A secondary analysis of 125 adult cardiac surgery patients that were randomised between fentanyl and remifentanil during surgery and genotyped.

Results

Patients in the fentanyl group with the COMT high-pain sensitivity haplotype required less postoperative morphine compared with the average-pain sensitivity haplotype (19.4 (16.5 to 23.0) vs 34.6 (26.2 to 41.4); p=0.00768), but not to the low-pain sensitivity group (30.1 (19.1 to 37.7); p=0.13). No association was found between *COMT* haplotype and other pain outcomes or *OPRM1* polymorphisms and the different pain modalities.

Conclusion

COMT haplotype appears to explain part of the variability in acute postoperative pain in adult cardiac surgery patients.

Introduction

Adequate pharmacological management of pain is hampered by large variability between individuals in pain sensitivity and in analgesic response. Factors contributing to the extensive variability observed in pain and analgesia are considered multifactorial, including among other sex[1,2], age[3], race[4,5], co-medication (chronic opioid history/opioid addiction), co-morbidities[6,7], psychological elements such as anxiety[8] and genetic predisposition[9]. The need for a personalized approach, by means of genetics, environmental, psychological and injury-specific factors, has been acknowledged previously[10]. Moreover, chronic postsurgical pain also necessitates the need for an individualized pain management approach. By identifying patients at risk for this chronic postoperative pain state prior to surgery, healthcare providers could prevent its occurrence by adaptions in the pre-operative and postoperative treatment.

The genetic contribution in pain and pain treatment has been extensively studied the last two decades in the adult population by use of knock-down animal studies, twin studies, candidate gene approaches and genome-wide analyses[11,12]. The most widely studied and confirmed variant is the mu-opioid receptor (*OPRM1)* polymorphism 118A>G, which has been associated with higher postsurgical opioid requirement in a recently performed meta-analysis[13]. The increased opioid requirement in 118G allele carriers was later confirmed in 1500 additional patients[14]. The 118G variant allele also relates with lower frequency of nausea and vomiting[14]. Both findings on opioid demand and adverse events are indicative for lower potency of exogenous opioids in carriers of the 118G allele.

Another important gene, repeatedly associated in studies with pain and pain treatment, is *COMT*, encoding the catechol-O-methyltransferase. The *COMT* rs4680 variant has been related with several phenotypes of pain[15] and opioid requirements[16–19]. Three different pain sensitivity haplotypes composed from this SNP and three other variants (rs4818, rs4633 and rs6269), being low-pain sensitivity (LPS), average-pain sensitivity (APS) and high-pain sensitivity (HPS) have been identified[20]. The pain sensitivity haplotypes have been attributed to the differences in COMT activity, with the LPS haplotype having 4.8-times higher activity compared with the APS and 11.4 to HPS haplotype[20]. COMT is responsible for the breakdown of catecholamines such as (nor)epinephrine and dopamine. Decreased COMT activity in rats has been associated with increased pain sensitivity via amplified firing at the β_2 and β_3-adrenergic receptors[21]. Altered dopamine levels in rats have been related with the expression of the endogenous opioid agonist, enkephalin[22]. Confirming this hypothesis, the *COMT* variant Val158Met (rs4680)

in healthy adults, leading to a fourfold decrease in activity[23], reduced mu-opioid receptor density[24].

Up to date these genes have not been addressed across three different pain aetiologies (acute and chronic postoperative pain and experimental pain) within the same individuals. The main aim of this genetic study was to assess if the highly investigated genetic variants in *OPRM1* and *COMT* are related with acute postoperative pain reflected by postoperative opioid consumption and could predict the development of chronic postsurgical pain in cohort of patients undergoing cardiac surgery[25–27]. Additionally, the relation between these genetic variants and preoperative and postoperative thermal pain sensitivity has been assessed.

Methods

This is a candidate gene association study performed as a secondary analysis of a randomised clinical trial evaluating the effect of remifentanil versus fentanyl during cardiac surgery on the incidence of acute and chronic thoracic pain in the St Antonius Hospital in Nieuwegein, The Netherlands. The study received approval from the Regional Medical Ethical Review Board (Verenigde Commissies Mensgebonden Onderzoek R13.013) and was registered on the Clinical Trials register (ClinicalTrials.gov number NCT02031016). The study protocol has been published previously[26]. Participants who signed written informed consent and from which a blood sample for DNA analysis was available were included in the current study. Since this is a secondary study, details about the primary clinical outcome and experimental pain thresholds can be found elsewhere[25,27].

Participants

Inclusion criteria for the original study were age between 18 and 85 years, weight between 45 and 140 kg and planned cardiac surgery via sternotomy (i.e., elective coronary artery bypass grafting (CABG) and/or valve replacement). Exclusion criteria were pregnancy/breastfeeding, language barrier, history of drug abuse, chronic pain conditions (e.g., peripheral neuropathy, fibromyalgia), remifentanil/fentanyl/morphine/paracetamol allergy, BMI over 35 kg/m^2 and prior cardiac surgery.

Study protocol

In the original study, patients were randomised intraoperatively to either receive remifentanil continuous infusion (start 0.15 mcg/kg ideal body weight/min; adjusted when necessary) or extra fentanyl bolus (200–500 mcg), both on top of standard care with fentanyl bolus (200–500 mcg) on predetermined times (prior,

during sternotomy, during aorta cannulation and during opening pericardium). The attending anaesthesiologist determined, based on patient's clinical monitoring (e.g., haemodynamics and sweating) and characteristics such as body weight or ejection fraction), the exact dose of fentanyl and whether additional fentanyl was required. Anaesthesia induction was standardized in all patients with intravenous midazolam (2.5 to 5.0 mg), followed by propofol bolus (1–2 mg/kg), pancuronium (0.05–2 mg/kg) and fentanyl (on time points as previously mentioned). Thirty minutes before end of surgery all patients received 5 to10mg morphine intravenously.

Postoperative pain management after transfer to the ICU and the post anaesthesia care unit included continuous morphine infusion (starting 2 mg/h) and paracetamol 4-times daily (oral/intravenous). Adaption of the morphine infusion and/or additional morphine bolus doses was standardized and based on the numerical rating scale (NRS). The NRS was assessed three-times daily by the nurse or was self-reported if possible, based on a previously reported pain titration protocol[28]. An NRS > 4 was indicative for insufficient pain control. In the case the patient was not or insufficiently awake the nurse judged pain with NRS. From 24-h postoperatively onward, patients experiencing insufficient pain control despite dose escalation or side effects, continued receiving morphine boluses or were switched, at discretion of the attending physician, to oral oxycodone or tramadol. The development of chronic thoracic pain was identified with a questionnaire partly based on the validated Brief Pain Inventory[29], which was sent by an e-mail or post mail at 3, 6 and 12 months after surgery by the same researcher. Chronic thoracic pain was defined as sternal and/or thoracic pain (NRS > 0) which the patient identified as related to surgery.

Quantitative sensory testing

Cold and heat detection and pain thresholds were determined in the cardiac patients one day before, 3 days after and 12 months after surgery with the Method of Limits (MLI) by use of the Thermal Sensory Analyser II 2001 (Medoc Advanced Medical Systems, Israel). The thermode (30 × 30 mm) was attached to the nondominant hand. Patients responded on the thermal stimuli by clicking a computer mouse with the dominant hand, when the detection or pain threshold was reached. Before formal determination of the thresholds started, a minimum of two training sessions with a test–retest difference below 20% was required. The thresholds were constructed by taking the average of four formal thresholds. Since the MLI method is depending on the reaction time of the individual, the analysis with the thermal thresholds was corrected for median reaction time. Reaction

time was determined with the open-source software (http://delphiforfun.org/Programs/Reaction_times.htm) by clicking the computer mouse in reaction to the appearance of a blue ball on a white screen. This response was rehearsed three-times and followed by five formal measurements, of which the mean reaction time was calculated per individual. All quantitative sensory testing tests in this study were performed by the same researcher (SdH).

Outcomes

The outcomes studied in this candidate gene study were cumulative postoperative morphine requirements during the first 24 h (mg/24 h) and 48 h (mg/48 h); the development of chronic thoracic pain at 3, 6 and 12 months after surgery (yes/no); and thermal pain thresholds before surgery, 3 days and 12 months after surgery. Opioid requirements during first 48 h were calculated as morphine equivalents[30,31]. All outcomes were assessed for a relation with the genetic variant *OPRM1* rs1799971, *COMT* rs4680, rs4818, rs4633, the *COMT* haplotype and the combined *OPRM1* rs1799971/*COMT* rs4680 effect.

Genotyping

The genetic analysis was performed at the department of Clinical Chemistry at the Erasmus University Medical Centre in Rotterdam (The Netherlands). DNA was extracted from 1 ml peripheral blood. DNA was isolated on the MagNA Pure LC 2.0 instrument (Roche®, Almere, The Netherlands) with the 'DNA Isolation Kit – Large volume' (Roche®, Almere, The Netherlands). The 7500 Fast Real-Time PCR System (software version 3.0.0; Applied Biosystems, Bleiswijk, The Netherlands) was used for determination of the *OPRM1* 118A>G (rs1799971), *COMT* 472G>A (rs4680), (rs4818) and (rs4633) genetic variants with ready-made TaqMan® SNP Genotyping Assays. All single nucleotide polymorphisms were checked for agreement with minor allele frequency reported in literature and violation of Hardy–Weinberg equilibrium (p-value > 0.013). R (version 3.1.1) haplo.stats package was used to estimate the *COMT* haplotype (posterior probability limit > 90%). LPS group was encoded by the GGC (rs4680, rs4818, rs4633 resp.) haplotype, APS by ACT and HPS by GCC[32]. Participants with LPS/LPS and LPS/APS alleles were combined in the 'LPS' group, APS/APS and LPS/HPS in the 'APS' group and HPS/HPS and APS/HPS alleles in the 'HPS' group. Additionally, as previous findings indicate the combined effect of *OPRM1* rs1799971 and *COMT* rs4680, we assessed this combined genotype[33,34], with group 1 represented by *OPRM1* 118AA genotype with *COMT* 472A allele carriage and group 2 by *OPRM1* 118G allele carriage with/or *COMT* 472GG genotype.

IBM SPSS Statistics 21.0 was used for the statistical analysis. As previously reported, subjects that received continuous remifentanil infusion during surgery were predisposed to higher morphine consumption (median: 34.3 mg/24 h [interquartile range (IQR): 25.3; 48.2]) postoperatively compared with the fentanyl randomization group (30.2 [19.2; 38.1]). Due to this difference the cohort was stratified according to randomization group in the analysis between genetics and opioid consumption. After stratification the analysis with *OPRM1* rs1799971 and combined *OPRM1* rs1799971/*COMT* rs4680 genotype in relation to postoperative morphine requirement was performed with an Student's *t*-test. The analysis between *COMT* haplotype, *COMT* rs4680, rs4818 and rs4633 SNP with postoperative morphine requirement was calculated with the analysis of variance (ANOVA) test. A binominal logistic regression analysis was used in order to assess if the genetic variants, by adjusting for randomization arm (correction only made in analysis at 3 months) and age, could predict the likelihood of patients developing chronic thoracic pain at 3, 6 and 12 months after surgery. The association with the MLI thermal thresholds has been corrected for the composite variable age and reaction time (FAC1_1) in a multiple linear regression. The corrected mean and standard deviations of the thermal thresholds are displayed per genotype group, which have been retrieved with two-way analysis of covariance (ANCOVA).

Per outcome (e.g., thermal pain, morphine requirement, chronic pain) six analysis (*OPRM1* rs1799971, *COMT* rs4680, rs4818, rs4633, *COMT* haplotype and combined *OPRM1* rs1799971/*COMT* rs4680 genotype) were performed. Therefore, a two-sided p-value of 0.05/6 = 0.0083 (Bonferroni correction) was considered statistically significant.

For the original study, a sample size calculation was performed on the primary end point chronic thoracic pain, and was based on the findings of a previous study[35]. This resulted in a total number of 117 patients, with a power of 0.80 and a two-sided significance level of 0.05. Taking into account a mortality rate of 8% 1-year after surgery[35], the total number of patients is 126, which results in 63 subjects per arm.

Results

The original randomised controlled trial included 126 subjects (63 remifentanil/63 fentanyl) undergoing cardiac surgery at the St Antonius Hospital Nieuwegein. The cohort existed of mainly male individuals (91%) and was almost completely of Caucasian origin (98%), the remaining 2% (n = 3) had Asian descent. The most frequent cardiac procedure was CABG (79%), followed by valve replacement

(13%) or patients having both procedures (8%). In almost all CABG patients (98%), the internal mammary artery (left, right or both) was used for coronary bypass. Totally, 56% of the patients was overweight (BMI: 25 to 29.9), 24% moderately obese (BMI: 30 to 35) and 20% had a normal BMI (18.5 to 24.9). For an overview of all demographic and clinical data according to randomization group see Table 1. One individual was excluded from further analysis due to a missing blood sample for DNA analysis. The selected genetic variants were in line with the frequencies reported in literature and did not deviate from the Hardy–Weinberg equilibrium (Table 2).

Genetics versus acute postoperative pain

After stratification according to the intraoperative randomization group, the *COMT* haplotype was related with postoperative morphine consumption (mg/24 h) within the intraoperative fentanyl group (p=0.009) but this was not the case for remifentanil (p=0.29). Post-hoc test (Bonferroni) correction confirmed that only the HPS haplotype group required significantly less morphine compared with the APS haplotype group (median 19.4 mg/24 h (16.5 to 23.0) vs 34.6 mg/24 h (IQR = 26.2 to 41.1); p=0.007). No significant difference could be observed between the LPS haplotype (30.1 mg/24 h (19.1 to 37.7)) with APS (p=0.13) or HPS (p=0.15) haplotype groups. Total postoperative opioid consumption within 48 h postoperatively was also decreased in the *COMT* HPS haplotype (p=0.025), but no longer significant after Bonferroni correction. No associations were found between postoperative opioid consumption with *OPRM1* rs1799971, the individual *COMT* SNPs (rs4680, rs4818 and rs4633) composing the COMT haplotype or the combined *OPRM1/COMT* genotype. These results are shown in Tables 3 and 4. One male Asian patient with an opioid requirement of 122.6 mg/48 h was identified as an outlier (Grubb's test, $p<0.05$). This patient with extremely high postoperative opioid consumption was found to be homozygote variant carrier of the *OPRM1* rs1799971 SNP.

Genetics versus Postoperative chronic pain

Chronic thoracic pain occurred 3, 6 and 12 months after cardiac surgery, respectively, in 53 patients (42.1%), 37 patients (29.8%) and 23 patients (18.8%). After stratification according to randomization group (only performed in the analysis at 3 months) and correction for age, the genetic variants (*OPRM1* rs1799971, *COMT* rs4680, rs4818, rs4633, *COMT* haplotype and combined *OPRM1* rs1799971/*COMT* rs4680 genotype) were not associated with the development of chronic thoracic pain at 3, 6 and 12 months after cardiac surgery.

Table 1. Demographics and clinical data cohort

	Fentanyl (n = 63)	**Remifentanil (n = 63)**	**P - value**
Gender (male/female)	57/6	58/5	0.75
Age (years)	66.1 (7.6)	62.1 (9.0)	0.007
BMI (kg/m^2)	28.0 (3.1)	27.5 (3.6)	0.47
Ethnicity			0.99
Caucasian	62	61	
Asian	1	2	
Diabetes (yes/no)	14/49	10/53	0.36
COPD (yes/no)	4/59	4/59	0.99
Depression (yes/no)	1/62	4/59	0.37
Type of surgery			0.40
CABG	51	49	
Valve replacement	9	7	
Both	3	7	
Length hospital admission (days)	5.0 (3.0 to 7.0)	5.0 (3.0 to 7.0)	0.67
Length ICU/PACU admission (hours)	19.5 (16.7 to 22.4)	19.6 (16.2 to 21.4)	0.77
NRS (before surgery)	0 (0 to 0)	0 (0 to 0)	0.77
Intra- and postoperative data			
Duration surgery (min)	187 (46.7)	198 (70.8)	0.32
Length of anaesthesia (min)	219 (49.0)	233 (72.1)	0.18
Time to extubation (min)	548 (479 to 724)	532 (465 to 605)	0.31
Intra-operative fentanyl (mg)	2350 (1750 to 3000)	1750 (1500 to 2500)	0.001
Intraoperative remifentanil (µg)	NA	2165 (696)	<0.001
Post-OK morphine consumption (mg/24 hour)	30.2 (19.2 to 38.1)	34.3 (25.3 to 48.2)	0.028
Post-OK opioid consumption (mg/48 hour)	39.0 (26.2 to 51.4)	46.8 (33.8 to 59.2)	0.047
Chronic thoracic pain 3 months after surgery (yes/no)	21/42	32/31	0.047
Chronic thoracic pain 6 months after surgery (yes/no)	20/42	17/45	0.56
Chronic thoracic pain 12 months after surgery (yes/no)	12/49	11/50	0.82

Continuous variables are displayed as mean (standard deviation) or median (interquartile range), depending on the distribution.

CABG: Coronary artery bypass grafting; IQR: Interquartile range; NRS: Numerical rating scale; PACU: Post anaesthesia care unit.

Table 2. Genotyping results according to randomization group

	Fentanyl	Remifentanil	MAF observed (%)	MAF literature* (%)	H-W equilibrium p-value**
OPRM1 (rs1799971)			14	15	0.19
118AA	46	49			
118AG	16	10			
118GG	1	3			
COMT (rs4680)			51	48	0.99
472GG	17	13			
472GA	30	33			
472AA	16	16			
COMT (rs4818)			38	42	0.68
408CC	25	24			
408CG	24	33			
408GG	14	5			
COMT (rs4633)			51	48	0.99
186CC	17	13			
186CT	30	33			
186TT	16	16			

*NCBI SNP database (European population); **Hardy-Weinberg (HW) equilibrium for the total cohort (*n* = 125).

HW: Hardy–Weinberg; MAF: Minor allele frequency.

Table 3. Morphine requirements until 24 hours after cardiac surgery

Fentanyl	n	Median	IQR	Lowest	Highest	p-value
OPRM1						0.75
AA	46	30.3	(19.2 to 37.3)	5.10	52.5	
G carrier	17	25.1	(20.2 to 38.3)	7.20	42.9	
OPRM1/COMT						0.67
118AA and 472A	32	30.2	(17.7 to 38.4)	5.10	51.2	
118G and/or 472GG	31	30.2	(21.4 to 38.1)	7.20	52.5	
COMT haplotype						0.009*
LPS	35	30.1	(19.1 to 37.7)	5.10	47.2	
APS	19	34.6	(26.2 to 41.4)	10.1	52.5	
HPS	9	19.4	(16.5 to 23.0)	13.2	33.4	
COMT rs4680						0.14
472GG	17	28.5	(20.3 to 36.3)	8.70	52.5	
472GA	30	26.1	(16.9 to 37.8)	5.10	43.0	
472AA	16	34.5	(27.2 to 41.1)	10.1	51.2	

Fentanyl	n	Median	IQR	Lowest	Highest	p-value
COMT rs4818						0.82
408CC	25	30.3	(18.7 to 37.9)	10.1	51.2	
408CG	24	32.6	(18.9 to 40.3)	5.10	52.5	
408GG	14	26.9	(19.2 to 35.6)	8.70	47.2	
COMT rs4633						0.14
186CC	17	28.5	(20.3 to 36.3)	8.70	52.5	
186CT	30	26.1	(16.9 to 37.8)	5.10	43.0	
186TT	16	34.5	(27.2 to 41.1)	10.1	51.2	

Remifentanil	n	Median	IQR	Lowest	Highest	p-value
OPRM1						0.25
AA	49	33.8	(25.2 to 42.0)	5.40	55.0	
G carrier	13	39.2	(22.6 to 49.5)	11.6	63.8	
OPRM1/COMT						0.48
118AA and 472A	36	33.8	(25.5 to 42.1)	5.40	53.3	
118G and/or 472GG	26	37.1	(20.9 to 43.9)	8.60	63.8	
COMT haplotype						0.39
LPS	31	36.4	(26.3 to 44.0)	11.6	55.0	
APS	23	28.7	(19.2 to 39.9)	5.40	63.8	
HPS	8	38.3	(29.3 to 41.6)	26.0	49.3	
COMT rs4680						0.66
472GG	13	36.4	(20.3 to 41.2)	8.60	55.0	
472GA	33	36.8	(26.2 to 43.5)	11.6	55.0	
472AA	16	31.3	(24.9 to 39.5)	5.40	63.8	
COMT rs4818						0.92
408CC	24	34.8	(25.5 to 40.7)	5.40	63.8	
Remifentanil	n	Median	IQR	Lowest	Highest	p-value
408CG	33	34.3	(23.1 to 43.5)	8.60	55.0	
408GG	5	36.4	(30.4 to 41.5)	29.4	44.0	
COMT rs4633						0.66
186CC	13	36.4	(20.3 to 41.2)	8.60	55.0	
186CT	33	36.8	(26.2 to 43.5)	11.6	55.0	
186TT	16	31.3	(24.9 to 39.5)	5.40	63.8	

**Post Hoc test Kruskal-Wallis illustrated a significant difference between APS and HPS (p=0.00768).*

APS: Average-pain sensitivity; HPS: High-pain sensitivity; IQR: Interquartile range; LPS: Low-pain sensitivity.

Table 4. Morphine-equivalent requirements until 48 hour after cardiac surgery

Fentanyl	n	Median	IQR	Lowest	Highest	p-value
OPRM1						0.99
AA	46	39.1	(25.5 to 52.6)	5.10	77.5	
G carrier	17	35.1	(25.9 to 54.6)	8.10	82.9	
OPRM1/COMT						0.17
118AA and 472A	32	34.8	(19.8 to 50.3)	5.10	76.2	
118G and/or 472GG	31	41.0	(27.9 to 58.1)	8.10	82.9	
COMT haplotype						*0.025*
LPS	35	41.0	(27.9 to 58.1)	5.10	69.8	
APS	19	43.1	(31.8 to 56.7)	16.0	82.9	
HPS	9	23.2	(18.7 to 34.2)	16.3	35.1	
COMT rs4680						0.27
472GG	17	41.0	(30.9 to 60.7)	8.70	77.5	
472GA	30	34.8	(19.0 to 52.8)	5.10	69.8	
472AA	16	41.1	(32.0 to 51.1)	16.0	82.9	
COMT rs4818						0.52
408CC	25	34.3	(22.1 to 48.8)	16.0	82.9	
408CG	24	46.8	(25.8 to 59.7)	5.10	77.5	
408GG	14	40.6	(33.1 to 51.9)	8.70	67.2	
COMT rs4633						0.27
186CC	17	41.0	(30.9 to 60.7)	8.70	77.5	
186CT	30	34.8	(19.0 to 52.8)	5.10	69.8	
186TT	16	41.1	(32.0 to 51.1)	16.0	82.9	
Remifentanil	n	Median	IQR	Lowest	Highest	p-value
OPRM1						0.25
AA	49	46.5	(33.8 to 54.9)	18.0	98.3	
G carrier	13	59.2	(34.7 to 71.8)	11.6	122.6	
OPRM1/COMT						0.27
118AA and 472A	36	45.4	(32.8 to 57.5)	18.0	98.3	
118G and/or 472GG	26	49.3	(37.1 to 66.1)	11.6	122.6	
COMT haplotype						0.83
LPS	31	46.4	(32.6 to 59.2)	11.6	98.3	
APS	23	37.7	(33.8 to 58.2)	18.0	122.6	
HPS	8	54.1	(46.9 to 60.4)	26.0	69.3	
COMT rs4680						0.82
472GG	13	46.4	(37.5 to 51.4)	18.6	75.0	
472GA	33	47.1	(33.7 to 60.8)	11.6	98.3	
472AA	16	35.2	(30.0 to 63.2)	18.0	122.6	
COMT rs4818						0.81
408CC	24	47.7	(33.8 to 60.4)	18.0	122.6	
408CG	33	44.3	(33.7 to 60.0)	11.6	98.3	
408GG	5	46.4	(36.7 to 50.1)	29.4	51.3	

Remifentanil	n	Median	IQR	Lowest	Highest	p-value
COMT rs4633						0.82
186CC	13	46.4	(37.5 to 51.3)	18.6	75.0	
186CT	33	47.1	(33.7 to 60.8)	11.6	98.3	
186TT	16	35.2	(30.0 to 63.2)	18.0	122.6	

**Post Hoc test ANOVA illustrated a significant difference between APS and HPS (p=0.021) and between LPS and HPS (p=0.049).*

APS: Average-pain sensitivity; HPS: High-pain sensitivity; IQR: Interquartile range; LPS: Low-pain sensitivity.

Genetics versus Preoperative and postoperative thermal pain thresholds

We have observed a trend between *COMT* haplotype with the pre-operative heat pain threshold (p=0.014) and cold pain threshold (p=0.045). Subjects with the LPS haplotype had the highest (mean: 44.9°C (standard error (SE): 0.32) heat pain thresholds followed by APS (44.2°C (0.39)) and HPS (43.2°C (0.62)). Individuals with the LPS haplotype were experiencing cold pain at a lower temperature compared with APS and HPS haplotype (7.52°C (0.98) vs 9.36°C (1.23) vs 11.7°C (1.94)). *COMT* rs4818 was associated with cold detection threshold (p=0.041). The trend between *COMT* haplotype and cold pain threshold remained 3 days after surgery (p=0.043), but not after 12 months. Also a trend was observed with the heat detection threshold and the *OPRM1* SNP at 12 months after surgery (p=0.010). However, none of these findings passed significance after Bonferroni correction (p=0.0083). The results are displayed in Table 5A–C. The mean and SE are corrected for the composite outcome age and reaction time.

Discussion

In an effort to assess the potential influence of *OPRM1* and *COMT* genetic variants on postoperative acute, chronic and experimental (thermal) pain, 125 cardiac surgery patients were genotyped and analyzed. We found that the *COMT* HPS haplotype was related with decreased postsurgical morphine requirement during the first 24 h. This effect was only found in individuals that were randomised to intraoperative fentanyl, but not in the remifentanil group. Additionally, a trend was found between the *COMT* haplotype with thermal pain, which was not significant after Bonferroni correction.

The observed trend between *COMT* haplotype and thermal pain points toward increased pain sensitivity reflected by increased heat pain at lower temperatures and increased cold pain at higher temperatures. Increased pain responsiveness in HPS haplotype carriers is in line with initial literature in 202 healthy female

volunteers with mixed racial background (85% European Americans) on multiple pain evoking stimuli, with only thermal pain significantly associated[36]. In contrast, in another mixed population (European Americans, African Americans, Asian Americans and Hispanics) of healthy subjects, no effect of the *COMT* haplotype was observed on thermal pain. In the latter study thermal pain was assessed via another method (briefly induced cold and heat pain) compared with the previous study[37], which could have confounded the results. Additionally, no effect of the COMT predicted phenotype group could be observed on thermal pain sensitivity in 1000 female patients undergoing breast surgery for cancer[38]. Focusing on other methods of experimentally induced pain, a study in healthy Chinese males could not confirm the effect of the *COMT* haplotype on pain evoked by transcutaneous electrical accupoint stimulation[39]. These studies suggest that the effect of *COMT* haplotype on pain seems to differ between pain modalities and patients, in the last case either due to ethnic background or diseased versus healthy subjects.

In our study, patients in the fentanyl group (n = 62) with the HPS haplotype had lower postoperative morphine need compared with the APS haplotype, while individuals with the HPS haplotype showed a trend towards higher pain responsiveness to experimental heat pain. These intuitively opposite effects can be attributed to the correlation between the dopaminergic and endogenous opioid system, as shown in animal models[40,41]. Stimulation of the dopamine system, which is comparable with the decreased COMT activity seen with the HPS haplotype, causes a decrease in the levels of endogenous peptides[40]. This decline leads to a compensatory rise in mu-opioid receptor expression, meaning that with the HPS haplotype there is less endogenous substrate to alleviate pain, but more receptors available for increased binding when exposed to exogenous opioids. Although our findings on morphine consumption are in line with the biological plausibility for the HPS and APS haplotype, we did not observe a higher postoperative consumption in the LPS group compared with the APS group. Also studies from literature on the direction of the effect of these haplotypes are inconclusive. For example, other studies found that individuals with the APS haplotype required the lowest morphine need[19,42]. Also opposite to our findings, a study in Han Chinese patients found higher postoperative fentanyl requirement after radical gastrectomy with the HPS haplotype[43].

Table 5a. Thermal detection and pain thresholds measured 1 day before cardiac surgery

	n	Heat detection threshold (°C)	n	Cold detection threshold (°C)	n	Heat pain threshold (°C)	n	Cold pain threshold (°C)
OPRM1								
118AA	92	36.3 (0.22)	94	29.7 (0.13)	95	44.4 (0.27)	95	8.40 (0.83)
118G allele	29	36.2 (0.40)	29	29.6 (0.24)	30	44.3 (0.48)	30	9.68 (1.48)
p-value*		0.82		0.89		0.81		0.45
COMT rs4680								
472GG	28	36.4 (0.41)	30	29.3 (0.23)	30	44.7 (0.48)	30	8.80 (1.49)
472GA	61	36.2 (0.28)	61	29.7 (0.16)	63	44.4 (0.33)	63	8.44 (1.02)
472AA	32	36.3 (0.38)	32	29.9 (0.22)	32	44.2 (0.46)	32	9.14 (1.44)
p-value*		0.87		0.10		0.51		0.87
COMT rs4818								
408CC	49	36.0 (0.31)	48	29.9 (0.18)	49	43.9 (0.37)	49	10.0 (1.15)
408CG	55	36.4 (0.29)	56	29.7 (0.17)	57	44.6 (0.34)	57	7.80 (1.07)
408GG	17	36.8 (0.52)	19	29.0 (0.28)	19	45.1 (0.59)	19	8.04 (1.85)
p-value*		0.16		0.014		0.051		0.22
COMT rs4633								
186CC	28	36.4 (0.41)	30	29.3 (0.23)	30	44.7 (0.48)	30	8.80 (1.49)
186CT	61	36.2 (0.28)	61	29.7 (0.16)	63	44.4 (0.33)	63	8.44 (1.02)
186TT	32	36.3 (0.38)	32	29.9 (0.22)	32	44.2 (0.46)	32	9.14 (1.44)
p-value*		0.87		0.10		0.51		0.87
COMT haplotype								
LPS	62	36.5 (0.27)	65	29.4 (0.15)	66	44.9 (0.32)	66	7.52 (0.98)
APS	42	36.2 (0.33)	42	29.9 (0.19)	42	44.2 (0.39)	42	9.36 (1.23)
HPS	17	35.4 (0.52)	16	29.9 (0.31)	17	43.2 (0.62)	17	11.7 (1.94)
p-value*		0.058		0.041		0.014		0.045
OPRM1/COMT								
118AA and 158Met	67	36.2 (0.26)	67	29.7 (0.15)	68	44.3 (0.32)	68	8.20 (0.97)
118G and/or 158Val/Val	54	36.3 (0.29)	56	29.5 (0.17)	57	44.5 (0.35)	57	9.31 (1.07)
p-value*		0.75		0.37		0.63		0.45

*P-value corrected for composite outcome age and reaction time.
Data are displayed as age and reaction time corrected mean with corresponding standard error. APS: Average-pain sensitivity; HPS: High-pain sensitivity; LPS: Low-pain sensitivity.

Table 5b. Thermal detection and pain thresholds measured 3 days after cardiac surgery

	n	Heat detection threshold (°C)	n	Cold detection threshold (°C)	n	Heat pain threshold (°C)	n	Cold pain threshold (°C)
OPRM1								
118AA	93	36.0 (2.22)	91	29.5 (0.17)	93	43.5 (0.29)	93	10.1 (0.92)
118G allele	30	36.2 (2.40)	30	29.5 (0.30)	30	43.0 (0.52)	30	12.5 (1.63)
p-value*		0.87		0.90		0.42		0.21
COMT rs4680								
472GG	29	36.7 (0.42)	29	29.3 (0.31)	29	43.7 (0.53)	29	10.3 (1.67)
472GA	62	35.7 (0.28)	60	29.7 (0.21)	63	43.2 (0.36)	63	10.8 (1.13)
472AA	31	36.1 (0.40)	31	29.3 (0.30)	31	43.3 (0.51)	31	10.8 (1.61)
p-value*		0.31		0.96		0.56		0.85
COMT rs4818								
408CC	47	35.9 (0.33)	47	29.5 (0.24)	48	42.9 (0.41)	48	11.8 (1.28)
408CG	56	35.9 (0.30)	56	29.5 (0.22)	56	43.4 (0.38)	56	10.5 (1.19)
408GG	19	36.9 (0.51)	19	29.4 (0.38)	19	44.1 (0.65)	19	8.33 (2.04)
p-value*		0.17		0.96		0.13		0.16
COMT rs4633								
186CC	29	36.7 (0.42)	29	29.3 (0.31)	29	43.7 (0.53)	29	10.3 (1.67)
186CT	62	35.7 (0.28)	61	29.7 (0.21)	63	43.2 (0.36)	63	10.8 (1.13)
186TT	31	36.1 (0.40)	31	29.3 (0.30)	31	43.3 (0.51)	31	10.8 (1.61)
p-value*		0.31		0.97		0.56		0.85
COMT haplotype								
LPS	66	36.1 (0.28)	66	29.6 (0.20)	66	43.7 (0.35)	66	9.29 (1.09)
APS	37	36.3 (0.37)	40	29.3 (0.26)	40	43.2 (0.44)	40	11.7 (1.40)
HPS	16	35.5 (0.57)	16	29.8 (0.41)	17	42.4 (0.68)	17	13.7 (2.14)
p-value*		0.54		0.96		0.086		0.043
OPRM1/COMT								
118AA and 158Met	65	35.8 (0.28)	66	29.6 (0.20)	67	43.2 (0.35)	67	10.1 (1.09)
118G and/or 158Val/Val	54	36.4 (0.31)	56	29.4 (0.22)	56	43.4 (0.38)	56	11.4 (1.19)
p-value*		0.17		0.48		0.70		0.44

*P-value corrected for composite outcome age and reaction time.
Data are displayed as age and reaction time corrected mean with corresponding standard error. APS: Average-pain sensitivity; HPS: High-pain sensitivity; LPS: Low-pain sensitivity.

Table 5c. Thermal detection and pain thresholds measured 12 months after cardiac surgery

	n	Heat detection threshold (°C)	n	Cold detection threshold (°C)	n	Heat pain threshold (°C)	n	Cold pain threshold (°C)
OPRM1								
118AA	80	36.2 (2.41)	81	29.9 (0.13)	83	47.2 (0.33)	83	8.80 (0.99)
118G allele	28	35.1 (1.20)	27	30.0 (0.23)	28	46.2 (0.58)	28	10.2 (1.72)
p-value*		0.010		0.60		0.13		0.48
COMT rs4680								
472GG	24	36.1 (0.45)	26	29.7 (0.23)	26	46.8 (0.60)	26	7.45 (1.77)
472GA	57	35.7 (0.29)	56	30.0 (0.16)	58	47.3 (0.40)	58	9.06 (1.18)
472AA	26	36.1 (0.44)	27	29.9 (0.23)	27	46.5 (0.59)	27	11.0 (1.73)
p-value*		0.92		0.61		0.68		0.16
COMT rs4818								
408CC	42	35.8 (0.34)	41	29.9 (0.18)	43	46.5 (0.47)	43	10.8 (1.36)
408CG	49	35.9 (0.32)	51	30.0 (0.17)	52	47.3 (0.42)	52	8.78 (1.24)
408GG	16	36.4 (0.56)	16	29.6 (0.30)	16	47.1 (0.77)	16	5.94 (2.24)
p-value*		0.41		0.49		0.32		0.062
COMT rs4633								
186CC	24	36.1 (0.45)	26	29.7 (0.23)	26	46.8 (0.60)	26	7.45 (1.77)
186CT	57	35.7 (0.29)	56	30.0 (0.16)	58	47.3 (0.40)	58	9.06 (1.18)
186TT	26	36.2 (0.44)	27	29.9 (0.23)	27	46.5 (0.59)	27	11.0 (1.73)
p-value*		0.92		0.61		0.68		0.16
COMT haplotype								
LPS	59	36.0 (0.29)	57	29.9 (0.15)	59	47.4 (0.39)	59	7.71 (1.17)
APS	32	36.1 (0.39)	36	29.9 (0.19)	36	46.4 (0.50)	36	10.9 (1.50)
HPS	16	35.1 (0.55)	15	30.0 (0.29)	15	47.0 (0.77)	16	10.5 (2.24)
p-value*		0.25		0.87		0.27		0.13
OPRM1/COMT								
118AA and 158Met	59	36.2 (0.29)	59	29.9 (0.15)	61	47.2 (0.39)	61	9.30 (1.16)
118G and/or 158Val/Val	48	35.6 (0.32)	50	29.9 (0.17)	50	46.6 (0.43)	50	8.98 (1.28)
p-value*		0.18		0.74		0.30		0.85

*P-value corrected for composite outcome age and reaction time.
Data are displayed as age and reaction time corrected mean with corresponding standard error. APS: Average-pain sensitivity; HPS: High-pain sensitivity; LPS: Low-pain sensitivity.

Although in our cohort patients with the LPS haplotype indeed had higher morphine consumption compared with the HPS haplotype, the difference was not significant. As described in our method section the possible *COMT* haplotype outcomes (LPS/LPS, LPS/APS, APS/APS, APS/HPS and LPS/HPS) have been converted into three possible haplotype outcomes. This could have confounded the association. Unfortunately, our study cohort size was insufficient to perform the six haplotype outcomes separately in the analysis. Besides, we have decreased this size even further by the performed stratification (fentanyl vs remifentanil) of our cohort.

Interestingly, the *COMT* genetic effect on postoperative opioid demand was only observed in the fentanyl randomised patients and not in the remifentanil group. It could be that due to the considerable shorter half-life of remifentanil (3–10 min) compared with fentanyl (1-4 h) the mu-opioid receptor gets desensitized. This desensitization can omit the *COMT* haplotype effect of differences in mu-opioid receptor expression as a consequence of the genetic altered COMT activity. Remifentanil is also associated with opioid-induced hyperalgesia[44], probably due to its effect on the N-methyl-D-aspartate receptor[45]. It has been hypothesized that signalling of this N-methyl-D-aspartate receptor may lead to opioid induced hyperalgesia[46]. This could also be the explanation of the increased morphine consumption directly after surgery and increased postoperative pain 3 months after surgery that were reported in the primary analysis of this study[25]. In this cohort, we were unable to confirm the *OPRM1* 118A>G effect on thermal, postoperative acute and chronic pain. Although we have observed a trend with the heat detection threshold 12 months after surgery, this was not significant after correction. Other studies investigating the effect of *OPRM1* 118A>G genotype on experimental and postoperative pain showed inconclusive results, as recently was reviewed elsewhere[47]. A gene–gene interaction between *OPRM1* and *COMT* could have biased the association with pain thresholds and opioid consumption[48]. However, this was not the case in our cohort, as no gene–gene *OPRM1 COMT* interaction has been observed.

A *OPRM1* 118 A>G gene–gender interaction has been described in the literature, with opposite effect found on pain between males and females[49–52]. These studies in general reported lower pain ratings among men that carry the 118G allele and higher pain ratings among woman with the 118G allele[49,50,52], with the exception of one study that found the effect to be in the opposite direction[51]. Since our cohort existed of primarily males and we were consequently unable to illustrate an effect on thermal pain the effect might be less evident in males. Not acknowledging the interaction between this polymorphism with gender (and other clinical factors)

might conceal the genotype effect on clinical outcomes and thus render its application for personalized pain treatment[53].

The gender–gene interaction is also described for *COMT*, namely in 143 healthy volunteers capsaicin-induced pain was solely higher among woman with the *COMT* HPS haplotype (low COMT activity)[54]. Decreased hepatic COMT activity has been reported in female individuals compared with males[55]. This gender difference may be related to oestrogen levels, which has been supported by a study in rats illustrating downregulation of COMT activity by oestrogen in the prefrontal cortex and the kidneys of the animals[56]. Due to the lower baseline levels in females they might be more prone to the decreased thermostability of the enzyme as a consequence of genetic variations in the *COMT* gene. In our primarily male cohort, we found an association between *COMT* haplotype and thermal pain thresholds. However, we were unable to assess if the effect of the *COMT* haplotype was larger in females due to the low inclusion rate of female subjects.

In this study, no genetic association between COMT and OPRM1 and the development of chronic pain was found. The role of the dopaminergic transmission in the development of chronic pain after surgery has been reviewed recently[57]. The COMT enzyme is one of the regulators of the dopaminergic transmission, by degradation of dopamine. As discussed in the previously mentioned review, studies have shown inconclusive results for this particular gene. One of the arguments that have been mentioned is that the development of chronic pain is complex and most likely caused by a combination of biological (e.g., genetic) factors, physical and social interaction[57]. The same argument is applicable for the *OPRM1* genetic variant. We believe that the *COMT* haplotype analysis will not have a purpose as a standalone test in guiding pain therapy with opioids. However, this biomarker could be valuable in a multifactorial prediction model of opioid response and should be validated in an algorithm including other genetic and nongenetic factors.

A limitation of the study is that the remifentanil group also received fentanyl during surgery. In our design, we decided not to compare fentanyl with a study arm with remifentanil as single analgesic since it was expected that high doses of remifentanil would be needed in this painful and extended procedure. However, it is possible that the association between the genetic variants tested and postoperative morphine requirements in the remifentanil group is not found since this group received more intraoperative opioids.

Conclusion

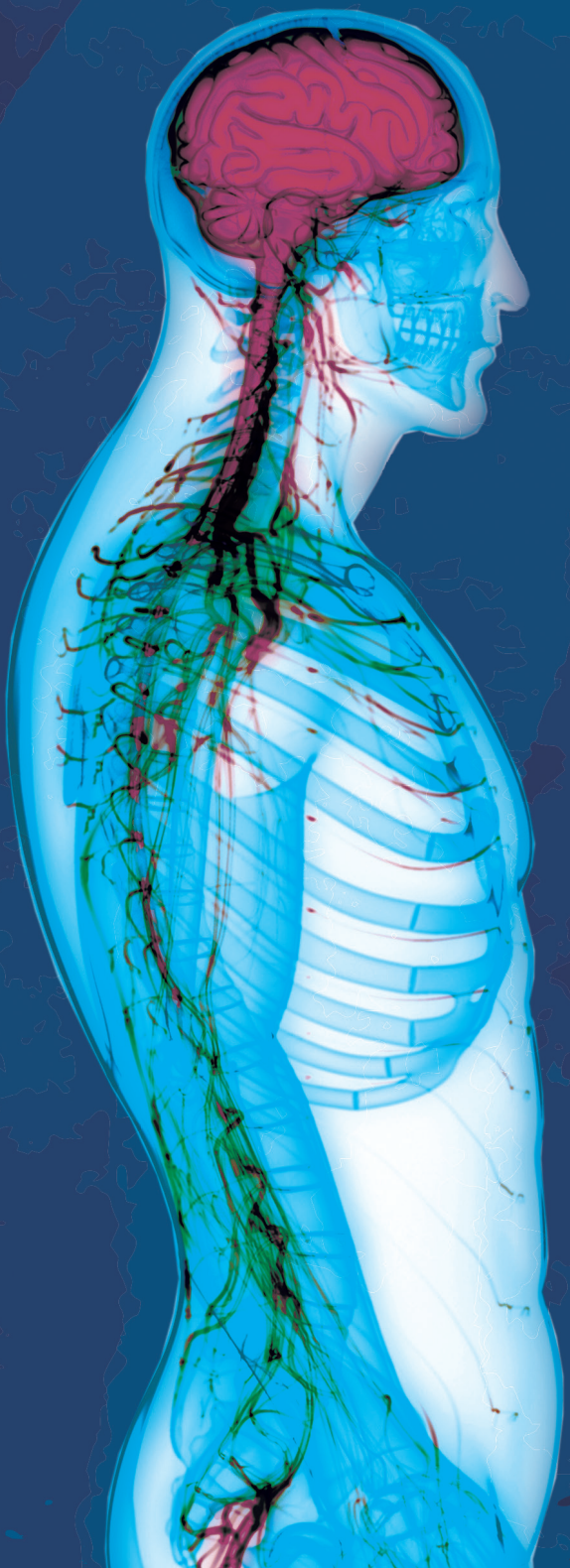
In conclusion, we found the *COMT* haplotype to be associated with acute postoperative pain reflected by postoperative opioid consumption. Patients in the fentanyl group with the *COMT* HPS haplotype group required less postoperative morphine compared with the APS group. The *COMT* haplotype explained part of the variability in experienced postoperative pain directly after surgery, but not on the longer term after surgery.

Literature

1. Mapplebeck, J. C. S., Beggs, S. & Salter, M. W. Sex differences in pain: a tale of two immune cells. *Pain* 157 Suppl, S2–S6 (2016).
2. Tighe, P. J., Riley, J. L. & Fillingim, R. B. Sex differences in the incidence of severe pain events following surgery: a review of 333,000 pain scores. *Pain Med.* 15, 1390–404 (2014).
3. Petrini, L., Matthiesen, S. T. & Arendt-Nielsen, L. The effect of age and gender on pressure pain thresholds and suprathreshold stimuli. *Perception* 44, 587–96 (2015).
4. Meints, S. M., Miller, M. M. & Hirsh, A. T. Differences in Pain Coping Between Black and White Americans: A Meta-Analysis. *J. pain* 17, 642–53 (2016).
5. Rahim-Williams, B., Riley, J. L., Williams, A. K. K. & Fillingim, R. B. A quantitative review of ethnic group differences in experimental pain response: do biology, psychology, and culture matter? *Pain Med.* 13, 522–40 (2012).
6. Leonard, B. E. Pain, Depression and Inflammation: Are Interconnected Causative Factors Involved? *Mod. trends pharmacopsychiatry* 30, 22–35 (2015).
7. Schug, S. A. & Raymann, A. Postoperative pain management of the obese patient. *Best Pract. Res. Clin. Anaesthesiol.* 25, 73–81 (2011).
8. Terry, M. J., Moeschler, S. M., Hoelzer, B. C. & Hooten, W. M. Pain Catastrophizing and Anxiety are Associated With Heat Pain Perception in a Community Sample of Adults With Chronic Pain. *Clin. J. Pain* 32, 875–81 (2016).
9. Angst, M. S. *et al.* Pain sensitivity and opioid analgesia: a pharmacogenomic twin study. *Pain* 153, 1397–1409 (2012).
10. Ahmedzai, S. H. Personalized medicine--one size fits one: tailoring pain therapy to individuals' needs. *J. Pain Palliat. Care Pharmacother.* 27, 83–5 (2013).
11. Clarke, H. *et al.* Genetics of chronic post-surgical pain: a crucial step toward personal pain medicine. *Can. J. Anaesth.* 62, 294–303 (2015).
12. Trescot, A. M. & Faynboym, S. A review of the role of genetic testing in pain medicine. *Pain Physician* 17, 425–45 (2014).
13. Hwang, I. C. *et al.* OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. *Anesthesiology* 121, 825–34 (2014).
14. Ren, Z.-Y. *et al.* The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: a systematic review and meta-analysis. *Pain Physician* 18, 131–52
15. Tammimäki, A. & Männistö, P. T. Catechol-O-methyltransferase gene polymorphism and chronic human pain: a systematic review and meta-analysis. *Pharmacogenet. Genomics* 22, 673–91 (2012).
16. Candiotti, K. A. *et al.* Catechol-o-methyltransferase polymorphisms predict opioid consumption in postoperative pain. *Anesth. Analg.* 119, 1194–200 (2014).
17. Cargnin, S. *et al.* An opposite-direction modulation of the COMT Val158Met polymorphism on the clinical response to intrathecal morphine and triptans. *J. pain* 14, 1097–106 (2013).
18. Rakvåg, T. T. *et al.* Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. *Mol. Pain* 4, 64 (2008).
19. Tan, E.-C. *et al.* Common variants of catechol-O-methyltransferase influence patient-controlled analgesia usage and postoperative pain in patients undergoing total hysterectomy. *Pharmacogenomics J.* 16, 186–92 (2016).

20. Diatchenko, L. *et al.* Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum. Mol. Genet.* 14, 135–43 (2005).
21. Nackley, A. G. *et al.* Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors. *Pain* 128, 199–208 (2007).
22. Zeng, B. Y., Jolkkonen, J., Jenner, P. & Marsden, C. D. Chronic L-DOPA treatment differentially regulates gene expression of glutamate decarboxylase, preproenkephalin and preprotachykinin in the striatum of 6-hydroxydopamine-lesioned rat. *Neuroscience* 66, 19–28 (1995).
23. Lotta, T. *et al.* Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry* 34, 4202–10 (1995).
24. Zubieta, J.-K. *et al.* COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 299, 1240–3 (2003).
25. de Hoogd, S. *et al.* Randomized Controlled Trial on the Influence of Intraoperative Remifentanil versus Fentanyl on Acute and Chronic Pain after Cardiac Surgery. *Pain Pract.* 18, 443–451 (2018).
26. de Hoogd, S. *et al.* Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials* 15, 466 (2014).
27. de Hoogd, S. *et al.* Short- and long-term impact of remifentanil on thermal detection and pain thresholds after cardiac surgery. *Eur. J. Anaesthesiol.* 36, 32–39 (2019).
28. Ahlers, S. J. *et al.* Efficacy of an intravenous bolus of morphine 2.5 versus morphine 7.5 mg for procedural pain relief in postoperative cardiothoracic patients in the intensive care unit: a randomised double-blind controlled trial. *Anaesth. Intensive Care* 40, 417–426 (2012).
29. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
30. Electronic Medicine Compendium (eMC). Summary of product characteristics - OxyContin 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg and 120 mg prolonged release tablets. Available at: www.medicines.org.uk/emc/medicine/29384.
31. Electronic Medicine Compendium (eMC). Summary of product characteristics - Tramadol 50 mg capsules. Available at: wwww.medicines.org.uk/emc/medicine/24675.
32. Nackley, A. G. *et al.* Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science* 314, 1930–3 (2006).
33. Matic, M. *et al.* Rescue morphine in mechanically ventilated newborns associated with combined OPRM1 and COMT genotype. *Pharmacogenomics* 15, 1287–95 (2014).
34. Reyes-Gibby, C. C. *et al.* Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. *Pain* 130, 25–30 (2007).
35. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
36. Diatchenko, L. *et al.* Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain* 125, 216–224 (2006).
37. Kim, H., Mittal, D. P., Iadarola, M. J. & Dionne, R. A. Genetic predictors for acute experimental cold and heat pain sensitivity in humans. *J. Med. Genet.* 43, e40 (2006).
38. Kambur, O. *et al.* Effect of catechol-o-methyltransferase-gene (COMT) variants on experimental and acute postoperative pain in 1,000 women undergoing surgery for breast cancer. *Anesthesiology* 119, 1422–33 (2013).

39. Xiang, X. *et al.* Catechol-O-methyltransferase polymorphisms do not play a significant role in pain perception in male Chinese Han population. *Physiol. Genomics* 44, 318–28 (2012).
40. George, S. R. & Kertesz, M. Met-enkephalin concentrations in striatum respond reciprocally to alterations in dopamine neurotransmission. *Peptides* 8, 487–92
41. Steiner, H. & Gerfen, C. R. Role of dynorphin and enkephalin in the regulation of striatal output pathways and behavior. *Exp. brain Res.* 123, 60–76 (1998).
42. De Gregori, M. *et al.* Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. *Eur. J. Clin. Pharmacol.* 69, 1651–8 (2013).
43. Zhang, F. *et al.* COMT gene haplotypes are closely associated with postoperative fentanyl dose in patients. *Anesth. Analg.* 120, 933–40 (2015).
44. Angst, M. S. & Clark, J. D. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 104, 570–587 (2006).
45. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
46. Guntz, E. *et al.* Effects of remifentanil on N-methyl-D-aspartate receptor: an electrophysiologic study in rat spinal cord. *Anesthesiology* 102, 1235–1241 (2005).
47. Gray, K., Adhikary, S. D. & Janicki, P. Pharmacogenomics of analgesics in anesthesia practice: A current update of literature. *J. Anaesthesiol. Clin. Pharmacol.* 34, 155–160
48. Khalil, H. *et al.* OPRM1 and COMT Gene-Gene Interaction Is Associated With Postoperative Pain and Opioid Consumption After Orthopedic Trauma. *Biol. Res. Nurs.* 19, 170–179 (2017).
49. Fillingim, R. B. *et al.* The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. *J. pain* 6, 159–67 (2005).
50. Hasvik, E. *et al.* Subjective health complaints in patients with lumbar radicular pain and disc herniation are associated with a sex - OPRM1 A118G polymorphism interaction: a prospective 1-year observational study. *BMC Musculoskelet. Disord.* 15, 161 (2014).
51. Linnstaedt, S. D. *et al.* μ-Opioid Receptor Gene A118 G Variants and Persistent Pain Symptoms Among Men and Women Experiencing Motor Vehicle Collision. *J. pain* 16, 637–44 (2015).
52. Olsen, M. B. *et al.* Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction. *J. Neurosci.* 32, 9831–4 (2012).
53. Belfer, I., Young, E. E. & Diatchenko, L. Letting the gene out of the bottle: OPRM1 interactions. *Anesthesiology* 121, 678–80 (2014).
54. Belfer, I. *et al.* Pain modality- and sex-specific effects of COMT genetic functional variants. *Pain* 154, 1368–76 (2013).
55. Boudíková, B., Szumlanski, C., Maidak, B. & Weinshilboum, R. Human liver catechol-O-methyltransferase pharmacogenetics. *Clin. Pharmacol. Ther.* 48, 381–9 (1990).
56. Schendzielorz, N., Rysa, A., Reenila, I., Raasmaja, A. & Mannisto, P. T. Complex estrogenic regulation of catechol-O-methyltransferase (COMT) in rats. *J. Physiol. Pharmacol.* 62, 483–90 (2011).
57. van Reij, R. R. I., Joosten, E. A. J. & van den Hoogen, N. J. Dopaminergic neurotransmission and genetic variation in chronification of post-surgical pain. *Br. J. Anaesth.* 123, 853–864 (2019).



Section III

Opioids after paediatric cardiac surgery

Chapter 7

Postoperative breakthrough pain in paediatric cardiac surgery is not reduced by increased morphine concentrations

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Pediatr Res. 2021

Abstract

Background

Morphine is commonly used for postoperative analgesia in children. Here, we studied the pharmacodynamics of morphine in children after cardiac surgery receiving protocolized morphine.

Methods

Data on morphine rescue requirements guided by validated pain scores in children (n = 35, 3 to 36 months) after cardiac surgery receiving morphine as loading dose (100 μg/kg) with continuous infusion (40 μg/kg/h) from a previous study on morphine pharmacokinetics were analysed using repeated Time-to-Event (RTTE) modelling.

Results

During the postoperative period (38 (IQR 23 to 46) hours), 130 morphine rescue events (4 (IQR 1 to 5) per patient) mainly occurred in the first 24h (107/130) at a median morphine concentration of 29.5 ng/ml (range 7-180 ng/ml). In the RTTE model, the hazard of rescue morphine decreased over time (half-life 18 hours; $p<0.001$), while the hazard for rescue morphine (21.9% at 29.5 ng/ml) increased at higher morphine concentrations ($p<0.001$).

Conclusion

In this study on protocolized morphine analgesia in children, rescue morphine was required at a wide range of morphine concentrations and further increase of the morphine concentration did not lead to a decrease in hazard. Future studies should focus on a multimodal approach using other opioids or other analgesics to treat breakthrough pain in children.

Introduction

Even though opioids are commonly used for pain treatment after major surgery in children, there is no consensus on the type and dose of analgesics to be used. Ineffective postoperative pain management increases the risk of delayed recovery, adverse behavioural and physiological responses[1]. A recent international survey of management of pain and sedation after paediatric cardiac surgery showed a large worldwide variability in choice and dosing of analgesics and sedatives after cardiac surgery in children[2]. The most commonly used drug was morphine, with a wide variation in continuous infusion dose from 10 to 60 µg/kg/h in children aged 0 to 36 months.

The pharmacokinetics of morphine have been studied extensively across the paediatric population in different kind of settings[3], including cardiac surgery[4,5]. Morphine is primarily metabolized through glucuronidation by UGT2B7[6]. Elimination of morphine directly reflects the formation of its two pharmacologically active metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Even though cardiac surgery is associated with changes in hepatic blood flow and tissue perfusion, no difference was reported in elimination clearance in children after major cardiac surgery compared to non-cardiac surgery[4]. Despite all the pharmacokinetic data of morphine, there are only a handful of reports studying morphine pharmacodynamics by relating morphine concentrations to pharmacodynamic endpoints. Two studies investigated the effect of morphine on pain during endotracheal tube suctioning in preterm neonates[7,8]. One study did not find a relation between morphine concentrations and changes in heart rate or the preterm infant pain profile (PIPP), while the other study with the use of Item Response Theory modelling found a weak relationship between morphine concentrations and procedural pain reduction, as established with COMFORT-B and VAS assessments. Recently, Elkomy et al. described the pharmacodynamics of morphine when given as repeated bolus doses in infants and young children after cardiac surgery, by modelling the repeated time-to-event (RTTE) of morphine administration[9]. This methodology quantifies the hazard for events, with in this study the hazard being defined as the expected number of rescue morphine doses per hour in an individual patient. Translating these events into a hazard allows us to demonstrate if factors like time, morphine concentrations or age have impact on the efficacy of morphine reflected by the expected number of rescue doses.

To date there is a paucity of data on the pharmacodynamics of morphine in young children after cardiac surgery when given as continuous infusion with rescue boluses. The objective of this study is to analyse using RTTE modelling the

analgesic efficacy of morphine when given as maintenance and rescue analgesic within the context of a standardized postoperative pain protocol with regular pain and distress measurements.

Methods

Clinical study

Data were collected during an observational, prospective study in 3 to 36-months-old children, which was performed at the Department of Anaesthesia and Intensive Care Medicine of Our Lady's Children's Hospital, Dublin[5]. The study protocol was approved by the local ethics committee and written informed consent for the study was obtained from the parents preoperatively. The main results including the population pharmacokinetic analysis of the morphine concentration time samples of 35 children have been reported before[5].

In short, patients with and without Down syndrome were included when between 3 and 36 months of age and scheduled for cardiac surgery with cardiopulmonary bypass for atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defect (AVSD), or tetralogy of Fallot (TOF) repair. Exclusion criteria were epilepsy, cerebral palsy or birth asphyxia, history of cardiothoracic surgery through sternotomy, preoperative mechanical ventilation, preoperative treatment with morphine or midazolam, and extracorporeal membrane oxygenation treatment after cardiopulmonary bypass.

All patients received standardized anaesthesia during cardiac surgery as well as standardized postoperative pain and distress management guided by pain and distress assessments by the caregiving nurse with a numeric rating scale (NRS) and the COMFORT-Behaviour scale (COMFORT-B). Morphine was administered as the primary analgesic agent at the end of surgery as a loading dose (100 μg/kg), followed by a continuous infusion of 40 μg/kg/h. In addition to morphine, intravenous acetaminophen was administered three times daily in the first 24 hours after surgery in a dose of 7.5 or 15 mg/kg, depending on weight (i.e. below or above 10 kg, respectively). In case of unacceptable pain (i.e. score combinations of COMFORT-B greater than 16 and NRS greater than 3), additional morphine boluses (20 to 40 μg/kg) were administered, and/or morphine maintenance infusion rates were increased. For rescue sedation, midazolam boluses (0.05 to 0.1 μg/kg) as needed was available. If further escalation for sedation was needed midazolam infusion (0.06 to 0.15 mg/kg/h) or enteral chloral hydrate (25 to 50 mg/kg every 6 h) was started. During the stay at the paediatric intensive care unit (PICU), the morphine dose was gradually decreased. Data collection was stopped

when intravenous morphine was switched to oral morphine, or on discharge from the PICU. Further details are described in the original article[5].

Repeated Time to Event modelling

In the present study, we used a repeated time-to-event (RTTE) model to estimate the hazard for a morphine rescue event during protocolized analgesia after cardiac surgery. The input data for a RTTE analysis consists of the times at which patients experience a morphine rescue event, which was defined as an additional bolus of morphine, an increase in infusion rate of the morphine infusion, or a restart of the infusion after a minimum break of 15 minutes and the times at which patient follow up stops (i.e. censoring event). Depending on the hazard model, the likelihood (L) of the observed event and censoring data is defined by:

$$L(event) = h(t) \times e^{-cumh(t)}$$

$$L(censoring) = e^{-cumh(t)}$$

Where *h(t)* is the hazard of needing rescue for an individual patient at the time of the event, and *cumh(t)* is the area under the hazard-time curve between the time of the previous event (or the time of follow-up start if the patient did not experience an event before time *t)* and the time *t* (the time of the event or the time of censoring).

Structural hazard model and covariate model

For the structural hazard model, baseline hazard models such as the constant hazard, Gompertz and Weibull models were tested to describe the effect of time after surgery on the hazard throughout the study period[10]. In addition, circadian-variation of the hazard after surgery was explored[11]. Morphine, M3G, and M6G concentrations as measured in the participants of the study and published before[5] were tested for their influence on the effect on the hazard for a morphine rescue event using immediate or delayed (i.e. with an effect compartment) drug effect models based on Emax or exponential functions. Finally, we explored the influence of covariates age, Down syndrome (yes/no), mechanical ventilation (yes/no) as predictors of inter-individual variability of the hazard. Potential covariates were tested in the repeated time-to-event model using the likelihood ratio test in a stepwise forward inclusion (α=0.05) and backwards elimination (α=0.01) procedure[12].

Model evaluation

Modelling was performed using NONMEM 7.3. Discrimination between models was made by the likelihood ratio test using the objective function value (OFV, i.e., -2

log likelihood [-2LL]). A decrease of 3.84 in the OFV value between nested models with one degree of freedom, representing a P-value of ≤ 0.05, was considered statistically significant. In addition, the kernel-based visual hazard comparison (kbVHC) was used to evaluate the model's ability to characterize the mean hazard over time[13]. In this method, CV_{target} controls the smoothness of the non-parametric hazard estimate of the kbVHC and this was set to 30%.

Results

Clinical study results

An overview of patient characteristics is shown in Table 1. The median age of the 35 children at surgery was 5.7 months (interquartile range (IQR) 4.3 to 8.3 months). The median postoperative study period at the PICU was 38 hours (IQR 23 to 46). During the first 24 hours, the median total dose of morphine was 940 μg/kg (IQR 116 to 183) or 31.3 μg/kg/h (24 to 36). On day 2, the median morphine dose was 320 μg/kg (IQR 102 to 524) or 16 μg/kg/h.

Figure 1 illustrates the median individual concentrations of morphine in the children over time. The figure shows that as a result of the postoperative pain protocol consisting of a loading dose with continuous infusion, the morphine concentrations are the highest directly after surgery and reached steady state after about 200 minutes. In the first 3 to 4 hours after surgery, morphine concentrations decreased from an average of 60 to 25 ng/ml (Figure 1). Overall these concentrations are, particularly in the first 24h hours, higher than a previously proposed target range for morphine of 10 to 20 ng/ml.

Over the study period, a total of 130 rescue morphine events were identified. The majority of events (n = 107) occurred in the first 24 hours, while the remaining events (n = 23) were in the second 24 hours. A total of 30 (86%) patients received a rescue dose of morphine, with a median of 4 rescue events (IQR 1-5) per patient. Of the 130 rescue events, 114 events (88%) concerned rescue boluses, 9 events (7%) were an increase in infusion rate and 7 patients (5%) received a bolus followed by an increase in infusion rate. Median time between events was 2.6 hours (IQR 1.1 to 4.5 hour). Of the 100 events that occurred after a previous event, 24% occurred within one hour of the previous event. Figure 2 shows the time points of the rescue morphine events with the corresponding morphine concentrations. Median morphine concentrations immediately prior to a rescue event were 29.5 ng/ml (IQR 23 to 43) with a range of 7 to 180 ng/ml. In total, 111 (85%) events occurred above a concentration of 20 ng/ml.

Table 1. Patient characteristics and details of postoperative administration of IV morphine

Variable	Patients (n = 35)
Male	15 (42.9)
Gestational age, weeks	39.0 (38.0 to 40.6)
Age at surgery, months	5.7 (4.3 to 8.3)
Weight at surgery, kg	6.1 (5.2 to 7.7)
Height at surgery, cm	65 (60 to 68)
Trisomy	21 (55.3)
Indication of surgery	
Atrial septal defect	1 (2.9)
Ventricular septal defect	9 (25.7)
AVSD	16 (45.7)
TOF	9 (25.7)
Morphine, day 1 (0 to 24 h), n = 35 patients	
Mean infusion rate, μg/kg/h	31.3 (24.1 to 36.1)
Total morphine, μg/kg	940 (784 to 1040)
Events	107 (82.3)
Morphine, day 2 (24 to 48 h), n = 25 patients*	
Mean infusion rate, μg/kg/h	16.0 (12.0 to 21.5)
Total morphine, μg/kg	320 (102 to 524)
Events	23 (17.7)
Midazolam	
Boluses per patient	4 (0 to 7)
Patients with infusion	13 (37.1)
Chloral hydrate boluses	0 (0 to 1)

*Data collection stopped according to protocol when patients were switched to oral morphine or discharged from the PICU
Data are presented as median (interquartile range) or number (%).
AVSD, atrioventricular septal defects; TOF, Tetralogy of Fallot.

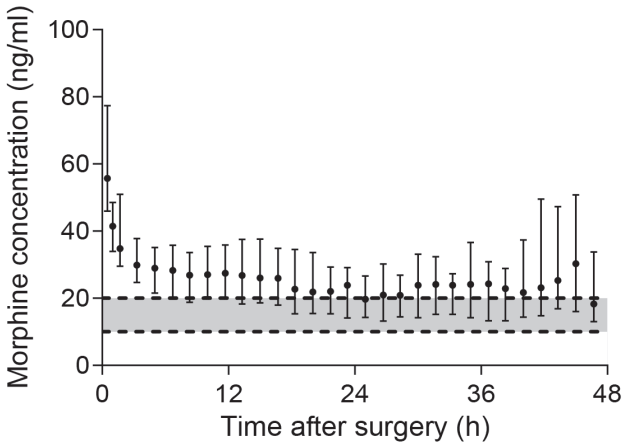


Figure 1. Median morphine concentrations versus time after surgery.
The whiskers indicate interquartile range. The number of patients is decreasing over time according to protocol when patients were switched to oral morphine or discharged from the PICU. The grey area indicates an earlier proposed therapeutic range of morphine (10 to 20 ng/ml)[15]. Data was derived from the earlier published PK model[5] that was based on the patients of the current study. The median postoperative study period at the PICU was 38 hours (IQR 23 to 46).

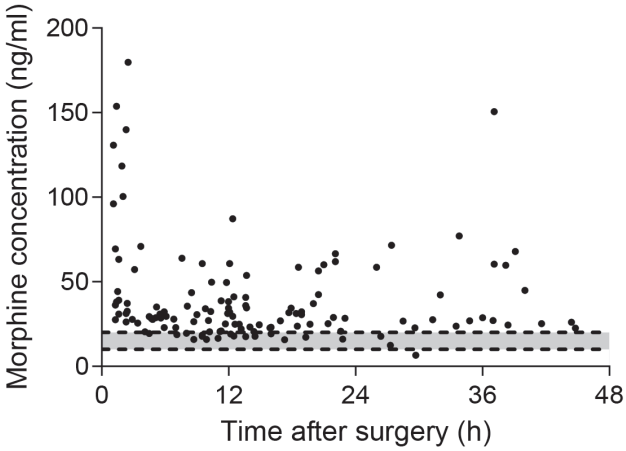


Figure 2. Morphine concentrations immediately prior to a rescue event versus time after surgery.
Solid black circle: rescue event which was defined as an additional bolus of morphine, an increase in infusion rate of the morphine infusion, or a restart of the infusion after a minimum break of 15 minutes. The grey area indicates an earlier proposed therapeutic range of morphine (10 to 20 ng/ml)[15].

Repeated Time to Event modelling

For the structural model describing the base hazard for a morphine rescue event, a Gompertz model was identified of which the parameters can be found in Table 2. The addition of morphine concentration as a predictor of individual deviations in the hazard, resulted in a statistical significant improvement of the model fit ($p<0.001$, Table 2). The hazard for rescue morphine increased at higher morphine concentrations (21.9% at the median concentration of 29.5 ng/ml).

Table 2. Parameter estimates of final pharmacokinetic-pharmacodynamic model of rescue morphine

Parameter (unit)	Submodel	Estimate (RSE)
Gompertz hazard	$HAZ_{base} \times e^{(HAZ_{slope} \times time_{since\ start})}$	
HAZ_{base} (h^{-1})		0.138(0%)
HAZ_{slope} (h^{-1})		-0.0387 (5%)
Morphine effect	$e^{(EFF_{morphine} \times C_{mor})}$	
$EFF_{morphine}$ (ml ng^{-1})		0.0067 (20%)
Inter-individual variability	$e^{(\eta i)}$	
Frailty ω^2 (-)		0.303 (30%)

Hazard is defined as expected number of events per time unit. The final hazard model is:

$$HAZ_{base} \times e^{(HAZ_{slope} \times time_{since\ start})} \times e^{(EFF_{morphine} \times C_{mor})} \times e^{(\eta i)}.$$

Where $Hazard_i$ = individual hazard estimate of subject i; HAZ_{base} = base hazard when $time_{since\ start}$ is 0; HAZ_{slope} = exponential slope base hazard over time; $time_{since\ start}$ = hours since patient started initial morphine infusion; $EFF_{morphine}$ = slope of exponential morphine effect; C_{mor} = morphine concentration in ng ml^{-1}; ηi = posthoc estimate of the individual frailty term of subject i; Frailty ω^2 = variance of frailty term; RSE = relative standard error

Figure 3 illustrates the identified exponential influence of morphine on the hazard showing that only small changes are expected below a morphine concentration of 100 ng/ml. At higher concentrations, the hazard for rescue medication increases more rapidly, however the number of observations are small. This results in a wider confidence interval at morphine concentrations higher than 50 ng/ml, indicating large uncertainty of the obtained function at higher concentrations.

For morphine and metabolite concentrations, adding an effect compartment or other drug effect models (i.e. Emax or exponential) did not improve the model (deltaOFV > 3.84).The model did also not improve significantly when circadian variation or the concentration of M3G or M6G were implemented as predictors for variability ($p>0.05$). Covariates such as age, Down syndrome and mechanical ventilation were not identified as a covariate with statistically significant impact on the model fit. The parameter estimates of the final model describing the hazard for rescue morphine in children after cardiac surgery are listed in Table 2. Figure

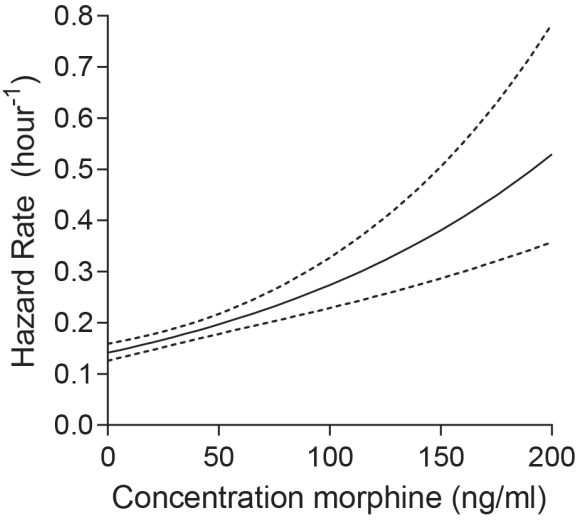


Figure 3. Hazard versus concentration of morphine
Concentration-effect relationship of morphine on the hazard of rescue morphine in children after cardiac surgery as estimated with the final repeated time-to-event model. The dotted lines demarcate the 95% confidence interval.

4 shows the results of the model validation plot kbVHC which illustrates that the hazard directly after surgery (HAZ_{base}) decreases over time after surgery (HAZ_{slope}, $p<0.001$) with a half-life of 18 hours. The figure also shows the comparison of the mean individual predicted hazard obtained with the final model versus the non-parametric kernel-based hazard. While the model-predicted and the non-parametric hazard both decreased over time, implying a good description of the data, the peak in the non-parametric hazard at 24 hours is not captured well by the model (Figure 4).

Discussion

In this study, data were analysed from 35 children aged 3 to 31 months after cardiac surgery who were treated according to a postoperative pain protocol consisting of a morphine loading dose of 100 µg/kg at the end of surgery followed by a continuous infusion of 40 µg/kg/h. Morphine rescue doses were given as bolus doses and/or increased continuous infusions. Prior research on the pharmacodynamics has mainly focussed on the relation between morphine concentrations and pain scores, experimental pain models, or surrogate endpoints such as pupil size[14]. In contrast, the current analysis uses the administration of rescue morphine as a clinically relevant event or indicator for lack of effect of the

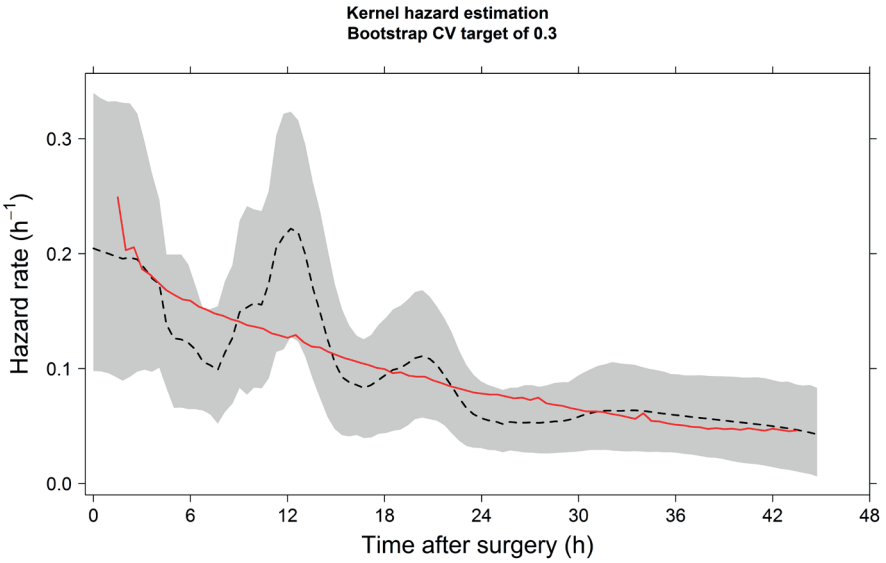


Figure 4. Model evaluation of the final PKPD model using the kbVHC.
Red solid line represents the mean of the model predicted individual hazard estimates. The black dashed line depicts the non-parametric kernel-based hazard in the data and the grey shaded area the 95% confidence interval.

current morphine dose. To this end, rescue events were identified and related to the corresponding morphine concentration, which was found to vary widely. RTTE modelling revealed that the hazard for rescue morphine decreased over time and increased when the morphine concentration increased ($p<0.05$). Here, we discuss the occurrence of rescue events in relation to the morphine concentration, the results of the RTTE analysis and the use of morphine for the treatment of breakthrough pain.

In our study, we identified 130 morphine rescue events during which rescue morphine was given following a standardized pain protocol, which was guided by COMFORT-B and NRS scores. These events of confirmed presence of pain were observed upon a standardized loading dose at the end of surgery followed by a continuous infusion. The concentrations of morphine that were found in this study were relatively high (Figure 1). Previously, a steady state target plasma concentration of morphine after major surgery in children and neonates of 10 to 20 ng/ml has been suggested[15]. The upper limit of 20 ng/ml is mainly based on one study where respiratory effects were reported after morphine infusion (median time of 20 h) in 30 children, aged 2 days to 1.6 years, undergoing cardiac surgery[16]. In another study in neonates and infants (0 to 52 weeks) after abdominal or thoracic

surgery, it was concluded adequate analgesia in neonates was provided with morphine trough concentrations between 15.4 and 22 ng/ml, whereas this was between 1.0 and 7.5 ng/ml for infants older than 4 weeks[17]. In the current study, concentrations of morphine were on average higher than 20 ng/ml, particularly in the first 3 to 4 hours after surgery. Comparing these concentrations is difficult without knowledge on the required target for different surgical procedures and populations. In our study, median morphine concentrations immediately prior to an event were 29.5 ng/ml with a range of 7 to 180 ng/ml with the majority of events (n = 111 (85%)) occurring above 20 ng/ml (Figure 2). These results indicate that more morphine is unlikely to reduce the number of events in patients. It therefore seems that, for now, titrating on effect is the only reasonable advice we can provide. In this respect, it would be interesting to investigate what the role is of individuals that are unlikely to respond to morphine rescue (i.e. non-responders). In other fields of research such as cancer patients or postoperative adult patients, non-response to morphine has been described[18–20]. The underlying mechanism of non-response is not known nor which patients are more prone to have absence of response to morphine or other opioids.

When focusing on the relationship between morphine concentration and the hazard for events which was analysed using RTTE modelling, we could not identify a reduction in hazard for rescue dosing upon an increase in morphine concentration. On the contrary, we identified an increased hazard for rescue medication upon higher morphine concentrations. However, as Figure 3 shows, the confidence interval in the steep part of the curve is wide, indicating that the actual increase in hazard as a result of increased morphine concentration could in fact also be small and/or confused by the delay in effect of morphine when given for breakthrough pain resulting in repeated dosages without awaiting the full effect. A recent study by Elkomy et al. investigated the pharmacodynamics of morphine in 20 children between 3 days to 5 years of age after cardiac surgery when using morphine boluses only[9]. In their study, a morphine concentration of 19.6 ng/ml resulted in a 50% reduction of the hazard for redosing with a wide 95% confidence interval of 5.9 to 49.5 ng/ml. The difference between their results and the concentration-effect relationship of morphine in our study might be related to the difference in study design, with Elkomy et al. studying morphine effects without continuous morphine infusion. The results of our study were obtained in the context of a morphine protocol consisting of both continuous and rescue doses, which reflects the current practice of postoperative care in children after cardiac surgery. The wide confidence intervals found for the concentration – effect relation of morphine in the two studies may indicate that the relation between the concentration of morphine and its efficacy is likely not very strong when studied

in the direct postoperative phase after cardiac surgery in children. Theoretically, opioid tolerance as well as opioid induced hyperalgesia could have played a role regarding the hazard that increases with increasing morphine concentrations. However, there are no studies in postoperative cardiac surgery infants that support this hypothesis.

Breakthrough pain is ideally treated by a fast-acting and highly effective analgesic. Our data shows that of the 100 events that occurred after a previous event, 24 (24%) events occurred within 1 hour of a previous event. This suggests that many of the rescue morphine dose given during the previous event did not adequately address the pain. In line with these observations, the results of our RTTE analysis demonstrated that an increase in morphine concentration does not result in a decrease in the hazard for rescue events, and could even result in an increase in hazard for a rescue event. One explanation for these results could be that morphine has a relatively long time to analgesic action, particularly when compared to short-acting opioids such as fentanyl and alfentanil[21]. While the concentration of morphine has been reported to reach its maximum as early as 20 minutes after intravenous bolus injection, the reported delay between peak blood drug concentration and peak pharmacodynamic effect reflected by a $t_{1/2ke0}$ is 1.6 to 3.9 h in volunteers and 1.7 h in postoperative patients, while for alfentanil and fentanyl a much shorter $t_{1/2ke0}$ (i.e. 1 and 6 min, respectively) has been reported[22,23]. Administration of more morphine as rescue treatment within a protocol of a continuous infusion of morphine should therefore be reconsidered, particularly in those cases where multiple rescue events occur within a short time frame. Instead, multimodal strategies should be further explored for the treatment of breakthrough pain in children[24].

From these results, it seems that studies aiming improving postoperative pain management should compare different dosing strategies (bolus dose versus increasing continuous infusion rate or both), the use of other opioids for breakthrough pain and/or the use of other non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs[25] or acetaminophen. Optimal use of intravenous acetaminophen is currently being studied in combination with, or as replacement for, morphine with the goal of improving postoperative pain management for children[26].

This study has potential limitations. First, this was a single centre, observational study which has its known limitations. Second, our analysis rests on the assumption that morphine reliefs pain in infants after cardiac surgery while this topic is still under debate, despite morphine being the most used analgesic after cardiac surgery[2]. In addition, the effect of morphine in this study is determined

by the events that are identified by nurses giving additional morphine rescue according to their protocol. Therefore, adherence to the pain protocol was of extra importance, while pain assessment in children is generally difficult. In our opinion, this reflects daily practice on the PICU and therefore it is not expected that this substantially influences our conclusions. In addition to this, it may well be that other factors such as requirements for sedation during mechanical ventilation and the treatment of discomfort have played a role. Pain assessment in children can be extremely challenging and while current measurement instruments like the COMFORT scale are validated[27], it is still difficult to differentiate between pain and agitation or distress in infants. Another limitation is that we could not identify a delay in morphine effect in relation to morphine concentration or a diurnal variation in the hazard that is suggested in the observations (Figure 4). Finally, the original study design has its own limitations such as unknown impact of altered PK after cardiopulmonary bypass, systemic inflammation, haemodilution, low cardiac output or impaired liver/kidney function. Also, the requirements of inotropics/vasopressors were not noted[5].

In conclusion, in this study on protocolized morphine analgesia in children, rescue morphine was required at a wide range of morphine concentrations and further increase of the morphine concentration did not lead to a decrease in hazard. Therefore, future research should focus on a multimodal approach using other opioids or other analgesics to treat breakthrough pain in children.

Acknowledgements

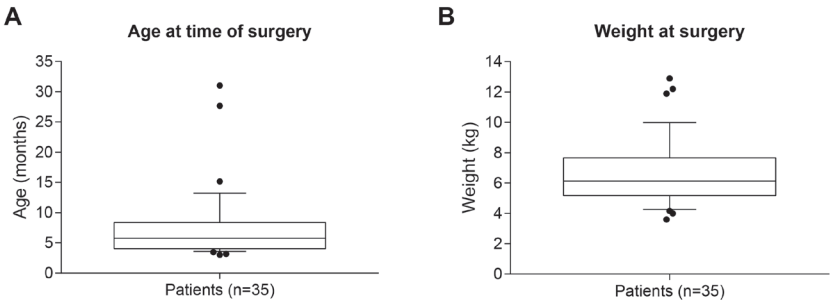
The authors thank Cormac V Breatnach, Department of Anaesthesia and Critical Care Medicine, Our Lady's Children's Hospital, Dublin, Ireland for his contribution to the original study and Ko Hagoort, Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands for text editing.

Literature

1. Weisman, S. J., Bernstein, B. & Schechter, N. L. Consequences of inadequate analgesia during painful procedures in children. *Arch. Pediatr. Adolesc. Med.* 152, 147–149 (1998).
2. Zeilmaker-Roest, G. A. *et al.* An international survey of management of pain and sedation after paediatric cardiac surgery. *BMJ Paediatr. Open* 1, e000046 (2017).
3. Krekels, E. H., Tibboel, D., Danhof, M. & Knibbe, C. A. Prediction of morphine clearance in the paediatric population : how accurate are the available pharmacokinetic models? *Clin. Pharmacokinet.* 51, 695–709 (2012).
4. Elkomy, M. H. *et al.* Pharmacokinetics of Morphine and Its Metabolites in Infants and Young Children After Congenital Heart Surgery. *AAPS J.* 18, 124–133 (2016).
5. Valkenburg, A. J. *et al.* Pharmacodynamics and Pharmacokinetics of Morphine After Cardiac Surgery in Children With and Without Down Syndrome. *Pediatr. Crit. Care Med.* 17, 930–938 (2016).
6. Coffman, B. L., Rios, G. R., King, C. D. & Tephly, T. R. Human UGT2B7 catalyzes morphine glucuronidation. *Drug Metab. Dispos.* 25, 1–4 (1997).
7. Anand, K. J. *et al.* Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br. J. Anaesth.* 101, 680–689 (2008).
8. Valitalo, P. A. *et al.* Morphine Pharmacodynamics in Mechanically Ventilated Preterm Neonates Undergoing Endotracheal Suctioning. *CPT pharmacometrics Syst. Pharmacol.* 6, 239–248 (2017).
9. Elkomy, M. H., Drover, D. R., Galinkin, J. L., Hammer, G. B. & Glotzbach, K. L. Pharmacodynamic Analysis of Morphine Time-to-Remedication Events in Infants and Young Children After Congenital Heart Surgery. *Clin. Pharmacokinet.* 55, 1217–1226 (2016).
10. Juul, R. V *et al.* Repeated Time-to-event Analysis of Consecutive Analgesic Events in Postoperative Pain. *Anesthesiology* 123, 1411–1419 (2015).
11. Junker, U. & Wirz, S. Influence of circadian rhythms on the therapy of severe pain. *J. Oncol. Pharm. Pract.* 16, 81–87 (2010).
12. Hutmacher, M. M. & Kowalski, K. G. Covariate selection in pharmacometric analyses: a review of methods. *Br. J. Clin. Pharmacol.* 79, 132–47 (2015).
13. Goulooze, S. C., Valitalo, P. A. J., Knibbe, C. A. J. & Krekels, E. H. J. Kernel-Based Visual Hazard Comparison (kbVHC): a Simulation-Free Diagnostic for Parametric Repeated Time-to-Event Models. *AAPS J.* 20, 5–9 (2017).
14. Martini, C., Olofsen, E., Yassen, A., Aarts, L. & Dahan, A. Pharmacokinetic-pharmacodynamic modeling in acute and chronic pain: an overview of the recent literature. *Expert Rev. Clin. Pharmacol.* 4, 719–728 (2011).
15. Anderson, B. J. & Holford, N. H. Pharmacokinetics and pharmacodynamics of analgesic drugs. in *Pain in Neonates and Infants: Pain Research and Clinical Management Series* (eds. Anand, K. J., Stevens, P. B. & McGrath, P.) 128 (Elsevier, 2009).
16. Lynn, A. M., Nespeca, M. K., Opheim, K. E. & Slattery, J. T. Respiratory effects of intravenous morphine infusions in neonates, infants, and children after cardiac surgery. *Anesth. Analg.* 77, 695–701 (1993).
17. Bouwmeester, N. J., van den Anker, J. N., Hop, W. C., Anand, K. J. & Tibboel, D. Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br. J. Anaesth.* 90, 642–652 (2003).

18. Roberts-Thomson, I. C., Jonsson, J. R., Pannall, P. R. & Frewin, D. B. Morphine responders with unexplained pain after cholecystectomy may have sympathetic overactivity. *Clin. Auton. Res.* 1, 59–62 (1991).
19. Riley, J. *et al.* No pain relief from morphine? Individual variation in sensitivity to morphine and the need to switch to an alternative opioid in cancer patients. *Support. Care Cancer* 14, 56–64 (2006).
20. Gram, M. *et al.* Prediction of postoperative opioid analgesia using clinical-experimental parameters and electroencephalography. *Eur. J. Pain* 21, 264–277 (2017).
21. Aubrun, F., Mazoit, J.-X. & Riou, B. Postoperative intravenous morphine titration. *Br. J. Anaesth.* 108, 193–201 (2012).
22. Mazoit, J. X., Butscher, K. & Samii, K. Morphine in postoperative patients: pharmacokinetics and pharmacodynamics of metabolites. *Anesth. Analg.* 105, 70–78 (2007).
23. Lötsch, J. Pharmacokinetic-pharmacodynamic modeling of opioids. *J. Pain Symptom Manage.* 29, S90-103 (2005).
24. Duedahl, T. H. & Hansen, E. H. A qualitative systematic review of morphine treatment in children with postoperative pain. *Paediatr. Anaesth.* 17, 756–74 (2007).
25. Saini, A., Maher, K. O. & Deshpande, S. R. Nonopioid analgesics for perioperative and cardiac surgery pain in children: Current evidence and knowledge gaps. *Ann. Pediatr. Cardiol.* 13, 46–55
26. Zeilmaker-Roest, G. A. *et al.* Intravenous morphine versus intravenous paracetamol after cardiac surgery in neonates and infants: a study protocol for a randomized controlled trial. *Trials* 19, 318 (2018).
27. van Dijk, M. *et al.* The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. *Pain* 84, 367–377 (2000).

Supplemental Material



Supplemental Figure 1. Age (A) and weight (B) distribution of the included patients (n = 35). Whiskers indicate the 10 and 90th percentile.

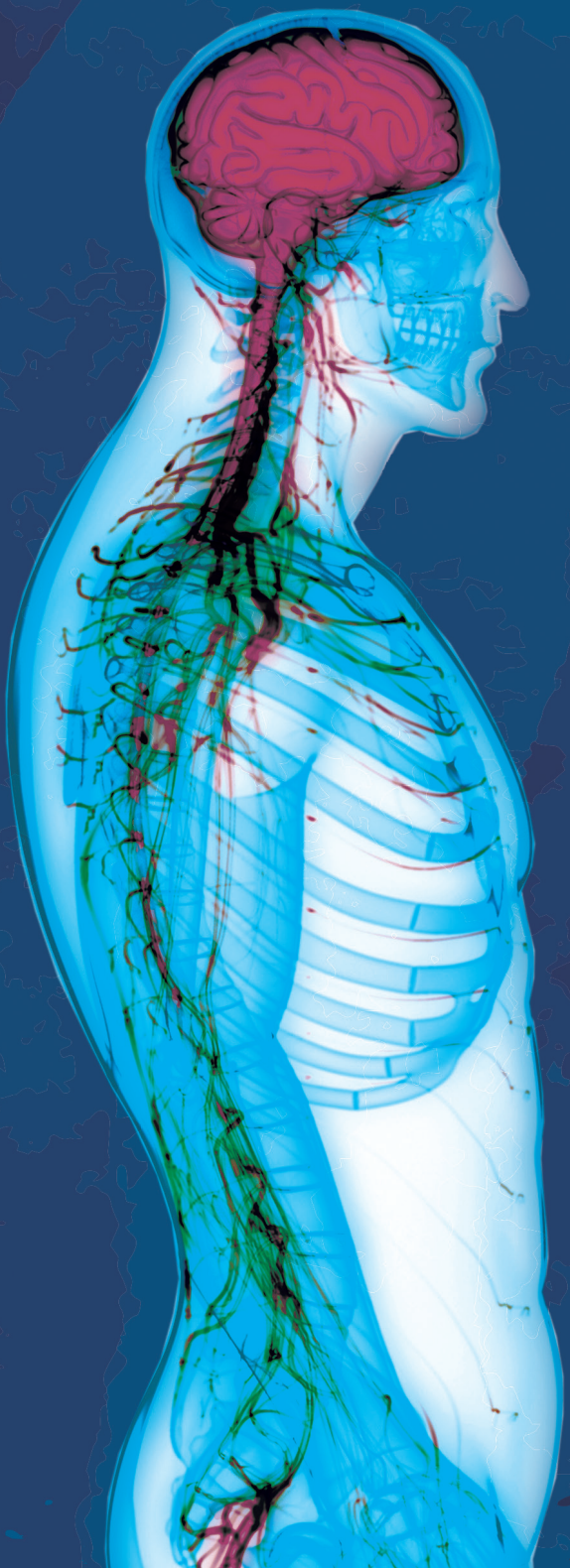
Supplemental file – NONMEM model code of final model

```
$SUBROUTINE ADVAN13 TOL=9

$MODEL
COMP    ; (CENTRAL,DEFOBS)              ; Morphine central compartment
COMP    ; (M3G)
COMP    ; (M6G)
COMP    ; (PERIPH)
COMP    ; (CENTRAL,DEFDOSE)             ;Midazolam central compartment
COMP    ; (PERIPHERAL)
COMP    ; (METAB-1_OH)
COMP     ;(METAB -1OHG)
COMP    ; (METAB, PERIP-1OHG)
COMP    ; (METAB -4OH)
COMP ; (CUMHAZ1)                        ; Cum. hazard of morphine rescue


$PK
IF (A_0FLG.EQ.1) THEN
A_0(5)=0
ENDIF
V1        = MORF_V1
QM3F    = MORF_QM3F
QM3E    = MORF_QM3E
V2        = MORF_V2
QM6F = MORF_QM6F
QM6E = MORF_QM6E
V3        = MORF_V3
Q12       = MORF_Q1
V4        = MORF_V4
CL3       = MIDA_CL3
V5        = MIDA_V1
CL1       = MIDA_CL1
Q56       = MIDA_Q
V6        = MIDA_V2
CL2       = MIDA_CL2
V9         = MIDA_V5
V8         = V9
```

```
VSS      = V5+V6
V7       = MIDA_V3
V10      = V7
Q89      = MIDA_Q1
CL4      = MIDA_CL4
CL5      = MIDA_CL5

K12 = QM3F/V1
K20 = QM3E/V2
K13 = QM6F/V1
K30 = QM6E/V3
K14 = Q12/V1
K41 = Q12/V4

K56=Q56/V5
K65=Q56/V6
K57=CL1/V5
K78=CL2/V3
K80=CL3/V7
K89=Q89/V9
K98=Q89/V9
K510=CL4/V5
K100=CL5/V7

VSS = V1 + V2
S1=V1
;S2=V2
S3=V3
S4=V4
S6=V6
S7 = V7
S8 = V8
S9 = V9

TALPHA = THETA(1)/60
ALPHA1= TALPHA *EXP(ETA(1))
SLPE = THETA(2)
TSLOPE=THETA(3)/60
```

```
$DES
DELT = T - START + 0.001
IF (DELT.GT.0) THEN
HAZNOW = ALPHA1 * EXP(SLPE * (A(1)/V1))* EXP(TSLOPE*DELT)
ELSE
HAZNOW = 0
ENDIF

DADT(1) =K41* A(4)- (K12+ K13+K14)*  A(1)
DADT(2) =K12* A(1)-  K20* A(2)
DADT(3) =K13* A(1)-  K30* A(3)
DADT(4) =K14* A(1)-  K41* A(4)
DADT(5) =-A(5) * K57-  A(5)* K56+  A(6)        *  K65    -  K510  *  A(5)     ;
DADT(6) =K56* A(5)-  K65* A(6)
DADT(7) =K57* A(5)-  K78* A(7)
DADT(8) =K78* A(7)-  K80* A(8)-  K89  *  A(8)+K98 * A(9)
DADT(9) =K89* A(8)-  K98* A(9)
DADT(10) =K510  * A(5)-  K100* A(10)
DADT(11) = HAZNOW

$ERROR
Cmida=A(5)/V5
CM3G = A(2)/V2
CM6G = A(3)/V3
Cmor=A(1)/V1 ;
PerMorf = A(4)

CUMHAZ1=A(11)

DELTAT = TIME - START + 0.001
IF (DELTAT.GT.0) THEN
HAZ1 = ALPHA1*EXP(TSLOPE * DELTAT)* EXP(SLPE * Cmor)
ELSE
HAZ1 = 0
ENDIF

PHAZ = TALPHA*EXP(TSLOPE * DELTAT)* EXP(SLPE * Cmor)
IF(NEWIND.NE.2) CUMLAST=0
CUMDIFF = CUMHAZ1 - CUMLAST
```

```
IF(DV.EQ.0.AND.MDV.EQ.0) THEN
Y=EXP(-(CUMHAZ1-CUMLAST))
ENDIF

IF(DV.EQ.1.AND.MDV.EQ.0) THEN
Y=EXP(-(CUMHAZ1-CUMLAST)) * HAZ1
CUMLAST = CUMHAZ1
ELSE
CUMLAST=CUMLAST
ENDIF

PX= Y
$THETA
(0.00001, 0.15) ; HAZbase
(-0.05) ; EFFmorphine
(-0.02) ; HAZslope

$OMEGA
0.567
```



Section IV

Pharmacokinetics of opioids in obese patients

Chapter 8

Obesity and drug pharmacology: A review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters

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Sjoerd de Hoogd
Roger J.M. Brüggemann
Catherijne A.J. Knibbe

Expert Opin Drug Metab Toxicol. 2018;14(3):275-285

Abstract

Introduction

Rising prevalence of obesity confronts clinicians with dosing problems in the (extreme) overweight population. Obesity has great impact on key organs that play a role in the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, however the ultimate impact of these changes on how to adapt the dose may not always be known.

Areas covered

In this review, physiological changes associated with obesity are discussed. An overview is provided on the alterations in absorption, distribution, drug metabolism and clearance in (morbid) obesity focusing on general principles that can be extracted from pharmacokinetic studies. Also, relevant pharmacodynamics considerations in obesity are discussed.

Expert opinion

Over the last two decades, increased knowledge is generated on PK and PD in obesity. Future research should focus on filling in the knowledge gaps that still remain, especially in connecting obesity-related physiological changes with changes in PK and/or PD and vice versa. Ultimately, we can use this knowledge to develop physiologically based PK and PD models on the basis of quantitative systems pharmacology principles. Moreover, efforts should focus on thorough prospective evaluation of developed model-based doses with subsequent implementation of these dosing recommendations in clinical practice.

Introduction

Since the 1980s, the global prevalence of obesity, which is defined as a body mass index (BMI) > 30 kg/m^2, has increased alarmingly[1]. In 2015, more than 100 million children and 600 million adults were estimated to be obese worldwide[2]. In 2014, nationwide representative surveys in the United States showed that 35-40% of the adult population met the criteria for obesity[3]. Recently, several leading medical associations classified obesity as a disease[4].

Obesity and in particular morbid obesity is known to influence several physiological processes such as gut permeability, gastric emptying, cardiac output, liver- and renal function[5]. As a consequence, pharmacokinetic (PK) properties of drugs may be altered in (morbidly) obese patients[6–8]. In addition, the pharmacodynamics (PD) of drugs may be different in obesity. For instance, benzodiazepines or opioid analgesics may have a more pronounced effect in obesity because of the increased incidence of obstructive sleep apnoea (OSA) in obese individuals. As a result, for different reasons adjusted doses may be necessary in obese patients. Although the number of publications on this topic is increasing over the last decades, evidence on PK, PK/PD and drug dosing strategies for specific drugs in obesity remains scarce, particularly for morbidly obese patients.

An important strategy for characterizing drug PK/PD profiles in special populations such as the obese is a model-based approach in which nonlinear mixed effect modelling has been instrumental[9]. With this approach PK and/or PD is modelled on a population level, while concurrently quantifying the inter-individual variability. Subsequently, it is assessed how patient-specific characteristics (covariates) can (partially) explain observed differences between patients. The fact that this approach can adequately deal with limited data makes it particularly suited for application in PK/PD of special populations such as neonates and children, but also for other special populations such as the obese.

Ideally, pharmacological and physiological knowledge obtained from different drugs and studies is integrated to identify drug-specific and system-specific properties that can be employed to guide drug dosing in the future [9]. To aid in this concept, this review aims to give an overview of the different physiological changes in obesity and to provide an update of the current knowledge on the influence of these changes in (morbid) obesity on different PK and/or PD parameters.

Obesity-related physiological changes

Obesity is defined as a body mass index (BMI) ≥ 30 kg/m^2, with morbid or severe obesity generally being defined as a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 kg/m^2 with

comorbidities[10]. It has become widely accepted that obesity is characterized by a chronic low-grade inflammation state of adipose tissue[11]. Together with significant anatomical and physiological alterations, this could influence the PK and/or PD of drugs.

In obesity, gut wall permeability as well as gastric emptying has been reported to be accelerated with obesity[12–14]. To provide nutrients and oxygen to the excess tissue, blood volume, capillary flow and cardiac output also increase in obese patients[15–17]. With this enhancement in cardiac output, liver blood flow is expected to increase with flow into the liver as the fraction of cardiac output remains stable[15]. However, due to non-alcoholic fatty liver disease (NAFLD) resulting in steatosis or steatohepatitis (NASH) together with sinusoidal narrowing, liver blood flow might decline over time, particularly in morbidly obese individuals[18,19]. Total protein concentrations and serum albumin seem to be unaltered by obesity, while alpha 1-acid glycoprotein (AAG) seems to be elevated in morbidly obese patients, although contradicting studies exist regarding the latter[20,21]. Effects of obesity on pulmonary function have been well established. Lung volumes, especially the residual capacity and expiratory reserve volume, are negatively correlated with BMI[22,23]. Furthermore, obesity is associated with asthma and can lead to OSA or obesity hypoventilation syndrome (OHS)[24]. The effect of obesity on renal function appears ambiguous, since some studies report an increase in glomerular filtration rate (GFR), while others show that severe overweight is strongly correlated with chronic kidney disease (CKD)[25–27]. It is now generally believed that during the lifespan of an obese patient, renal clearance is initially enhanced by a compensatory hyperfiltration and hyperperfusion, though eventually declines as a result of a constantly elevated intra-glomerular pressure[25,27]. An overview of physiological changes associated with obesity is shown in Figure 1.

Body size descriptors

Beside total body weight (TBW) in (morbidly) obese patients, other body size descriptors have been proposed to guide drug dosing (Table 1). Lean body weight (LBW) or fat free mass (FFM) globally represents bone tissue, muscles, organs and blood volume and was reported to relate well with renal function in obesity [28,29]. Strictly, in contrast to FFM, LBW does include a small fraction of adipose tissue (cellular membrane lipids) and therefore does not always exactly correspond to FFM. However, in relation to TBW, this portion is generally small (3-5%) and therefore these two descriptors can in general be used in the same way[29]. LBW or FFM is commonly calculated using the Janmahasatian method, taking into account TBW, height and gender[29]. Since the introduction of this formula, LBW is increasingly

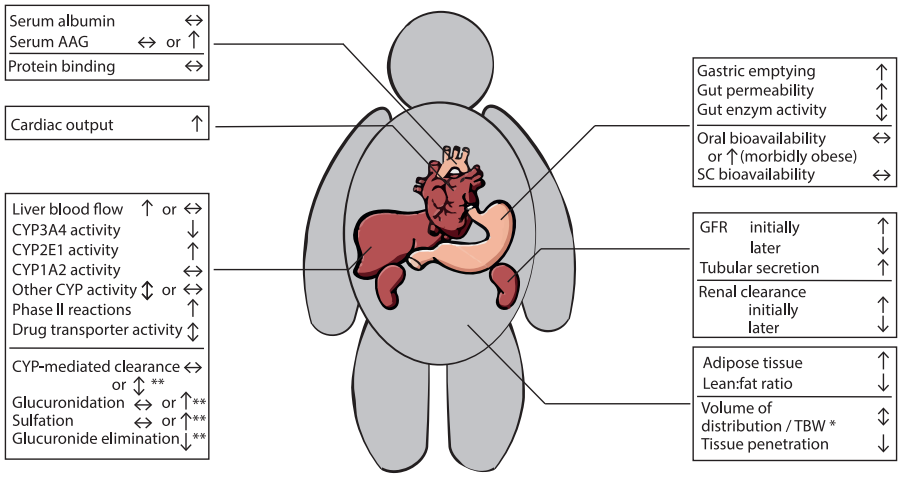

Figure 1. Summary of physiological changes in obesity and corresponding effects on PK parameters. ↑ increases with obesity, ↓ decreases with obesity, ↕ can either increase or decrease with obesity, ↔ unaltered with obesity. AAG, alpha 1-acid glycoprotein; GFR, Glomerular Filtration Rate; TBW, total body weight.

being proposed as a body size descriptor in obesity pharmacology, especially for renally cleared drugs[30]. However, as LBW also takes gender into account with higher LBW in males compared to females even when TBW is the same, it should be realized that the use of this descriptor leads to substantially higher dosages in males compared to females, even in case of similar body weights[29]. Therefore, when conducting a PK study, both genders should be included in sufficient amount as gender is a driver in the calculation of LBW. Besides TBW and LBW, other body size descriptors such as ideal body weight (IBW) or adjusted body weight have occasionally been proposed to guide drug dosing for specific drugs[31–33], even though to date there seems limited interest in these scalars. BMI, widely used in defining and quantifying obesity, as a descriptor of body shape and not body composition, also seems less suitable for use as body size descriptor for drug dosing in the obese[34]. Finally, estimated body surface area (BSA) is traditionally used when dosing cancer chemotherapy[35]. From this overview, it seems that each body size descriptor has its own (dis)advantages for application in drug dosing in obesity, while no body size descriptor has been shown to be universally applicable for prediction of PK parameters in obesity[36]. Besides the body side descriptor, also the scaling factor is of relevance when relating parameters to weight. While one may anticipate a linear (scaling factor of 1) or allometric (scaling factor of 0.75) function between TBW and clearance, assuming that obese individuals differ only in being larger than normal weight individuals, this seems a considerable simplification[34].

In this respect it is also important to realize that for instance LBW and BSA relate in a nonlinear manner to TBW[6]. As a consequence, the use of another descriptor will influence the value of the exponent or scaling factor. Moreover, even though an increase in a certain parameter or dose may be anticipated for obese individuals, plasma clearance or volume of distribution is not always reported to increase or might even decrease, implying a zero or negative value for the scaling factor[6,7].

Influence of obesity on pharmacokinetic and pharmacodynamic parameters

Obesity and drug absorption

After oral ingestion of a drug, the absorption from the intestine is determined by the rate of absorption (k_a) and the total amount of drug absorbed (bioavailability, or F). F is dependent upon fraction absorbed (F_a) and gut and hepatic (first pass) metabolism (F_g and F_h). Since it is known that, in obesity, gut permeability increases and gastric emptying is accelerated, while CYP-mediated gut and or liver metabolism might also be affected, it is plausible that obesity influences overall oral absorption[7,12–14,41]. Although beyond the scope of this review, we know that in addition to obesity itself, also diet and bariatric surgery might greatly affect PK in terms of rate and/or extend of drug absorption. Therefore, obese individuals are prone to changes in F or k_a.

The classic approach to quantify F is by obtaining data after both oral and intravenous (IV) administration of a drug within the same subjects on separate occasions. However, since this method requires an experimental setting and a washout period, only few such studies have been done in the obese population[42–47]. In these studies, regarding cyclosporine, dexfenfluramine, midazolam, moxifloxacin, propranolol and trazodone, no significant differences were observed in bioavailability or (if reported) rate of absorption between obese and lean subjects, although for propranolol, a trend towards a higher bioavailability was observed[45].

Another method to determine oral bioavailability is via a semi-simultaneous design, in which F can be studied in a single occasion[48,49]. A disadvantage of this approach is that absorption has to be virtually complete before the IV formulation is administered, which may be difficult to predict in obese patients. Nevertheless, a semi-simultaneous study design can provide useful information on drug absorption in morbidly obese patients as was demonstrated for midazolam[50]. In this trial, morbidly obese subjects undergoing bariatric surgery received midazolam orally, followed by an IV dose after 150 minutes. In this study, a higher

Table 1. Body size descriptors with corresponding formula's.

Body size descriptor	Formula	Reference
Total body weight (TBW)	-	-
Body Mass Index (BMI)	$\mathrm{BMI\ (kg/m^2)} = \frac{\mathrm{TBW\ (kg)}}{\mathrm{HT^2\ (m^2)}}$	37
Body Surface Area (BSA)	$\mathrm{BSA\ (m^2)} = 0.007184 \times \mathrm{TBW\ (kg)}^{0.425} \times \mathrm{HT\ (m)}^{0.725}$	38
Ideal Body Weight (IBW)	$\mathrm{IBW\ (female, kg)} = 45.4 + 0.89 \times (\mathrm{HT\ (cm)} - 152.4)$	39
Adjusted Body Weight (ABW)	$\mathrm{ABW\ (kg)} = \mathrm{IBW} + \mathrm{F} \times (\mathrm{TBW} - \mathrm{IBW})$ F = drug specific correction factor (generally 0.3-0.6)	40
Lean Body Weight (LBW)	$\mathrm{LBW\ (male, kg)} = \frac{9.27 \times 10^3 \times \mathrm{TBW\ (kg)}}{6.68 \times 10^3 + 216 \times \mathrm{BMI\ (kg/m^2)}}$ $\mathrm{LBW\ (female, kg)} = \frac{9.27 \times 10^3 \times \mathrm{TBW\ (kg)}}{8.78 \times 10^3 + 244 \times \mathrm{BMI\ (kg/m^2)}}$	29

F in the obese group (60% vs. 28%) was found. The increase in F was hypothesized to be related to a decreased gut CYP3A4 activity and/or an increased gut blood flow or permeability[44,50]. Notably, in contrast to the earlier mentioned 'classic approach' studies, where some included obese subjects with average body weights of <120 kg, the latter midazolam study included patients with mean body weight of 144 kg (range 112 to 186 kg). Therefore, it might be possible that alterations in F are only significant in severely obese individuals.

In addition to these results, studies on orally administered levothyroxine and acetaminophen found a delay in time to peak concentration (T_{max}) in morbid obesity compared to lean subjects[51,52]. In contrast, for morphine, similar absorption rates were found in morbidly obese patients in comparison to what is found in healthy volunteers[53,54]. It should however be noted that T_{max} is also determined by elimination clearance and therefore does not necessarily represent drug absorption rate. Unfortunately, in these studies no data were obtained after IV administration, hence no definite conclusions can be drawn upon bioavailability of these drugs. Despite this limitation, the authors of the acetaminophen study do relate the fact that they found a lower area-under-the-curve (AUC) in the obese population to a

lower bioavailability. It can however not be excluded that the lower AUC is caused by an augmented drug clearance rather instead of hampered bioavailability, which was reported later in another study[55].

Since morbidly obese patients are characterized by an excess of (subcutaneous) adipose tissue, one could hypothesize that drug absorption from parenteral forms such as intramuscular or subcutaneous injection might be altered as well in obese patients. Only few studies have assessed drug absorption in these situations. Enoxaparin was investigated in a study in moderately obese (mean TBW 100 kg, range 78 to 144 kg) and non-obese volunteers[56]. Participants received enoxaparin subcutaneously once daily for four consecutive days and once intravenously with a washout period of at least seven days in between. No difference in F was observed between obese and non-obese individuals. In another study, twelve moderately obese Chinese women (BMI 28.2 to 32.8 kg/m^2) and twelve non-obese women (BMI 19.8 to 22.0 kg/m^2) were given an intramuscular and subcutaneous injection with a fixed dose of 10.000 IU of human chorionic gonadotropin with a four week interval[57]. In this population, the AUC was substantially lower in the obese group with both routes of administration. While this may be caused by a decreased absorption in obesity, another explanation could be an increased clearance in the obese individuals. In addition, in two other studies a delayed absorption in obese patients was seen for subcutaneous administered insulin lispro, but not for nadroparin[58,59]. For nadroparin, also an increase in apparent clearance with body weight was reported which may not only be the result of an increase in clearance but could theoretically also be due to a decrease in (subcutaneous) bioavailability. However, as in this study no information was available upon IV administration of nadroparin, we cannot distinguish between the two explanations.

With respect to drug absorption, it seems that the evidence on the effect of (severe) obesity is limited. Despite an apparent increase in gut permeability and possible decrease in gut CYP3A4 metabolism in obesity, only for midazolam an increased bioavailability was reported[50]. Since in the midazolam study severely obese patients were studied, it could be speculated that bioavailability is only significantly increased in case of extreme obesity. The drug absorption rate or bioavailability from subcutaneous injections seems to be unaltered in obesity, however there is not yet enough evidence to draw firm conclusions.

Obesity and drug distribution

Volume of distribution (V_d) is an important theoretical PK parameter defining the peak concentration (C_{max}) after each dose of a drug, and, together with drug clearance, determines the elimination half time of a drug. The first is of particular

significance for choosing the optimal loading dose, the latter for time to reach steady state in a multiple dosage regimen.

In morbidly obese patients, changes in V_d might depend on several drug properties, such as the lipophilicity of the drug, ionization properties, blood:plasma ratio and protein binding[60,61]. As such, lipophilicity alone does not necessarily predict the change in V_d[5,60]. In theory, lipophilic compounds are expected to easily diffuse into adipose tissue, and therefore V_d is expected to increase with TBW for these drugs. This principle is illustrated in study with diazepam[62]. In this study in six moderately obese and five normal weight subjects, this highly lipophilic drug shows a dramatic increase in V_d with increasing body weight. On the contrary, hydrophilic drugs are expected to be restricted to aqueous compartments such as blood and extracellular water. Since the volume of these compartments does not linearly increase with TBW, V_d/TBW is expected to decrease for these drugs. This is delineated by ranitidine, a hydrophilic drug, in which one study showed that V_d/TBW decreased in obese subjects[63]. However, as stated earlier, lipophilicity does not necessarily predict changes in V_d[5]. For example, propofol and digoxin, both (highly) lipophilic drugs, do not show an increase in V_d in obese patients[64,65]. In addition, it has been shown that the V_d of vancomycin, which is a water-soluble drug, shows a strong linear increase with TBW[66,67]. As such, lipophilicity should be considered only one of the drug properties to consider when predicting changes in volume of distribution related in obesity.

Concerning serum protein concentrations in obesity, albumin and total protein concentrations seem to be unaltered between lean and obese subjects, although AAG, which is particularly important in binding basic drugs, could be elevated in morbid obese patients[20]. Differences in protein binding in relation to PK parameters such as V_d or CL in obese and non-obese patients have been assessed in studies concerning alprazolam, cefazolin, daptomycin, lorazepam, midazolam, oxazepam, propranolol and triazolam[21,44,68–71]. In these studies, unbound concentrations appeared unchanged in morbidly obese patients. In addition to unbound fractions, the study with daptomycin also reported serum albumin concentrations, which were unaltered in morbid obesity[70]. In the propranolol study, albumin concentrations were reduced, with AAG serum concentrations unaltered[21]. While the latter is in contrast with what was reported earlier[20], this explains the unchanged protein binding for propranolol, which is mainly AAG-bound. In a study regarding clindamycin in obese children, V_d decreased with increasing AAG and albumin serum concentrations[72]. Unfortunately, unbound clindamycin concentrations were not measured, so it remains unclear whether free concentrations were influenced[72].

Another important aspect of drug distribution in morbidly obese individuals concerns tissue penetration. This can be especially relevant for antibiotics used for localized infections or perioperative prophylaxis, where sufficient tissue concentrations need to be achieved in order to be effective. To measure concentrations at the target site, it is for instance possible to measure drug concentrations in the epithelial lining fluid for pulmonary penetration or in interstitial fluid (ISF) using microdialysis techniques[73,74]. Drug concentrations in the ISF are measured by inserting a probe, which is continuously perfused with a physiological solution, in the tissue of interest. A major advantage of this method is that it enables us to measure the unbound (pharmacologically active) drug on multiple time-points. This is in contrast with the classic approach that uses tissue biopsy specimens, which are homogenized before measurement of drug concentrations. As a consequence, overall drug concentrations are determined, thereby mixing up intra- and extracellular concentrations, and both bound and unbound concentrations, instead of the pharmacologically active, unbound, drug concentration only. Since most anti-infective drugs are distributed exclusively to the intra- or extracellular space, PK studies employing this technique should be interpreted with caution[75,76].

So far, studies regarding tissue penetration in morbid obesity using microdialysis have been done for cefazolin, cefuroxime and ciprofloxacin[69,77,78]. Ciprofloxacin was administered as a single IV bolus dose to twelve obese subjects (mean weight 122 ± 22.6 kg) and twelve normal weight controls, after which ciprofloxacin concentrations were measured in plasma and ISF of skeletal muscle and subcutaneous tissue[77]. Plasma concentrations of ciprofloxacin were significantly higher in the obese, while ISF concentrations were similar. The authors conclude that, to yield adequate concentrations in peripheral tissue, ciprofloxacin should be dosed on actual body weight, although it is unclear whether the resulting high (peak) plasma concentrations might lead to increased side effects. Besides, fluoroquinolones are primarily used in pulmonary infections or urinary tract infections. Since tissue penetration in these organ systems may be different from subcutaneous tissue, future research should focus on whether the same hampered tissue penetration also applies for these organ systems[79]. For cefazolin, which is commonly used as a prophylactic agent during surgery, a study using microdialysis techniques showed that in morbidly obese patients (mean weight 140 kg, range 107 to 175 kg) cefazolin concentrations in the ISF of the subcutaneous tissue were significantly lower after a single 2 g IV dose compared to non-obese patients[69]. Subsequent Monte Carlo simulations demonstrated a reduced probability of target attainment for obese patients with a BMI > 40 kg/m^2, with specifications for different minimal inhibitory concentrations and duration of surgery. As a consequence, the Dutch guidelines

for perioperative antibiotic prophylaxes prescribe for morbidly obese patients a single dose of 3 g cefazolin instead of 2 g[80]. Lastly, a microdialysis study in six obese patients (109 to 140 kg) showed that cefuroxime distributed extensively into ISF in muscle and subcutaneous tissue and seems to yield adequate concentrations for common pathogens such as *Staphylococcus aureus*, but not for *Escherichia coli*[78]. Unfortunately, no control group was included in this study, so no definite conclusions can be made upon changes in tissue penetration in obese versus non-obese individuals.

In conclusion, it is evident that changes in volume distribution are difficult to predict upfront based on drug properties such as lipophilicity alone, and that ionization properties, blood:plasma ratio and protein binding need to be taken into account as well. Protein serum concentrations seem unaltered in obese, with the exception of AAG which is reported to be elevated in some studies. Nonetheless, it has not been shown that this leads to relevant pharmacokinetic changes yet. Lastly, differences in tissue penetration between obese and non-obese individuals can be significant. Until now, this has been studied for several antibiotics. In studies regarding cefazolin and ciprofloxacin, tissue penetration was significantly reduced. As a result, higher dosages and/or increased frequency of dosing might be necessary even when this leads to higher plasma concentrations.

Obesity and drug clearance

As clearance impacts the maintenance dose of drugs, it is generally considered as the PK parameter with the greatest impact for clinical applications.

The liver forms the main organ responsible for drug metabolism, where enzymes are responsible for modification and conjugation of drugs (phase I and II reactions, respectively). It is noted that these reactions can also take place in other tissues such as plasma, kidneys or the gut wall. Hepatic drug metabolism is dependent on intrinsic liver clearance (Cl_{int}), which is determined by enzyme activity and transporters in the liver. Together with hepatic blood flow (Q_h) and protein binding (f_u), Cl_{int} determines the hepatic plasma clearance (Figure 2). Variation in these parameters may more or less influence the hepatic plasma clearance of a drug depending on its hepatic extraction ratio. The extraction ratio depicts the efficiency of an organ to clear a drug from the circulating blood. High extraction ratio drugs typically have a clearance independent of enzyme capacity or plasma protein binding and depend primarily on hepatic blood flow. In contrast, the clearance of low or intermediate extraction ratio drugs is mainly dependent of the intrinsic metabolizing capacity of the liver (Figure 2).

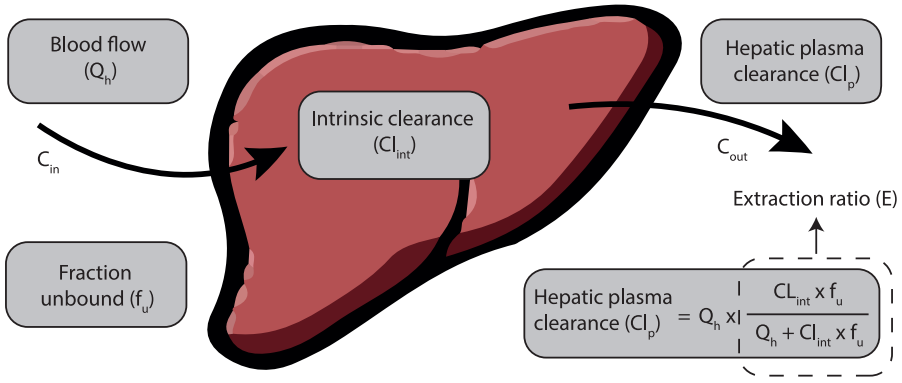

Figure 2. Overview of processes involved in hepatic metabolism. Intrinsic clearance (Cl_{int}) is influenced by enzyme activity and transporters in the liver. Together with the fraction unbound (f_u) and hepatic blood flow (Q_h), Cl_{int} determines the hepatic plasma clearance (Cl_p). The extent to which Cl_p is influenced by variation in these parameters depends on the extraction ratio E, with high extraction ratio drugs mainly being influenced by Q_h, and medium to low extraction ratio drugs mainly being influenced by Cl_{int}.

In obesity, the prevalence of liver abnormalities is extremely high and in patients undergoing bariatric surgery, can exceed over 90%[81]. Abnormal fat deposition and inflammation in the liver results in a range of conditions from steatosis to NASH and can influence hepatic enzyme and drug transporter expression and/or activity as well as liver blood flow. With respect to the influence of obesity on hepatic blood flow, different scenarios can be hypothesized. While it is known that cardiac output increases with obesity, one study showed that liver blood flow increases with liver blood flow being a percentage of cardiac output[15]. This was confirmed with studies on propofol and fentanyl, where an increased clearance with increasing TBW was seen[64,82–84]. Since both drugs are high extraction drugs, changes in clearance are expected to represent changes in liver blood flow. However, due to fatty liver disease, liver microcirculation was shown to decrease in animal models[19].

When considering Cl_{int}, hepatic drug metabolism is generally divided into phase I and phase II reactions. Phase I reactions are mediated by enzymes, the most important being the cytochrome P450 system. About 50% of all metabolized drugs are metabolized by CYP3A4, which is primarily present in hepatocytes and the gut wall. Midazolam is primarily metabolized by CYP3A and generally considered a probe for CYP3A enzyme activity. Several animal and in vitro human studies showed a reduced CYP3A4 activity related to obesity or NAFLD[85–88]. It has been hypothesized that low-grade inflammation decreases expression of pregnane

X receptor (PXR) and constitutively activated receptor (CAR) resulting in less expression of certain CYP enzymes, including CYP3A4[89]. However, in morbidly obese patients, midazolam plasma clearance appeared to be unchanged when compared to healthy volunteers[44,50]. Since midazolam is considered a medium-to-high extraction ratio drug, it might be possible that reduced CYP3A4 activity is compensated by an increased liver size or liver blood flow. A follow-up study in the same study population one year later showed that, after weight loss, midazolam clearance exceeded clearance in the non-obese population. To explain this, it was hypothesized that CYP3A4 activity is restored, thereby surpassing the expected reduction in liver size after bariatric surgery[90].

Besides CYP3A, other CYP enzymes are involved in phase I drug metabolism, albeit to a much smaller extent. Orally administered chlorzoxazone, which is a probe drug for CYP2E1, has a higher metabolic clearance (CL/F) in obese patients compared to non-obese subjects[91]. Unfortunately, the number of participants in this study was small and chlorzoxazone was not administered IV, so CL could not be assessed apart from F. An increase in CYP2E1 activity might be likely as this was also seen in another study where acetaminophen was administered intravenously in obese patients[55]. In contrast to CYP3A4 and CYP2E1, no significant impact of obesity on CYP1A2 activity was seen in a study regarding caffeine, which is metabolized via this enzyme. In this study, where caffeine was administered in an oral dose of 200 mg to obese and non-obese subjects, CL/F was comparable in both groups[92].

Given the potential pathophysiological effects of obesity on the human body, duration of obesity might also be an important factor in hepatic metabolism. This is illustrated by the results on a study on midazolam in obese adolescents and obese adults where in obese adolescents, mean midazolam clearance was higher compared to obese adults[93]. These results are surprising as body weights were similar in these two populations. Particularly because in (non-obese) adolescents typically lower clearance values may be assumed for which 0.75 allometric scaling on the basis of body weight is relatively undebated[94,95]. Therefore, the larger clearance in obese adolescents was explained by the lack of suppression of CYP3A in view of the relative short duration of obesity compared to obese adults. Similar results were found for clearance of fentanyl (a high extraction ratio drug for which liver blood flow is relevant) which appeared larger in obese adolescents compared to literature values in obese adults which may aim at less liver changes with respect to liver flow in obese adolescents compared to obese adults[96]. Finally, a strong positive correlation was found between the severity of hepatic steatosis and increase in CYP2E1-mediated metabolic clearance of chlorzoxazone, which adds to this hypothesis[91].

Phase II conjugation reactions generally seem to be elevated in morbid obesity, as can be illustrated by studies performed with low-to-medium extraction ratio drugs such as acetaminophen, oxazepam and lorazepam[55,71]. When glucuronidation and sulfation of acetaminophen in morbidly obese patients were studied together with data from healthy volunteers in a meta PK analysis, a significant increase in both of these pathways was found[55]. Also in the studies regarding oxazepam and lorazepam, of which excretion is primarily dependent on glucuronidation, drug clearance markedly increased in the obese population[71].

However, recent studies on morphine which is also mainly glucuronidated showed somewhat surprising results. In these studies, higher morphine glucuronide concentrations were seen in obese compared to non-obese as well in NASH patients[97–99]. Two of these studies showed similar morphine concentrations together with increased glucuronide concentrations, which indicated no significant increase in glucuronidation, but instead a decrease in clearance of glucuronides[98,99]. As discussed earlier, the lack of increase in glucuronidation clearance may be explained by the fact that morphine is a medium-to-high extraction ratio drug, assuming liver blood flow was unchanged in these populations. A decreased elimination clearance of morphine glucuronides in both obese and NASH patients might be explained by the involvement of drug transporters such as multidrug resistance proteins (MRP) 2 and 3. It was shown in rat models that NASH, commonly associated with obesity, influences transporter expression[100]. These specific transporters are responsible for the transport of bile acids, anionic drugs and hepatically derived metabolites (such as glucuronides) from hepatocytes to the blood plasma (MRP3) or hepatocytes to the bile (MRP2)[101]. The results from the morphine studies led to the conclusion that elimination of glucuronides is possibly decreased due to a suppression of MRP2 and upregulation of MRP3 in obese patients[98,99].

Over the last years, increasing evidence is generated on altered drug transporter function in obesity. Despite the fact that literature is still scarce, most knowledge has been generated on transporter activity in NASH, a condition that is common in the obese population[81]. In addition to earlier described changes in MRP2 and MRP3, studies suggest that NASH might also influence the functionality of other drug transporters such as organic anion transporting polypeptides (OATP) and organic anion transporters (OAT), which play an important role in uptake of several drugs such as statins or angiotensin-converting enzyme (ACE)-inhibitors such as enalapril[102,103].

In conclusion, based on the provided examples, it is clear that predicting drug clearance in obesity for hepatically metabolized drugs is challenging. In general,

enzyme activity of CYP2E1 and phase II metabolism seems to increase, while CYP3A4 activity seems to decrease and CYP1A2 is likely to be unaffected. However, for translating these results into overall plasma clearance, several factors should be taken into account, such as drug properties like extraction ratio, liver size, duration of obesity and an additional influence from transporters (see also Figure 2). Regarding renal drug clearance, the relationship between obesity and kidney function is complex, since obesity is associated with an enhanced renal function, but also an important risk factor for the development of CKDs[25,104].

In clinical practice, GFR is often estimated using creatinine clearance (CL_{cr}) as a surrogate estimate. In these situations, estimated GFR (eGFR) is calculated by imputing serum creatinine in a formula together with other patient characteristics such as race, age, gender or body weight. Nowadays, mostly the modification of diet in renal disease (MDRD) and the CKD and epidemiology (CKD-EPI) formulas are employed, of which the latter has the advantage that it is also accurate in renal functions above 60 mL/min/1.73 m^2 [105]. However, these methods express eGFR normalized to BSA (mL/min/1.73 m^2), and tend to overestimate the GFR in patients with a large body weight when corrected for BSA and expressed as absolute eGFR in mL/min[106,107]. This is also the case with the Cockcroft-Gault (CG) formula, which uses TBW to estimate CL_{cr}. For example, calculation of CL_{cr} using CG formula with TBW in morbidly obese subjects overestimated clearance with +107.4 mL/min compared to CL_{cr} measured with 24-h urine collection[106]. Recently, several studies suggest to use LBW in the CG formula to adequately estimate GFR in obese patients[106–108]. This seems plausible, since it was shown that LBW normalizes changes in GFR in obese patients[28].

As a consequence of an enhancement in GFR, it might be expected that drug excretion increases in obesity when renal drug excretion is dependent upon GFR. For instance, gentamicin, tobramycin and vancomycin, almost exclusively excreted unchanged via urine, showed an increased clearance in morbidly obese patients[40,66,67]. In contrast, this influence of obesity on drug clearance was not seen for cefazolin or fluconazole, both renally excreted drugs that showed similar total drug clearances in morbidly obese subjects[69,109]. However, fluconazole was studied in a group of obese and non-obese critically ill patients with no differences in CL_{cr} within these groups[109]. In the study regarding cefazolin, even though renal function was anticipated to be unaffected, no CL_{cr} or eGFR values were reported while in addition the sampling time may have been too short to pick of changes in clearance[69]. An increase in renal excretion in obese is also consistently seen in several studies on oseltamivir and its active metabolite oseltamivir carboxylate, both undergoing active renal tubular secretion besides GFR-mediated clearance[110–112],

indicating that tubular secretion might also be augmented in obese. This was supported by studies regarding procainamide, metformin and ciprofloxacin, drugs that undergo active tubular secretion, where an increase in clearance was seen in obese patients or with increasing body weight[113–115]. These drugs are partly excreted via the organic cation transporters (OCT) drug transporter system, which might be enhanced in NASH or obesity. Although a trend in increased OCT2 renal expression was seen in a mouse study, this hypothesis remains uncertain[116]. In another study, clearance of lithium was shown to be enhanced in obesity, even though no difference in CL_{cr} was found[117]. The authors conclude that an increase in lithium clearance could be explained by an impaired tubular reuptake of lithium in overweight patients.

In summary, despite an initial increase in GFR in overweight patients, renal drug clearance does not necessarily increase. This might be explained by the fact that on the longer term, GFR might actually decrease in obesity. Another possibility is that studied patients might have a reduced renal function due to comorbidities such as sepsis. The distinction between glomerular and tubular processes in renal excretion is difficult. However, it appears that, in general, tubular secretion is enhanced in obesity. A summary of relevant physiological changes in obesity and corresponding effects on PK parameters is shown in Figure 1.

Obesity and pharmacodynamic changes

While much pharmacological research in obesity focusses on drug PK, this might not necessarily suffice for translation to an optimized drug dosing regimen. More evidence shows that PD changes, i.e. a difference in drug efficacy or toxicity even when corrected for PK differences, play an important role as well. For example, adipocytes secrete adipokines such as leptin, which reduces macrophage and T-cell differentiation and activity[118]. It has been demonstrated that due to this cross talk between adipose tissue and the immune system, several infectious diseases in obese patients are associated with a worse outcome compared to the normal weight population. It can be hypothesized that not only PK changes of antimicrobial drugs (leading to lower plasma concentrations) but also changes in drug effectiveness (due to changes in the immune system) could underlie a worsened outcome from infections[118]. An interesting example of the relevance of changes in the PD is depicted by the intravenous anaesthetic propofol. The PK/PD profile of propofol was investigated in twenty morbidly obese patients, based on propofol blood concentrations and bispectral index monitoring[64]. Clearance increased allometrically with an exponent of 0.72, but similar maximal effect (E_{max}) or propofol concentrations at half-maximum effect (E_{50}) were observed for obese individuals when compared to literature values of lean subjects. In contrast, a

more recent Chinese PD study showed similar results on PK, with an increased clearance in morbid obesity, but a reduction in E_{50} for obese individuals[82]. The authors hypothesize that this might be caused by an increased sensitivity of the brain to propofol. Also, differences in co-medication might underlie these differences, even though both obese and non-obese patients underwent similar gastrointestinal surgery. For reasons of changes in PD, the authors advise LBW-based dosing of propofol, where lower plasma concentrations yield similar sedative effects[82]. Another example of a PD study was done with the neuromuscular blocking agent atracurium, for which in a PK study a similar V_d and Cl in obese and non-obese patients was found[119]. Whether atracurium should be dosed on TBW or IBW was investigated in a subsequent PD study[33]. In this study, twenty morbidly obese patients (range 112 to 260 kg) were randomised to receive either atracurium dosed on TBW or IBW. The PD endpoint, i.e. time to recovery of the neuromuscular blockade, was significantly prolonged in the TBW group. It was concluded that atracurium should be dosed on IBW, since this gave full recovery after 60 minutes, allowing conditions for adequate intubation and no antagonists would be needed[33]. A last example of a possible difference in PD in obese can be found in the use of hypnosedative agents. As stated earlier in this review, obesity is associated with OSA. In theory, hypnosedative agents such as benzodiazepines or opioid analgesics could worsen OSA-related symptoms by reducing effective breathing. Despite the fact that deleterious effects of these drugs on parameters such as apnoea-hypopnoea index or oxygen saturation are still under debate, caution is advised when sedative drugs are used in obese patients with OSA[120,121].

To conclude, only few studies have been done including PD parameters in morbid obesity. To be able to adequately translate PK models into dosing regimens for certain pharmacological domains, for example anaesthetics, antibiotics or sedatives, more research is warranted on PD of these drugs in obesity.

Expert opinion

Since the prevalence of obesity is appallingly increasing, physicians and pharmacists are increasingly confronted with drug dosing problems in (severely) overweight patients. Fortunately, more evidence on PK and to a lesser extent on PD in morbid obesity is generated, particularly in the last two decades. However, as we showed in this review, we are still unsure what the exact effect of obesity is for many drugs. This relates to the fact that there is a lack of specific and quantitative information on obesity related changes in physiological parameters like hepatic blood flow, gastric permeability and enzyme and transporter activity. It is clear that translation of a single drug property into a subsequent effect on a

PK parameter, as has been tried with lipophilicity and volume of distribution, is not adequate and tends to oversimplify the matter.

Despite more insight in the changing metabolic and elimination pathways associated with obesity, there are still gaps in our current knowledge. The lack of studies that simultaneously investigate oral and IV administered drugs in both obese and non-obese individuals makes it difficult to determine the effect of obesity on oral bioavailability. Also, only a few studies report unbound concentrations of drugs, so information on the influence of obesity on protein binding is limited. More insight is needed in the pathophysiological changes that accompany with severe or prolonged obesity with respect to the liver, liver blood flow, (hepatic) transporters, gut metabolism and perfusion. Taken together, one of the major challenges nowadays in the field of obesity-PK/PD is to gather quantitative information on these parameters for the development of physiologically based PK models in which various drug and patient properties can be integrated. With such models, PK/PD and ultimately drug dosing of other drugs can be predicted for individual patients. This 'quantitative systems pharmacology' approach is currently an important, rising field in PK/PD research[122]. With this approach, quantitative PK and physiological information is incorporated that can be applied to predict the PK and/or PD for new or existing drugs to yield appropriate dosing recommendations. Until then, assumptions and simplifications have to be employed in these models where current evidence is inconclusive, which is the case in several domains in obesity, as we have shown in this review. Therefore, future research should focus on filling in these knowledge gaps to aid in the development of quantitative systems pharmacology models.

A second challenge is the implementation of dose recommendations for obese patients in clinical practice. Most PK studies conclude with dosing recommendations based on the developed PK/PD model, but implementation of these recommendations is often overlooked. Depending on the strength of the underlying evidence and the type of drug, this can be either done in a clinical study, or by implementing the dose recommendations in daily practice with close monitoring of relevant outcomes and drug levels by therapeutic drug monitoring (prospective evaluation). One example from our own research group was the prospective validation of an amikacin dose regimen based on an earlier developed neonatal PK/PD model[123]. The use of this regimen yielded adequate peak and through concentrations across the entire neonatal population in a prospective study where only limited sampling was applied[124]. Another example is the successful implementation of a cefazolin dose regimen in the Dutch guidelines for perioperative antibiotic prophylaxes as mentioned elsewhere in this review69,80.

Regarding implementation, dilemmas may rise especially for drugs known to be toxic when high plasma concentrations are reached but where current evidence suggests they should be dosed on TBW. An example is vancomycin, where studies recommend dosing based on TBW to reach adequate drug exposure in the obese as both Vd and Cl increase. However, high peak concentrations of vancomycin may increase the risk of nephrotoxicity. Therefore, physicians are generally reluctant to prescribe doses > 4000 mg/day in morbidly obese patients, and as a consequence morbidly obese patients might initially be undertreated for infectious diseases.

In conclusion, over the last two decades, more and more knowledge is gained on obesity pharmacology. Future research should focus on filling in the knowledge gaps, especially in connecting obesity-related physiological changes with changes in PK/PD for specific drugs. Ultimately, we can use this knowledge in development of physiologically based PK/PD models using quantitative systems pharmacology approaches. In addition, researchers must also focus on prospective evaluation of developed models, and implementation of subsequent dosing recommendations in clinical practice.

Literature

1. Flegal, K. M., Carroll, M. D., Kuczmarski, R. J. & Johnson, C. L. Overweight and obesity in the United States: prevalence and trends, 1960-1994. *Int. J. Obes. Relat. Metab. Disord.* 22, 39–47 (1998).
2. GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N. Engl. J. Med.* 377, 13–27 (2017).
3. Flegal, K. M., Kruszon-Moran, D., Carroll, M. D., Fryar, C. D. & Ogden, C. L. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA* 315, 2284–91 (2016).
4. Jensen, M. D. *et al.* 2013 AHA/ACC/TOS Guideline for the management of overweight and obesity in adults. *J. Am. Coll. Cardiol.* 63, 2985–3023 (2014).
5. Jain, R. *et al.* Implications of obesity for drug therapy: limitations and challenges. *Clin. Pharmacol. Ther.* 90, 77–89 (2011).
6. Knibbe, C. A. J. *et al.* Drug disposition in obesity: toward evidence-based dosing. *Annu. Rev. Pharmacol. Toxicol.* 55, 149–67 (2015).
7. Brill, M. J. *et al.* Impact of obesity on drug metabolism and elimination in adults and children. *Clin. Pharmacokinet.* 51, 277–304 (2012).
8. Hanley, M. J., Abernethy, D. R. & Greenblatt, D. J. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin. Pharmacokinet.* 49, 71–87 (2010).
9. Krekels, E. H. J. *et al.* Evidence-based drug treatment for special patient populations through model-based approaches. *Eur. J. Pharm. Sci.* 109S, S22–S26 (2017).
10. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--The evidence report. National Institutes of Health. *Obes. Res.* 6 Suppl 2, 51S-209S (1998).
11. Wellen, K. E. & Hotamisligil, G. S. Obesity-induced inflammatory changes in adipose tissue. *J. Clin. Invest.* 112, 1785–8 (2003).
12. Cardoso-Júnior, A. *et al.* Gastric emptying of solids and semi-solids in morbidly obese and non-obese subjects: an assessment using the 13C-octanoic acid and 13C-acetic acid breath tests. *Obes. Surg.* 17, 236–41 (2007).
13. Teixeira, T. F. S. *et al.* Intestinal permeability parameters in obese patients are correlated with metabolic syndrome risk factors. *Clin. Nutr.* 31, 735–40 (2012).
14. Xing, J. & Chen, J. D. Z. Alterations of gastrointestinal motility in obesity. *Obes. Res.* 12, 1723–32 (2004).
15. Alexander, J. K. *et al.* Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. *Cardiovasc. Res. Cent. Bull.* 1, 39–44 (1962).
16. Lemmens, H. J. M., Bernstein, D. P. & Brodsky, J. B. Estimating blood volume in obese and morbidly obese patients. *Obes. Surg.* 16, 773–6 (2006).
17. Herrera, M. F. & Deitel, M. Cardiac function in massively obese patients and the effect of weight loss. *Can. J. Surg.* 34, 431–4 (1991).
18. Ong, J. P. *et al.* Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. *Obes. Surg.* 15, 310–315 (2005).
19. Farrell, G. C., Teoh, N. C. & Mccuskey, R. S. Hepatic microcirculation in fatty liver disease. *Anat. Rec. Adv. Integr. Anat. Evol. Biol.* 291, 684–692 (2008).
20. Benedek, I. H. *et al.* Serum alpha 1-acid glycoprotein and the binding of drugs in obesity. *Br. J. Clin. Pharmacol.* 16, 751–4 (1983).

21. Cheymol, G., Poirier, J. M., Barre, J., Pradalier, A. & Dry, J. Comparative pharmacokinetics of intravenous propranolol in obese and normal volunteers. *J. Clin. Pharmacol.* 27, 874–9 (1987).
22. Jones, R. L. & Nzekwu, M.-M. U. The effects of body mass index on lung volumes. *Chest* 130, 827–33 (2006).
23. Rubinstein, I., Zamel, N., DuBarry, L. & Hoffstein, V. Airflow limitation in morbidly obese, nonsmoking men. *Ann. Intern. Med.* 112, 828–32 (1990).
24. Davis, G., Patel, J. A. & Gagne, D. J. Pulmonary considerations in obesity and the bariatric surgical patient. *Med. Clin. North Am.* 91, 433–42 (2007).
25. Ribstein, J., du Cailar, G. & Mimran, A. Combined renal effects of overweight and hypertension. *Hypertens. (Dallas, Tex. 1979)* 26, 610–5 (1995).
26. Kasiske, B. L. & Crosson, J. T. Renal disease in patients with massive obesity. *Arch. Intern. Med.* 146, 1105–9 (1986).
27. Kovesdy, C. P., Furth, S., Zoccali, C. & World Kidney Day Steering Committee. Obesity and kidney disease: Hidden consequences of the epidemic. *Physiol. Int.* 104, 1–14 (2017).
28. Janmahasatian, S., Duffull, S. B., Chagnac, A., Kirkpatrick, C. M. J. & Green, B. Lean body mass normalizes the effect of obesity on renal function. *Br. J. Clin. Pharmacol.* 65, 964–965 (2008).
29. Janmahasatian, S. *et al.* Quantification of lean bodyweight. *Clin. Pharmacokinet.* 44, 1051–65 (2005).
30. Han, P. Y., Duffull, S. B., Kirkpatrick, C. M. J. & Green, B. Dosing in obesity: a simple solution to a big problem. *Clin. Pharmacol. Ther.* 82, 505–508 (2007).
31. Meyhoff, C. S. *et al.* Should dosing of rocuronium in obese patients be based on ideal or corrected body weight? *Anesth. Analg.* 109, 787–792 (2009).
32. Schwartz, S. N., Pazin, G. J., Lyon, J. A., Ho, M. & Pasculle, A. W. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. *J. Infect. Dis.* 138, 499–505 (1978).
33. Van Kralingen, S. *et al.* Comparative evaluation of atracurium dosed on ideal body weight vs. total body weight in morbidly obese patients. *Br. J. Clin. Pharmacol.* 71, 34–40 (2011).
34. Eleveld, D. J., Proost, J. H., Absalom, A. R. & Struys, M. M. R. F. Obesity and allometric scaling of pharmacokinetics. *Clin. Pharmacokinet.* 50, 751–756 (2011).
35. Griggs, J. J. *et al.* Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J. Clin. Oncol.* 30, 1553–61 (2012).
36. Green, B. & Duffull, S. B. What is the best size descriptor to use for pharmacokinetic studies in the obese? *Br. J. Clin. Pharmacol.* 58, 119–133 (2004).
37. Keys, A., Fidanza, F., Karvonen, M. J., Kimura, N. & Taylor, H. L. Indices of relative weight and obesity. *J. Chronic Dis.* 25, 329–43 (1972).
38. Du Bois, D. & Du Bois, E. F. A formula to estimate the approximate surface area if height and weight be known. 1916. *Arch. Intern. Med.* 863–871 (1916).
39. McCarron, M. & Devine, B. Gentamicin therapy. *Drug Intell. Clin. Pharm.* 8, 650–655 (1974).

40. Bauer, L. A., Edwards, W. A. D., Dellinger, E. P. & Simonowitz, D. A. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. *Eur. J. Clin. Pharmacol.* 24, 643–647 (1983).
41. Ulvestad, M. *et al.* Impact of OATP1B1, MDR1, and CYP3A4 expression in liver and intestine on interpatient pharmacokinetic variability of atorvastatin in obese subjects. *Clin. Pharmacol. Ther.* 93, 275–82 (2013).
42. Flechner, S. M., Kolbeinsson, M. E., Tam, J. & Lum, B. The impact of body weight on cyclosporine pharmacokinetics in renal transplant recipients. *Transplantation* 47, 806–810 (1989).
43. Cheymol, G., Weissenburger, J., Poirier, J. M. & Gellee, C. The pharmacokinetics of dexfenfluramine in obese and non-obese subjects. *Br. J. Clin. Pharmacol.* 39, 684–7 (1995).
44. Greenblatt, D. J. *et al.* Effect of age, gender, and obesity on midazolam kinetics. *Anesthesiology* 61, 27–35 (1984).
45. Bowman, S. L., Hudson, S. A., Simpson, G., Munro, J. F. & Clements, J. A. A comparison of the pharmacokinetics of propranolol in obese and normal volunteers. *Br. J. Clin. Pharmacol.* 21, 529–532 (1986).
46. Greenblatt, D. J. *et al.* Trazodone kinetics: effect of age, gender, and obesity. *Clin. Pharmacol. Ther.* 42, 193–200 (1987).
47. Kees, M. G., Weber, S., Kees, F. & Horbach, T. Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients. *J. Antimicrob. Chemother.* 66, 2330–2335 (2011).
48. Karlsson, M. O. & Bredberg, U. Estimation of bioavailability on a single occasion after semisimultaneous drug administration. *Pharm. Res.* 6, 817–21 (1989).
49. Bredberg, U., Karlsson, M. O. & Borgström, L. A comparison between the semisimultaneous and the stable isotope techniques for bioavailability estimation of terbutaline in humans. *Clin. Pharmacol. Ther.* 52, 239–48 (1992).
50. Brill, M. J. E. *et al.* Midazolam pharmacokinetics in morbidly obese patients following semi-simultaneous oral and intravenous administration: a comparison with healthy volunteers. *Clin. Pharmacokinet.* 53, 931–41 (2014).
51. Lee, W. H., Kramer, W. G. & Granville, G. E. The effect of obesity on acetaminophen pharmacokinetics in man. *J. Clin. Pharmacol.* 21, 284–287 (1981).
52. Michalaki, M. A. *et al.* Impaired pharmacokinetics of levothyroxine in severely obese volunteers. *Thyroid* 21, 477–481 (2011).
53. Lloret-Linares, C. *et al.* Effect of a Roux-en-Y gastric bypass on the pharmacokinetics of oral morphine using a population approach. *Clin. Pharmacokinet.* 53, 919–930 (2014).
54. Hoskin, P. J. *et al.* The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br. J. Clin. Pharmacol.* 27, 499–505 (1989).
55. van Rongen, A. *et al.* Morbidly Obese Patients Exhibit Increased CYP2E1-Mediated Oxidation of Acetaminophen. *Clin. Pharmacokinet.* 55, 833–847 (2016).
56. Sanderink, G.-J. *et al.* The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. *Clin. Pharmacol. Ther.* 72, 308–318 (2002).
57. Chan, C. C. W. *et al.* Bioavailability of hCG after intramuscular or subcutaneous injection in obese and non-obese women. *Hum. Reprod.* 18, 2294–2297 (2003).

58. Diepstraten, J. *et al.* Population pharmacodynamic model for low molecular weight heparin nadroparin in morbidly obese and non-obese patients using anti-Xa levels as endpoint. *Eur. J. Clin. Pharmacol.* 71, 25–34 (2015).
59. Rassard, P. A. B. *et al.* Dose-dependent delay of the hypoglycemic effect of short-acting insulin analogs in obese subjects with a pharmacokinetic and pharmacodynamic study. *Diabetes Care* 33, 0–5 (2010).
60. Berezhkovskiy, L. M. On the accuracy of estimation of basic pharmacokinetic parameters by the traditional noncompartmental equations and the prediction of the steady-state volume of distribution in obese patients based upon data derived from normal subjects. *J. Pharm. Sci.* 100, 2482–97 (2011).
61. Hinderling, P. H. Red blood cells: a neglected compartment in pharmacokinetics and pharmacodynamics. *Pharmacol. Rev.* 49, 279–95 (1997).
62. Abernethy, D. R., Greenblatt, D. J., Divoll, M. & Shader, R. I. Prolonged accumulation of diazepam in obesity. *J. Clin. Pharmacol.* 23, 369–76 (1983).
63. Davis, R. L., Quenzer, R. W., Bozigian, H. P. & Warner, C. W. Pharmacokinetics of ranitidine in morbidly obese women. *DICP* 24, 1040–3 (1990).
64. Van Kralingen, S. *et al.* Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. *Clin. Pharmacokinet.* 50, 739–50 (2011).
65. Abernethy, D. R., Greenblatt, D. J. & Smith, T. W. Digoxin disposition in obesity: Clinical pharmacokinetic investigation. *Am. Heart J.* 102, 740–744 (1981).
66. Adane, E. D., Herald, M. & Koura, F. Pharmacokinetics of Vancomycin in Extremely Obese Patients with Suspected or Confirmed Staphylococcus aureus Infections. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* 35, 127–139 (2015).
67. Blouin, R. A., Bauer, L. A., Miller, D. D., Record, K. E. & Griffen, W. O. Vancomycin pharmacokinetics in normal and morbidly obese subjects. *Antimicrob. Agents Chemother.* 21, 575–580 (1982).
68. Abernethy, D. R., Greenblatt, D. J., Divoll, M., Smith, R. B. & Shader, R. I. The influence of obesity on the pharmacokinetics of oral alprazolam and triazolam. *Clin. Pharmacokinet.* 9, 177–83 (2017).
69. Brill, M. J. E. *et al.* Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. *J. Antimicrob. Chemother.* 69, 715–723 (2014).
70. Pai, M. P. *et al.* Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. *Antimicrob. Agents Chemother.* 51, 2741–2747 (2007).
71. Abernethy, D. R., Greenblatt, D. J., Divoll, M. & Shader, R. I. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. *J. Lab. Clin. Med.* 101, 873–880 (1983).
72. Smith, M. J. *et al.* Pharmacokinetics of clindamycin in obese and nonobese children. *Antimicrob. Agents Chemother.* 61, 1–12 (2017).
73. Brunner, M., Derendorf, H. & Müller, M. Microdialysis for in vivo pharmacokinetic/pharmacodynamic characterization of anti-infective drugs. *Curr. Opin. Pharmacol.* 5, 495–9 (2005).
74. Rodvold, K. A., George, J. M. & Yoo, L. Penetration of anti-infective agents into pulmonary epithelial lining fluid: focus on antibacterial agents. *Clin. Pharmacokinet.* 50, 637–64 (2011).

75. Marchand, S., Chauzy, A., Dahyot-Fizelier, C. & Couet, W. Microdialysis as a way to measure antibiotics concentration in tissues. *Pharmacol. Res.* 111, 201–207 (2016).
76. Mouton, J. W. *et al.* Tissue concentrations: do we ever learn? *J. Antimicrob. Chemother.* 61, 235–7 (2008).
77. Hollenstein, U. M., Brunner, M., Schmid, R., M, M. & Müller, M. Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. *Int. J. Obes. Relat. Metab. Disord.* 25, 354–8 (2001).
78. Barbour, A. *et al.* Soft tissue penetration of cefuroxime determined by clinical microdialysis in morbidly obese patients undergoing abdominal surgery. *Int. J. Antimicrob. Agents* 34, 231–235 (2009).
79. Zeitlinger, M. A. *et al.* A pilot study testing whether concentrations of levofloxacin in interstitial space fluid of soft tissues may serve as a surrogate for predicting its pharmacokinetics in lung. *Int. J. Antimicrob. Agents* 29, 44–50 (2007).
80. Stichting Werkgroep Antibiotica Beleid (SWAB). Guideline: Perioperative antibiotic prophylaxis. (2017).
81. Machado, M., Marques-Vidal, P. & Cortez-Pinto, H. Hepatic histology in obese patients undergoing bariatric surgery. *J. Hepatol.* 45, 600–6 (2006).
82. Dong, D. *et al.* Morbid obesity alters both pharmacokinetics and pharmacodynamics of propofol: Dosing recommendation for anesthesia induction. *Drug Metab. Dispos.* 44, 1579–1583 (2016).
83. Diepstraten, J. *et al.* An integrated population pharmacokinetic meta-analysis of propofol in morbidly obese and nonobese adults, adolescents, and children. *CPT pharmacometrics Syst. Pharmacol.* 2, e73 (2013).
84. Ingrande, J., Brodsky, J. B. & Lemmens, H. J. M. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. *Anesth. Analg.* 113, 57–62 (2011).
85. Yoshinari, K., Takagi, S., Yoshimasa, T., Sugatani, J. & Miwa, M. Hepatic CYP3A expression is attenuated in obese mice fed a high-fat diet. *Pharm. Res.* 23, 1188–200 (2006).
86. Kolwankar, D. *et al.* Association between nonalcoholic hepatic steatosis and hepatic cytochrome P-450 3A activity. *Clin. Gastroenterol. Hepatol.* 5, 388–93 (2007).
87. Ghose, R. *et al.* Role of high-fat diet in regulation of gene expression of drug metabolizing enzymes and transporters. *Life Sci.* 89, 57–64 (2011).
88. Woolsey, S. J., Mansell, S. E., Kim, R. B., Tirona, R. G. & Beaton, M. D. CYP3A activity and expression in nonalcoholic fatty liver disease. *Drug Metab. Dispos.* 43, 1484–90 (2015).
89. Banerjee, M., Robbins, D. & Chen, T. Targeting xenobiotic receptors PXR and CAR in human diseases. *Drug Discov. Today* 20, 618–28 (2015).
90. Brill, M. J. *et al.* The Pharmacokinetics of the CYP3A Substrate Midazolam in Morbidly Obese Patients Before and One Year After Bariatric Surgery. *Pharm. Res.* 32, 3927–3936 (2015).
91. Emery, M. G. *et al.* CYP2E1 activity before and after weight loss in morbidly obese subjects with nonalcoholic fatty liver disease. *Hepatology* 38, 428–435 (2003).
92. Caraco, Y., Zylber-Katz, E., Berry, E. M. & Levy, M. Caffeine pharmacokinetics in obesity and following significant weight reduction. *Int. J. Obes. Relat. Metab. Disord.* 19, 234–9 (1995).

93. van Rongen, A. *et al.* Population pharmacokinetics of midazolam and its metabolites in overweight and obese adolescents. *Br. J. Clin. Pharmacol.* 80, 1185–96 (2015).
94. FDA. Food and drug administration, Center for Drug Evaluation and Research, Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) meeting. March 14, 2012.
95. Calvier, E. A. M. *et al.* Allometric scaling of clearance in paediatric patients: When does the magic of 0.75 fade? *Clin. Pharmacokinet.* 56, 273–285 (2017).
96. Vaughns, J. D. *et al.* Use of fentanyl in adolescents with clinically severe obesity undergoing bariatric surgery: A pilot study. *Paediatr. Drugs* 19, 251–257 (2017).
97. Lloret-Linares, C. *et al.* The effect of morbid obesity on morphine glucuronidation. *Pharmacol. Res.* 118, 64–70 (2017).
98. de Hoogd, S. *et al.* Influence of Morbid Obesity on the Pharmacokinetics of Morphine, Morphine-3-Glucuronide, and Morphine-6-Glucuronide. *Clin. Pharmacokinet.* 56, 1577–1587 (2017).
99. Ferslew, B. C. *et al.* Altered morphine glucuronide and bile acid disposition in patients with nonalcoholic steatohepatitis. *Clin. Pharmacol. Ther.* 97, 419–427 (2015).
100. Dzierlenga, A. L. *et al.* Mechanistic basis of altered morphine disposition in nonalcoholic steatohepatitis. *J. Pharmacol. Exp. Ther.* 352, 462–70 (2015).
101. van der Schoor, L. W. E., Verkade, H. J., Kuipers, F. & Jonker, J. W. New insights in the biology of ABC transporters ABCC2 and ABCC3: impact on drug disposition. *Expert Opin. Drug Metab. Toxicol.* 11, 273–93 (2015).
102. Fisher, C. D. *et al.* Experimental non-alcoholic fatty liver disease results in decreased hepatic uptake transporter expression and function in rats. *Eur. J. Pharmacol.* 613, 119–27 (2009).
103. Ali, I. *et al.* Transporter-mediated alterations in patients with NASH increase systemic and hepatic exposure to an OATP and MRP2 substrate. *Clin. Pharmacol. Ther.* (2017). doi:10.1002/cpt.997
104. Chagnac, A. *et al.* Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. *Nephrol. Dial. Transplant* 23, 3946–52 (2008).
105. Levey, A. S. & Inker, L. A. Assessment of glomerular filtration rate in health and disease: A state of the art review. *Clin. Pharmacol. Ther.* 102, 405–419 (2017).
106. Demirovic, J. A., Pai, A. B. & Pai, M. P. Estimation of creatinine clearance in morbidly obese patients. *Am. J. Heal. Syst. Pharm.* 66, 642–8 (2009).
107. Pai, M. P. Estimating the glomerular filtration rate in obese adult patients for drug dosing. *Adv. Chronic Kidney Dis.* 17, 53–62 (2010).
108. Lim, W. H., Lim, E. M. & McDonald, S. Lean body mass-adjusted Cockcroft and Gault formula improves the estimation of glomerular filtration rate in subjects with normal-range serum creatinine. *Nephrology* 11, 250–256 (2006).
109. Alobaid, A. S. *et al.* Effect of obesity on the population pharmacokinetics of fluconazole in critically ill patients. *Antimicrob. Agents Chemother.* 60, 6550–6557 (2016).
110. Chairat, K. *et al.* Population pharmacokinetics of oseltamivir and oseltamivir carboxylate in obese and non-obese volunteers. *Br. J. Clin. Pharmacol.* 81, 1103–1112 (2016).

111. Thorne-Humphrey, L. M. *et al.* Oseltamivir pharmacokinetics in morbid obesity (OPTIMO trial). *J. Antimicrob. Chemother.* 66, 2083–2091 (2011).

112. Jittamala, P. *et al.* Pharmacokinetics of orally administered oseltamivir in healthy obese and nonobese Thai subjects. *Antimicrob. Agents Chemother.* 58, 1615–1621 (2014).

113. Christoff, P. B., Conti, D. R., Naylor, C. & Jusko, W. J. Procainamide disposition in obesity. *Drug Intell. Clin. Pharm.* 17, 516–22 (1983).

114. Allard, S., Kinzig, M., Boivin, G., Sörgel, F. & LeBel, M. Intravenous ciprofloxacin disposition in obesity. *Clin. Pharmacol. Ther.* 54, 368–73 (1993).

115. Bardin, C. *et al.* Population pharmacokinetics of metformin in obese and non-obese patients with type 2 diabetes mellitus. *Eur. J. Clin. Pharmacol.* 68, 961–968 (2012).

116. More, V. R. & Slitt, A. L. Alteration of hepatic but not renal transporter expression in diet-induced obese mice. *Drug Metab. Dispos.* 39, 992–999 (2011).

117. Reiss, R. a *et al.* Lithium pharmacokinetics in the obese. *Clin. Pharmacol. Ther.* 71, 1501–1508 (2015).

118. Huttunen, R. & Syrjänen, J. Obesity and the risk and outcome of infection. *Int. J. Obes.* 37, 333–340 (2013).

119. Varin, F. *et al.* Influence of extreme obesity on the body disposition and neuromuscular blocking effect of atracurium. *Clin. Pharmacol. Ther.* 48, 18–25 (1990).

120. Jullian-Desayes, I. *et al.* Impact of concomitant medications on obstructive sleep apnoea. *Br. J. Clin. Pharmacol.* 83, 688–708 (2017).

121. Mason, M., Cates, C. J. & Smith, I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. *Cochrane Database Syst. Rev.* CD011090 (2015).

122. Goulooze, S. C. *et al.* Towards personalized treatment of pain using a quantitative systems pharmacology approach. *Eur. J. Pharm. Sci.* 109S, S32–S38 (2017).

123. De Cock, R. F. W. *et al.* Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. *Clin. Pharmacokinet.* 51, 105–17 (2012).

124. Smits, A. *et al.* Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice. *Antimicrob. Agents Chemother.* 59, 6344–51 (2015).

Chapter 9

The influence of morbid obesity on the pharmacokinetics of morphine and morphine-3 and morphine-6-glucuronide

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Clin Pharmacokinet. 2017;56(12):1577-1587

Abstract

Introduction

Obesity is associated with many pathophysiological changes that may result in altered drug metabolism. The aim of this study is to investigate the influence of obesity on the pharmacokinetics of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) through a combined analysis in morbidly obese patients and non-obese healthy volunteers.

Methods

In this analysis, data from 20 morbidly obese patients (mean body mass index 49.9 kg/m^2 (range 37.6 to 78.6 kg/m^2) and weight 151.3 kg (range 112 to 251.9 kg)) and 20 healthy volunteers (mean weight 70.6 kg (range 58 to 85 kg)) were included. Morbidly obese patients received 10 mg intravenous (I.V.) morphine after gastric bypass surgery, with additional morphine I.V. doses as needed. Healthy volunteers received an I.V. bolus morphine 0.1 mg/kg followed by an infusion of 0.030 mg/kg/h for 1 h. Population pharmacokinetic modelling was performed using NONMEM 7.2.

Results

In morbidly obese patients, elimination clearance of M3G and M6G was decreased substantially compared to healthy volunteers ($p<0.001$). Regarding glucuronidation, only a slight decrease in formation of M6G and a delay in formation of M3G was found (both $p<0.001$). Obesity was also identified as a covariate for the peripheral volume of distribution of morphine ($p<0.001$).

Conclusion

Metabolism of morphine is not altered in morbidly obese patients. However, decreased elimination of both M3G and M6G is evident, resulting in substantial increase in exposure to these two metabolites. A rational explanation of this finding is that it results from alterations in membrane transporter function and/or expression in the liver.

Introduction

The prevalence of obesity (body mass index (BMI) > 30 kg/m^2) and morbid obesity (BMI > 40 kg/m^2) is increasing, with around 600 million obese people worldwide[1]. Obesity is associated with an increase in morbidity and mortality and numerous chronic diseases such as diabetes mellitus, cardiovascular diseases, and cancer.

There are several (patho)physiological changes associated with morbid obesity that may impact the pharmacokinetics of drugs. Obesity has been associated with changes in the expression and function of metabolic processes such as cytochrome P450 and conjugation enzymes, fatty liver infiltration, non-alcoholic steatohepatitis (NASH), and altered transporters[2]. These changes have been shown to impact metabolism of certain drugs, with for instance, increased glucuronidation of paracetamol in morbidly obese patients[3], whereas the metabolism of midazolam is unaltered in morbidly obese patients undergoing bariatric surgery compared to non-obese control patients[4], but was found to increase after gastric bypass-induced weight loss one year after surgery[5]. Data on liver blood flow, glomerular filtration and/or tubular-mediated mechanisms in morbidly obese patients are more inconclusive with, for example, data of unchanged cefazolin clearance in morbidly obese patients and unchanged or increased liver blood flow[2,6].

Morphine is primarily metabolized by the liver uridine diphosphate glucuronosyltransferases (UGT) 2B7 to pharmacologically active metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G has potential antagonistic or hyperalgesic properties[7], while M6G appears to contribute to analgesia and sedation[8]. Despite the extensive use of morphine, data on the PK of morphine and glucuronide metabolites in morbidly obese patients are limited. A previous study reported an increased ratio between morphine metabolites and morphine after oral administration of morphine in gastric bypass patients when comparing their results to data in the literature[9–11]. In another study, intravenous morphine was administered to 14 healthy volunteers and the results compared to seven obese patients with biopsy-confirmed NASH. This study also suggested a higher area under the curve (AUC) of morphine glucuronides in NASH patients compared with healthy volunteers[12].

In view of higher susceptibility for pain and the increased use of opioids in obese individuals[13], and the fact that the adverse effects of opioids are feared in obese populations because of increased risk for respiratory depression, respiratory failure, and other opioid adverse effects[14,15], knowledge on the pharmacokinetics of morphine and its metabolites in morbidly obese patients is necessary. This study investigates the pharmacokinetics of morphine and its pharmacologically

active glucuronides in morbidly obese patients using a population approach on the basis of a combined dataset of morbidly obese patients together with a historic cohort of healthy volunteers[16,17]

Methods

Patients

The data obtained in the morbidly obese patients were collected as part of a study in which the pharmacokinetics of multiple drugs was investigated[18–20]. Anesthesia was standardized with induction of anaesthesia with propofol, atracurium and fentanyl, after which anaesthesia was maintained with continuous infusions of propofol and remifentanil. For this original study, 20 morbidly obese patients (BMI > 40 kg/m^2) were included who were scheduled to undergo laparoscopic gastric banding, gastric sleeve, or gastric bypass surgery (Table 1). Inclusion criteria were age between 18 and 60 years, BMI > 40 kg/m^2, American Society of Anesthesiologists (ASA) physical status classification of II or III, and a normal renal and liver function as assessed by routine laboratory testing. Exclusion criteria were pregnancy, breastfeeding, and a known allergy to morphine. This study was approved by the local human research and ethics committee of the St. Antonius Ziekenhuis (VCMO, NL35861.100.11) and conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO) of The Netherlands. Before participation, all patients gave written informed consent.

For the control group, data were available from 20 healthy volunteers, 10 of each sex, who were enrolled as part of two other studies of which detailed information can be found in the references[16,17]. The subjects were healthy and did not have a history of illicit substance abuse. Approval was obtained from the Human Ethics Committee (Commissie Medisch Ethiek, Leids Universitair Medisch Centrum, Leiden, The Netherlands: protocol No. P00.034). Written and oral informed consent was given.

Study design

In the prospective observational study (ClinicalTrials.gov:NCT01097148), 20 morbidly patients were studied on the day of gastric bypass surgery and afterwards. According to standard care, all patients received a bolus injection of 10 mg intravenous morphine at the end of the procedure for the prevention and/or treatment of postoperative pain. If needed based on the local postoperative pain protocol (Numerical Rating Scale ≥ 4), patients received additional intravenous boluses of morphine. Blood samples were drawn before induction of anaesthesia

(*t* = 0) and after 5, 15, 30, 45, 75, 90, 120, 150, 250, 420 min after first dose of intravenous morphine. Samples were immediately stored on ice, and within 1 h, samples were centrifuged for 10 min at 4ºC temperature to obtain plasma samples and stored immediately at −80°C until analysis. The healthy volunteers received an intravenous morphine bolus 0.10 mg/kg dose followed by an infusion of 0.03 mg/kg/h for 1 h. Blood samples were collected at fixed times (*t* = 5, 10, 20, 30, 40, 50, 60, 65, 70, 80, 100, 130, 180, 300, and 420 min) after morphine bolus dose.

Analysis

Samples from both studies were analysed in the same laboratory using a solid-phase extraction and reverse-phase high-performance liquid chromatography, which has been published previously[16]. The Lower Limit of Quantification (LLOQ) for the obese population was 1 μg/L for morphine, 2 μg/L for M3G, and 1 μg/L for M6G. For the analytic method of the healthy volunteer study, the LLOQ values for morphine and M3G were 2 and 30 μg/L. For M6G, the LLOQ values were 2, 5, and 6 μg/L.

Population Pharmacokinetic Analysis and Internal Model Validation

Morphine and metabolite data of both datasets were analysed using non-linear mixed-effects modelling with NONMEM Version 7.2 software (Icon Development Solutions, Hanover, MD, USA)[21]. Pirana Version 2.9.1[22], R Version 3.0.1[23], Xpose Version 4.5.0[22] and Psn Version 3.6.2[22] software were used to evaluate and visualize the data. Identifiability of the model was verified using COMBOS (UCLA Biocybernetics Laboratory Los Angeles, CA, USA) software application (see Electronic Supplementary Material 1)[24]. Concentrations were expressed in nanomoles per litre, using the molecular weights of morphine, M3G and M6G (285.33 and 461.46 g/mol, respectively). The amount of administrated morphine was corrected for morphine hydrochloride (molecular weight 321.8 g/mol). In the obese population, no data were below the LLOQ. In the healthy volunteer study, 5% (n = 16 of 311) of the morphine concentrations, 4.5% (n = 14 of 311) of the M3G concentrations, and 9.6% (n = 30 of 311) of the M6G concentrations were below the LLOQ. The first below quantification observations were replaced with LLOQ/2 and the rest were discarded, according to the M6 method for handling data below the limit of quantification in population pharmacokinetic studies[25].

Discrimination between different models was made by likelihood ratio test using the objective function value (OFV, i.e., -2 log likelihood [-2LL]). A *p*-value of <0.05, representing a decrease of 3.84 in the OFV value between nested models with one degree of freedom, was considered statistically significant. In addition, goodness-of-fit plots for morphine, M3G and M6G (observed vs. individual-predicted concentrations,

observed vs. population-predicted concentrations, conditional weighted residuals (CWRES) vs. time, and CWRES vs. population-predicted concentrations plots) were used for diagnostic purposes. Residual variability was tested using proportional, additive, or combined proportional and additive error models. Furthermore, the confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual plots were used to evaluate the model. The delay in formation of morphine metabolites was captured by testing a varying number of transit compartments. Mean transit time (MTT) was calculated from the transit compartment rate constant (Ktr) with *n*/Ktr, where *n* is the number of transit compartments.

The non-glucuronide clearance (direct unchanged urinary clearance and nonglucuronide metabolic clearance) was assumed to be 35% of total clearance of a 70-kg healthy subject, based on previous reports[26]. Total clearance (CL_{total}) was calculated as M3G clearance (CL_{M3G}) + M6G clearance (CL_{M6G}) + non-glucuronide clearance ($CL_{nonglucuronide}$). The volume of distribution of the two metabolites M3G and M6G was assumed to be equal ($V_{M3G} = V_{M6G}$), owing to their comparable molecular structure and weight. Bootstrap procedure using 200 replicates was used to obtain non-parametric confidence intervals and to assess model robustness[27]. Predictability was evaluated with the normalised prediction distribution error method (2000 samples). Results of the normalised prediction distribution error are incorporated in Figure 2 as a replacement of CWRES vs. time and CWRES vs. population-predicted concentrations.

Covariate analysis

Covariates were plotted independently against the individual estimates of pharmacokinetic parameters to visualize potential relations. Total Body Weight (TBW) was the main covariate of interest in this study. Age and sex were tested in preliminary models but were further explored in the final model. BMI was not tested because no individual height was available of the healthy volunteers.

Continuous covariates were tested using both power and linear equations:

$$P_i = P_p \times \left(1 + Y \times \left(COV - COV_{median}\right)\right), \quad (1)$$

$$P_i = P_p \times \left(COV - COV_{median}\right)^X, \quad (2)$$

In which P_i and P_p represent individual and population parameter estimates, COV represents the covariate, COV_{median} represents the median of the value of the covariate for the population, *Y* represents a correlation factor between the population parameter and the change in covariate value for a linear function, and *X* represents the exponential scaling factor for a power function. The categorical

covariate (sex) was examined by calculating a separate parameter for each category of the covariate.

Potential covariates were separately entered into the model and statistically tested by use of the likelihood ratio test. In addition, if applicable, it was evaluated whether the inter-individual variability (eta) in the parameter concerned decreased upon inclusion of the covariate on the parameter and whether the plot of the eta vs. covariate was improved. Finally, using forward inclusion (p <0.05, OFV decrease >3.8) and backward deletion (p <0.001, OFV decrease 10.8), it was justified to include the covariate.

Simulations

The final population pharmacokinetic model was used to simulate concentration–time curves. An intravenous bolus of 10 mg morphine HCL was simulated in four patients; two extremes of dataset (resp. 56 and 251.9 kg) and two patients in-between. Morphine as well as M3G and M6G concentrations were plotted vs. time.

Statistical Analysis

Continuous data are presented as median (interquartile range (IQR)) and analysed using the Mann-Whitney test, or as mean ± standard deviation and analysed using Student's *t* test, where appropriate.

Results

Patients

Twenty morbidly obese patients and 20 healthy volunteers were available for analysis. In total, in the obese group, 196 morphine, 196 M3G, and 196 M6G plasma samples were included for analysis. In the healthy volunteers, a total of 290 plasma samples of morphine, 289 plasma samples of M3G, and 285 plasma samples of M6G were included. Differences were the result of the samples below the LLOQ. A summary of patient characteristics is presented in Table 1. Morbidly obese patients received a higher morphine dose compared to the healthy volunteers (15.7±4.0 mg vs. 9.2±1.2 mg, p<0.05).

Table 1. Summary of patients characteristics

	Morbidly obese patients (n = 20)	**Healthy volunteers (n = 20)**	**p-value**
Male/female	9/11	10/10	0.752
Age (years)	44.1 ± 10.6 (22 to 59)	25.5 ± 4.1 (20 to 36)	0.000
Body weight (kg)	150.5 ± 33.3 (112.0 to 251.9)	70.6 ± 8.82 (56.0 to 85.0)	<0.001
Body mass index (kg/m^2)	49.9 ± 10.2 (37.9 to 78.6)		
Type of surgery (n,%)			
Gastric bypass	10 (50.0)	N/A	N/A
Gastric banding	7 (35.0)		
Gastric sleeve	3 (15.0)		
No. of samples per patient			<0.001
Morphine, median (IQR)	10 (10 to 10)	15 (14 to 15)	
M3G	10 (10 to 10)	15 (14 to 15)	
M6G	10 (10 to 10)	15 (13 to 15)	
Total amount of morphine (mg)	15.7 (4.0)	9.2 (1.2)	<0.001
Serum creatinine, median (IQR) (µmol/L)	63 (60 to 81)*	80 (-)	0.014

Values are expressed as mean ± standard deviation (range) unless specified otherwise.
IQR,interquartile range; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide,
N/A = not applicable
* = one value missing.

Population Pharmacokinetic Model and Internal Model Evaluation

A three-compartment model for morphine, and a one-compartment model for M3G and M6G, with equalized volumes of distribution, best fitted the data (Figure 1). The introduction of multiple transit compartments in the formation of the glucuronides (for M3G n = 5, mean transit time = 3.05 min; for M6G n = 2, mean transit time = 12.7 min) improved the model significantly ($p<0.001$). Residual variability was best described by proportional error models, one for each compound, and calculated separately for each group. Table 2 shows the parameter estimates of the simple model without covariates.

In the covariate analysis, no substantial influence of TBW on the clearance of morphine was found. Significant influence of TBW was found on several other parameters, all in a non-linear manner. Elimination clearance of both metabolites decreased with TBW ($CL_{E\ M3G}$ $p<0.001$, -16 OFV, $CL_{E\ M6G}$ $p<0.001$, -92 OFV), and peripheral volume of morphine increased significantly with increasing TBW ($p<0.001$, -34 OFV). Formation clearance of M6G decreased with increasing TBW ($CL_{F\ M6G}$ $p<0.001$, -26 OFV). Formation of M3G was delayed with increasing bodyweight

because the mean transit time was increased with TBW (Ktr ($p<0.001$, -28 OFV). Imputing these functions resulted in reduction in interindividual variability ($CL_{F\ M3G}$ 24.3% to 20.8%, $CL_{E\ M3G}$ 89.0% to 65.9%, $V_{M3G}=V_{M6G}$ 32.3% to 29.7%, and Ktr2 37.7% to 36.8% (see Table 2).

Goodness-of-fit plots of the final covariate model are shown in Figure 2. The empirical Bayes estimates (EBEs) after adding the covariate functions are shown in Figure 3. This figure shows the population-predicted outcomes of the final covariate model and the influence of TBW on the parameters, where adding TBW improved the model significantly. Final model parameters are summarized in Table 2. The bootstrap analysis was successful in 98.5% of the runs and the obtained parameter confidence intervals were highly similar to the confidence intervals obtained from the standard errors (Table 2).

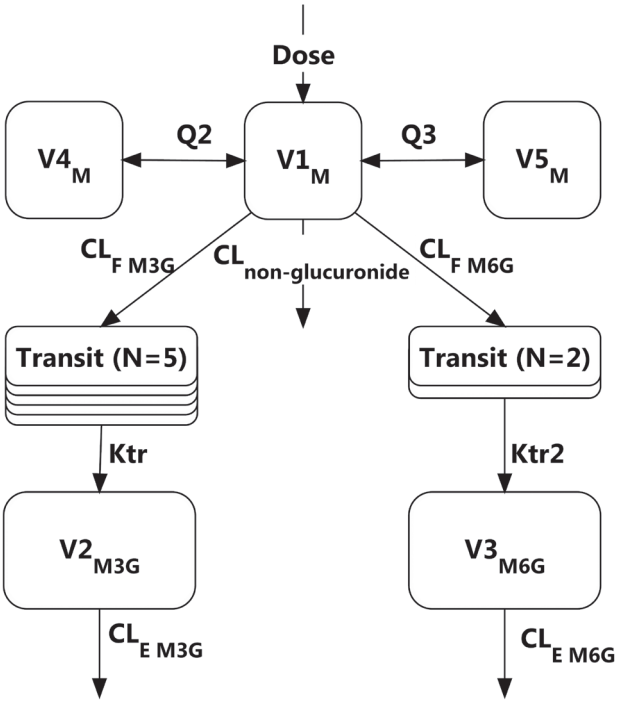


Figure. 1 Schematic illustration of the population pharmacokinetic model of morphine and morphine glucuronides.
CLF formation clearance; CLE elimination clearance; Ktr, transit rate constant; M3G morphine-3-glucuronide; M6G morphine-6-glucuronide; Q, inter-compartimental clearance from the central compartment of morphine to the peripheral compartments of morphine; V1, central volume of distribution; $V2_M$,$V4_M$, peripheral compartments of morphine. $V3_{M6G}=V2_{M3G}$, $CL_{non\text{-}glucuronide}$ = 35% of Cl_{total} (70 kg), CL_{total} = $Cl_{non\text{-}glucuronide}$ + $CL_{F\ M3G}$ + $CL_{F\ M6G}$

Table 2. Population pharmacokinetic parameters of the base and final pharmacokinetic model for morphine and glucuronides in healthy volunteers and morbidly obese patients and results of the bootstrap analysis

Parameter	Base model (RSE%)	Final model (RSE%)	Bootstrap (95% confidence interval)
*Morphine**			
$CL_{F\ M3G}$ (L/min)	0.725 (4.0)	0.748 (3.0)	0.748 (0.706 to 0.797)
$CL_{F\ M6G}$ (L/min)	0.128 (6.0)	-	
$CL_{F\ M6G} = CL_{F\ M6G,\ 98.5\ kg} \cdot (TBW/98.5)^{K}$			
$CL_{F\ M6G,\ 98.5\ kg}$ (L)	-	0.129 (5.0)	0.130 (0.119 to 0.140)
K	-	-0.329 (36.0)	-0.310 (-0.534 to -0.125)
$V1_{M}$ (L)	3.96 (5.0)	4.62 (9.0)	4.66 (3.95 to 5.59)
$V4_{M}$ (L)	5.76 (18.0)	9.52 (33.0)	9.91 (6.10 to 15.7)
$V5_{M}$ (L)	101 (5.0)		
$V5_{M} = V_{98.5\ kg} \cdot (TBW/98.5)^{L}$		-	
$V_{98.5\ kg}$ (L)	-	118 (9.0)	117.5 (103.7 to 136.6)
L	-	0.483 (48.0)	0.453 (0.112 to 0.859)
Q2 (L/min)	0.625 (7.0)	0.814 (20.0)	0.834 (0.598 to 1.16)
Q3 (L/min)	1.27 (5.0)	1.29 (5.0)	1.28 (1.15 to 1.41)
Ktr (min^{-1})	1.58 (9.0)		
$Ktr = Ktr_{98.5\ kg} \cdot (TBW/98.5)^{M}$			
$Ktr_{98.5\ kg}$	-	1.68 (9.0)	1.71 (1.51 to 1.98)
M	-	-0.701 (30.0)	-0.71 (-0.106 to 0.375)
Ktr2 (min^{-1})	0.151 (5.0)	0.159 (7.0)	0.158 (0.146 to 0.172)
Metabolites (M3G, M6G)			
V_{M3G}=V_{M6G} (L)	6.47 (7.0)	5.29 (13.0)	5.33 (4.28 to 6.52)
$CL_{E\ M3G}$ (L/min)	0.131 (14.0)	-	
$CL_{E\ M3G} = CL_{E\ M3G,\ 98.5\ kg} \cdot (TBW/98.5)^{N}$			
$CL_{E\ M3G,\ 98.5\ kg}$ (L)	-	0.134 (10.0)	0.134 (0.110 to 0.155)
N	-	-1.08 (22.0)	-1.06 (-1.53 to -0.60)
$CL_{E\ M6G}$ (L/min)	0.171 (15.0)	-	
$CL_{E\ M6G} = CL_{E\ M6G,\ 98.5\ kg} \cdot (TBW/98.5)^{O}$			
$CL_{E\ M6G,\ 98.5\ kg}$ (L)	-	0.149 (10.0)	0.154 (0.125 to 0.186)
O	-	-1.03 (31.0)	-1.06 (-1.64 to -0.56)
Interindividual variability (%)			
$CL_{F\ M3G}$	24.3 (12.0)	20.8 (10.0)	20.3 (16.8 to 23.4)
$CL_{E\ M3G}$	89.0 (19.0)	65.9 (20.0)	62.9 (41.9 to 86.1)
V_{M3G}=V_{M6G}	32.3 (12.0)	29.7 (12.0)	29.2 (22.6 to 35.8)
Ktr2	37.7 (13.0)	36.8 (13.0)	35.9 (27.1 to 43.6)
Residual variability (%)			
Healthy volunteers			
Proportional error for morphine	15.1 (16.0)	14.0 (7.0)	13.8 (12.0 to 15.7)
Proportional error for M3G	18.0 (25.0)	17.9 (12.0)	18.0 (14.3 to 21.5)
Proportional error for M6G	30.4 (19.0)	29.5 (8.0)	29.3 (24.2 to 32.8)

Parameter	Base model (RSE%)	Final model (RSE%)	Bootstrap (95% confidence interval)
Morbidly obese patients			
Proportional error for morphine	37.3 (22.0)	37.9 (11.0)	37.1 (29.2 to 44.7)
Proportional error for M3G	18.4 (17.0)	17.1 (8.0)	17.1 (14.9 to 19.1)
Proportional error for M6G	32.8 (37.0)	28.1 (9.0)	26.5 (21.5 to 30.7)
OFV (-2LL)	10311.38	10116.1	10038.1 (9774 to 10306)

* formation clearances are reported as absolute values, with $CL_{F\,M3G}$ and $CL_{F\,M6G}$ being 65% of total morphine clearance (see also Figure 1). CL_F, formation clearance; CL_E, elimination clearance; KTR, transit rate constant; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; OFV, objective function variable; Q, inter-compartimental clearance from the central compartment of morphine to the peripheral compartments of morphine; RSE, relative standard error; TBW, total body weight; V, volume of distribution (See also Figure 1)

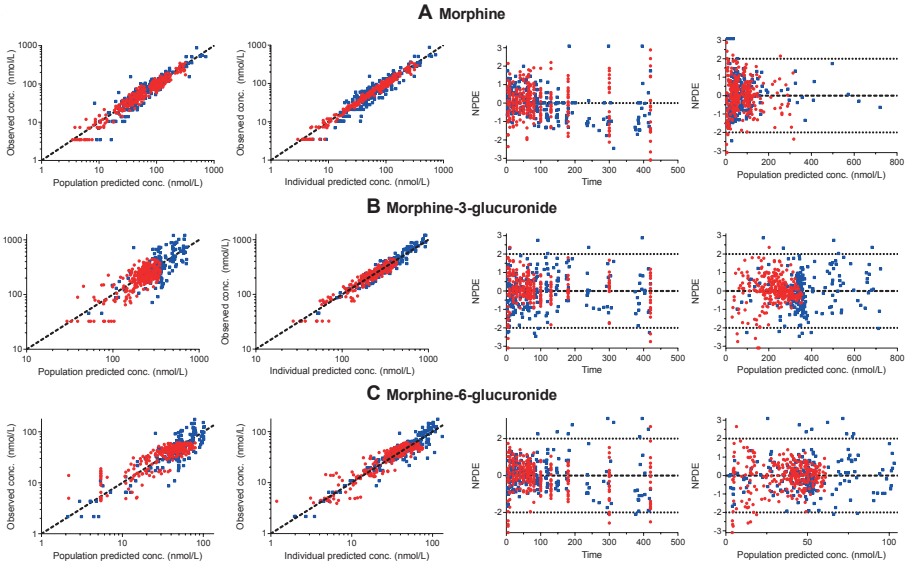


Figure 2. Goodness-of-fit plots of morbidly obese individuals (n = 20, blue rounds) and healthy volunteers (n = 20, red rounds). On the first row morphine (A), second row morphine-3-glucuronide (B), third row morphine-6-glucuronide (C). Please note scale differences in y-axis. NPDE; normalised prediction distribution error.

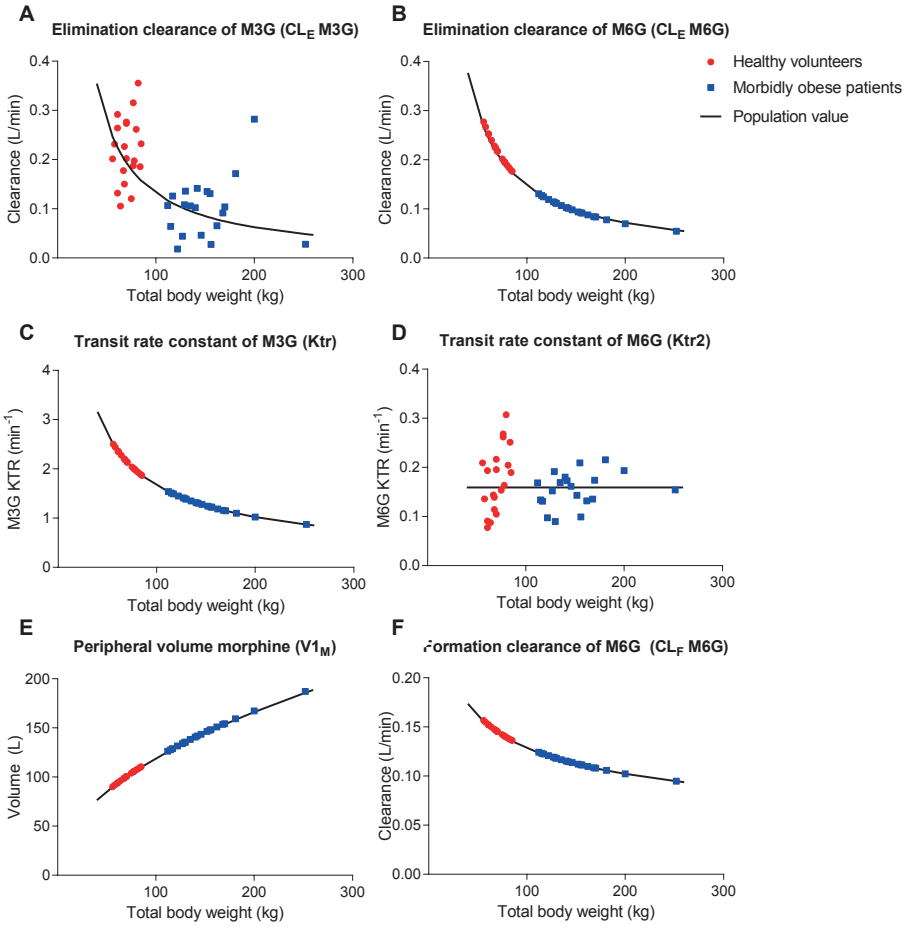


Figure 3. Post hoc parameters estimates of morbidly obese individuals (n = 20, filled squares) and healthy volunteers (n = 20, open rounds) from the final model *versus* total body weight, including morphine-3-glucuronide elimination clearance (CL_E M3G) *versus* total body weight (a), morphine-6-glucuronide elimination clearance (CL_E M6G) *versus* total body weight (b), morphine-3-glucuronide transit rate constant (Ktr) *versus* total body weight (c), morphine-6-glucuronide transit rate constant (Ktr2) *versus* total body weight (d), peripheral volume of distribution of morphine ($V1_M$) *versus* total body weight (e), formation clearance of morphine-6-glucuronide (CL_F M6G) *versus* total body weight (f).

Simulations

Figure 4 shows the model-predicted concentration-time profiles of morphine and its metabolites after an intravenous bolus dose of 10 mg of morphine and a 48-h continuous infusion of 2 mg hr^{-1} in four representative individuals from this study with a TBW of 56 kg, 75 kg, 125 kg and 253 kg. The figure shows that the pharmacokinetic profile of morphine (panels A,D) in this weight range is

comparable. However, more pronounced differences are shown in the morphine glucuronides. Here, when a bolus of morphine is given, the maximum concentration of M3G is higher in obese patients (panel B). In addition, as a result of decreased elimination clearance, the AUC is also increased in these patients. For M6G (panel C), an effect of TBW on formation clearance and elimination clearance results in lower peak concentrations, but an increased AUC in obese patients. After a continuous infusion of 48 h of infusion, the 253-kg patient has approximately a five times higher concentration of M3G and a three times higher concentration of M6G compared with the 56-kg healthy volunteer (panels D,E).

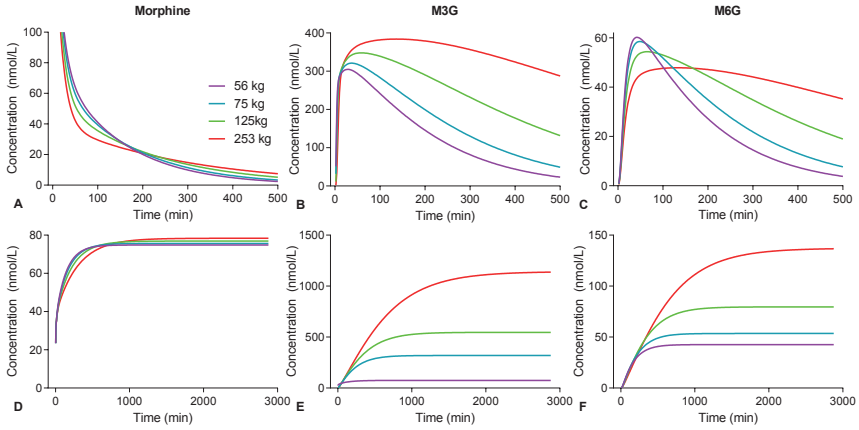


Figure 4. Population predicted morphine, morphine-3-glucuronide, morphine-6-glucuronide concentrations over time in four typical study patients (56, 75, 125 and 253 kg after a 10 mg intravenous bolus dose of morphine hydrochloride (a,b,c) and a 2.0 mg/h continuous infusion of morphine hydrochloride for 48 hours (d,e,f).

Discussion

As limited data are available on the pharmacokinetics of morphine in morbidly obese patients, this study aimed to evaluate the influence of obesity on the metabolism of intravenously administered morphine and its pharmacologically active glucuronides (M3G and M6G). The results of this study show that, besides a slight decrease in formation of M6G, the formation clearance of the main metabolite M3G is similar between the groups, although the formation was delayed. It has been reported before, that UGT-mediated drug metabolism is potentially increased in obese patients in comparison with non-obese patients[28]; for example, for paracetamol glucuronidation (and sulphation) is increased in obese patients[3]. The lack of influence of obesity on morphine glucuronidation in

the present study may be explained by the fact that morphine is a medium-to-high extraction ratio drug, assuming liver blood flow remains unchanged in morbidly obese patients[2]. Such drugs are rapidly metabolized depending on hepatic blood flow and are relatively insensitive to changes in enzyme activity[14].

The most important finding of the current study is the decrease in elimination clearance of both morphine glucuronides, and the resulting increased exposure to these metabolites that may therefore be expected in the obese patients (Figure 4). Increased AUC ratios of glucuronides:morphine in obese patients when compared to the metabolic ratios reported for healthy adults in the literature has been reported before[10]. However, from a physiological perspective these results are somewhat unexpected because the elimination of morphine glucuronides in animals is mainly through renal excretion; i.e., only about 20% of the morphine glucuronides is excreted through bile[29–31]. Therefore, we did not expect such a dramatic reduction in glucuronide clearance in the obese patients, as the routine blood tests of renal function around surgery show no indication that our obese patients had an impaired renal function. A more likely explanation is that elimination of the morphine glucuronides in the bile plays a much larger role in special patient populations than previously thought, implying a significant role for hepatic transporters.

Multidrug resistance proteins MRP2 (ABCC2) and MRP3 (ABCC3) are known to be involved in the transport of morphine and metabolites. MRP2 is mainly involved in the efflux of molecules from hepatocytes to the bile, while MRP3 is involved in the efflux from hepatocytes to plasma[32]. A decrease in MRP2 activity could therefore lead to a decrease in morphine glucuronide elimination. It is also likely that obese individuals could have decreased MRP2 as a result of NASH. This condition is associated with alterations in the expression and function of metabolizing enzymes and transporters[33,34]. In a NASH model in the rat, impaired function of MRP2 resulted in significantly reduced biliary excretion of M3G[32]. Furthermore, there is genetic evidence in humans that the activity of MRP2 is critical for biliary excretion of substrates. In an inherited medical condition known as Dubin-Johnson syndrome, dysfunctional mutations in the *MRP2* gene cause impairment in biliary excretion of bilirubin, such as bilirubin glucuronides. Together with upregulation of MRP3, this results in jaundice in patients with Dubin-Johnson syndrome[35].

A recent clinical study measured bile acids as a surrogate parameter for activity of protein expression of the hepatic basolateral efflux transporter Mrp-3[12]. Seven obese patients (mean BMI of 32 kg/m^2) with confirmed NASH were included in a non-compartmental analysis and no differences in the pharmacokinetics of

morphine compared with healthy subjects were found. Healthy volunteers had no liver biopsy to confirm the absence of NASH. However, an increase of around 50% in the AUC of the glucuronides in the patients with NASH was reported[12]. Upregulated MRP3 could increase the efflux from the hepatocytes to plasma, thereby reducing the concentrations available to be excreted to bile by MRP2 and thus increasing the residence time of M3G in plasma. The question is whether a combination of upregulated MRP3 and a decreased functional MRP2 can account completely for the increased exposure to morphine glucuronides in obese patients. This study of Ferslew et al. shows that increasing severity of NASH correlates with increasing bile acids, meaning that increasing NASH severity may further increase MRP3-mediated efflux clearance[12]. Taking into consideration that our patients have a far greater BMI index (mean 49.9 kg/m^2) compared to this study, the impact of the MRP2/MRP3 transporters is potentially even greater.

Remarkably, accumulation of the morphine glucuronides is also seen in other patient populations. The study of Ahlers et al. compared ICU patients (i.e. cardiac surgery patients and critically ill patients) with healthy volunteers and found that M3G elimination clearance was decreased independently of the creatinine levels[36]. Because these patients had a BMI of around 28 kg/m^2, it is possible that obesity related factors may have caused these results. Moreover, another study found increased expression of MRP3 protein in post-mortem biopsy samples of critically ill ICU patients[37]. Similar results on accumulation of morphine glucuronides have been reported in children undergoing cardiac surgery compared with non-cardiac surgery children[38]. Whether induction or inactivation of transporters in the acute setting such as surgery can play a role in the metabolism of drugs is area for future research. For example, a rat model of acute sepsis showed upregulation of MRP3 mRNA levels[39].

The time-concentration simulations in Figure 4 illustrate the large increase in exposure to M3G and M6G that may be expected in individuals of varying body weights. Although the structure of the metabolites is quite similar, the effect of TBW on their profiles is different. This is the result of the different covariate functions on the M6G compared to M3G, and possibly of the lower fraction of morphine that is converted to M6G and the different UGT enzymes responsible for glucuronidation of the metabolites[8]. The clinical relevance of increased concentrations of M3G and M6G is however not clear. The general assumption is that M3G, although showing higher plasma concentrations, has lower opioid receptor binding affinity compared to morphine and lacks opioid activity, although some studies have reported anti-analgesic effects[40–42]. However, M6G binds with high affinity to the opioid receptor and contributes to the analgesic properties of

morphine[8]. There is a slow equilibration of the glucuronides between plasma and effect sites in the central nervous system, which is why the contribution of the glucuronides can become more important in prolonged exposure or decreased clearance for example in renal failure[43]. Recently it has become clear that morbidly obese patients 6 months after gastric bypass surgery had an increase in morphine exposure after oral administration[9]. The exposure of morphine increased probably because of an increase in absorption, while the exposure of glucuronides remained the same compared to pre-surgery state. This suggests a pathophysiological change after weight loss such as decrease in glucuronidation capacity, an increase in elimination clearance, or altered liver blood flow and/or liver membrane transporters.

There were some limitations in this study. First, even though the impact is expected to be small since morphine is administered at the end of surgery, the effects of anaesthesia and surgery on the pharmacokinetics of morphine and its metabolites cannot be assessed. Second, morbidly obese patients were not screened for the presence of NASH because no liver biopsy was taken. Third, TBW was the only body size descriptor available to investigate in this study. Last, no urinary samples were available to measure the concentrations of morphine and its metabolites. In this study, the measurements of morphine, M3G and M6G concentrations came from the same blood samples. The measurements can therefore be assumed to be correlated. While it would have been technically possible to estimate the intra-sample correlations between the concentrations, this was not considered relevant for the estimation of the pharmacokinetic parameters, their variances, and their covariates.

Future studies evaluating the influence of hepatic transporters and bile acid homeostasis in morbidly obese patients and after bariatric surgery are needed to understand more of the pathophysiological changes associated with obesity. In addition, studies should evaluate the clinical effects of increased morphine glucuronides in terms of efficacy and safety.

Conclusion

In morbidly obese patients, the pharmacokinetics of morphine are comparable to healthy volunteers, thus no weight-based dosing adjustments are necessary for pharmacokinetic purposes. However, the elimination clearance of both M3G and M6G are significantly decreased resulting in increased exposure to the metabolites, especially with prolonged administration of morphine. A suggested underlying mechanism is a change in membrane transporters that are associated with

patients with NASH, a hepatic condition common in obese individuals. Additional mechanisms of increased glucuronide concentrations is area for future research, together with the pharmacodynamic and clinical consequences of increased M3G and M6G concentrations, especially.

Acknowledgements

Sabine Ahlers is acknowledged for her contributions to this work. Part of this work was carried out on the Dutch national e-infrastructure with the support of SURF Foundation.

Literature

1. (WHO), W. H. O. Factsheet obesity and overweight. 2016,
2. Knibbe, C. A. *et al.* Drug disposition in obesity: toward evidence-based dosing. *Annu. Rev. Pharmacol. Toxicol.* 55, 149–167 (2015).
3. van Rongen, A. *et al.* Morbidly Obese Patients Exhibit Increased CYP2E1-Mediated Oxidation of Acetaminophen. *Clin. Pharmacokinet.* 55, 833–847 (2016).
4. Brill, M. J. *et al.* Midazolam pharmacokinetics in morbidly obese patients following semi-simultaneous oral and intravenous administration: a comparison with healthy volunteers. *Clin. Pharmacokinet.* 53, 931–941 (2014).
5. Brill, M. J. *et al.* The Pharmacokinetics of the CYP3A Substrate Midazolam in Morbidly Obese Patients Before and One Year After Bariatric Surgery. *Pharm. Res.* 32, 3927–3936 (2015).
6. Brill, M. J. *et al.* Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. *J. Antimicrob. Chemother.* 69, 715–723 (2014).
7. Martini, C., Olofsen, E., Yassen, A., Aarts, L. & Dahan, A. Pharmacokinetic-pharmacodynamic modeling in acute and chronic pain: an overview of the recent literature. *Expert Rev. Clin. Pharmacol.* 4, 719–728 (2011).
8. Sverrisdottir, E. *et al.* A review of morphine and morphine-6-glucuronide's pharmacokinetic-pharmacodynamic relationships in experimental and clinical pain. *Eur. J. Pharm. Sci.* 74, 45–62 (2015).
9. Lloret-Linares, C., Scherrmann, J.-M. & Declèves, X. The effect of morbid obesity on morphine glucuronidation. *Pharmacol. Res.* 114, 299–300 (2016).
10. Lloret-Linares, C. *et al.* Oral Morphine Pharmacokinetic in Obesity: The Role of P-Glycoprotein, MRP2, MRP3, UGT2B7, and CYP3A4 Jejunal Contents and Obesity-Associated Biomarkers. *Mol. Pharm.* 13, 766–773 (2016).
11. Lloret-Linares, C. *et al.* Effect of a Roux-en-Y gastric bypass on the pharmacokinetics of oral morphine using a population approach. *Clin. Pharmacokinet.* 53, 919–930 (2014).
12. Ferslew, B. C. *et al.* Altered morphine glucuronide and bile acid disposition in patients with nonalcoholic steatohepatitis. *Clin. Pharmacol. Ther.* 97, 419–427 (2015).
13. Hitt, H. C., McMillen, R. C., Thornton-Neaves, T., Koch, K. & Cosby, A. G. Comorbidity of obesity and pain in a general population: results from the Southern Pain Prevalence Study. *J. Pain* 8, 430–436 (2007).
14. Lloret Linares, C. *et al.* Pharmacology of morphine in obese patients: clinical implications. *Clin. Pharmacokinet.* 48, 635–51 (2009).
15. Rose, D. K., Cohen, M. M., Wigglesworth, D. F. & DeBoer, D. P. Critical respiratory events in the postanesthesia care unit. Patient, surgical, and anesthetic factors. *Anesthesiology* 81, 410–418 (1994).
16. Sarton, E. *et al.* Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 93, 1245–54; discussion 6A (2000).
17. Romberg, R. *et al.* Pharmacokinetic-pharmacodynamic modeling of morphine-6-glucuronide-induced analgesia in healthy volunteers: absence of sex differences. *Anesthesiology* 100, 120–133 (2004).
18. van Kralingen, S. *et al.* Pharmacokinetics and protein binding of cefazolin in morbidly obese patients. *Eur. J. Clin. Pharmacol.* 67, 985–92 (2011).

19. van Kralingen, S. *et al.* Comparative evaluation of atracurium dosed on ideal body weight vs. total body weight in morbidly obese patients. *Br. J. Clin. Pharmacol.* 71, 34–40 (2011).
20. Diepstraten, J. *et al.* Population pharmacodynamic model for low molecular weight heparin nadroparin in morbidly obese and non-obese patients using anti-Xa levels as endpoint. *Eur. J. Clin. Pharmacol.* 71, 25–34 (2015).
21. Beal, S., Sheiner, L. B., Boeckmann, A. & Bauer, R. J. *NONMEM user's guide (1989-2009)*. (Ellicott City: Icon Development Solutions, 2009).
22. Keizer, R. J., Karlsson, M. O. & Hooker, A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. *CPT pharmacometrics Syst. Pharmacol.* 2, e50 (2013).
23. Team., R. D. C. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. *Vienna R Found. Stat. Comput.* (2008).
24. Meshkat, N., Kuo, C. E. & DiStefano 3rd, J. On finding and using identifiable parameter combinations in nonlinear dynamic systems biology models and COMBOS: a novel web implementation. *PLoS One* 9, e110261 (2014).
25. Beal, S. L. Ways to fit a PK model with some data below the quantification limit. *J. Pharmacokinet. Pharmacodyn.* 28, 481–504 (2001).
26. Andersen, G., Christrup, L. & Sjogren, P. Relationships among morphine metabolism, pain and side effects during long-term treatment: an update. *J. Pain Symptom Manage.* 25, 74–91 (2003).
27. Yafune, A. & Ishiguro, M. Bootstrap approach for constructing confidence intervals for population pharmacokinetic parameters. I: A use of bootstrap standard error. *Stat. Med.* 18, 581–599 (1999).
28. Brill, M. J. *et al.* Impact of obesity on drug metabolism and elimination in adults and children. *Clin. Pharmacokinet.* 51, 277–304 (2012).
29. Christrup, L. L. Morphine metabolites. *Acta Anaesthesiol. Scand.* 41, 116–122 (1997).
30. Ouellet, D. M. & Pollack, G. M. Biliary excretion and enterohepatic recirculation of morphine-3-glucuronide in rats. *Drug Metab. Dispos.* 23, 478–484 (1995).
31. Garrett, E. R. & Jackson, A. J. Pharmacokinetics of morphine and its surrogates. III: Morphine and morphine 3-monoglucuronide pharmacokinetics in the dog as a function of dose. *J. Pharm. Sci.* 68, 753–771 (1979).
32. Dzierlenga, A. L. *et al.* Mechanistic basis of altered morphine disposition in nonalcoholic steatohepatitis. *J. Pharmacol. Exp. Ther.* 352, 462–470 (2015).
33. Fisher, C. D. *et al.* Hepatic cytochrome P450 enzyme alterations in humans with progressive stages of nonalcoholic fatty liver disease. *Drug Metab. Dispos.* 37, 2087–2094 (2009).
34. Hardwick, R. N. *et al.* Altered UDP-glucuronosyltransferase and sulfotransferase expression and function during progressive stages of human nonalcoholic fatty liver disease. *Drug Metab. Dispos.* 41, 554–561 (2013).
35. Konig, J., Rost, D., Cui, Y. & Keppler, D. Characterization of the human multidrug resistance protein isoform MRP3 localized to the basolateral hepatocyte membrane. *Hepatology* 29, 1156–1163 (1999).
36. Ahlers, S. J. *et al.* Morphine Glucuronidation and Elimination in Intensive Care Patients: A Comparison with Healthy Volunteers. *Anesth. Analg.* 121, 1261–1273 (2015).

37. Vanwijngaerden, Y. M. *et al.* Critical illness evokes elevated circulating bile acids related to altered hepatic transporter and nuclear receptor expression. *Hepatology* 54, 1741–1752 (2011).
38. Valkenburg, A. J. *et al.* Pharmacodynamics and Pharmacokinetics of Morphine After Cardiac Surgery in Children With and Without Down Syndrome. *Pediatr. Crit. Care Med.* 17, 930–938 (2016).
39. Cherrington, N. J., Slitt, A. L., Li, N. & Klaassen, C. D. Lipopolysaccharide-mediated regulation of hepatic transporter mRNA levels in rats. *Drug Metab. Dispos.* 32, 734–741 (2004).
40. Smith, M. T., Watt, J. A. & Cramond, T. Morphine-3-glucuronide--a potent antagonist of morphine analgesia. *Life Sci.* 47, 579–585 (1990).
41. Gong, Q. L., Hedner, T., Hedner, J., Bjorkman, R. & Nordberg, G. Antinociceptive and ventilatory effects of the morphine metabolites: morphine-6-glucuronide and morphine-3-glucuronide. *Eur. J. Pharmacol.* 193, 47–56 (1991).
42. Mercadante, S. The role of morphine glucuronides in cancer pain. *Palliat. Med.* 13, 95–104 (1999).
43. Dahan, A. & Lotsch, J. Morphine is not a prodrug. *Br. J. Anaesth.* 114, 1005–1006 (2015).

Supplemental Material

Output COMBOS: http://biocyb1.cs.ucla.edu/combos/

Only Positive Solutions
CLf3 is uniquely identifiable
CLf6 is uniquely identifiable
Q1 is locally identifiable with 2 solutions
Q2 is locally identifiable with 2 solutions
V1 is uniquely identifiable
V2 is locally identifiable with 2 solutions
V3 is locally identifiable with 2 solutions
CLe3 is uniquely identifiable
V4 is uniquely identifiable
CLe6 is uniquely identifiable

COMBOS Runtime = 25.00 seconds

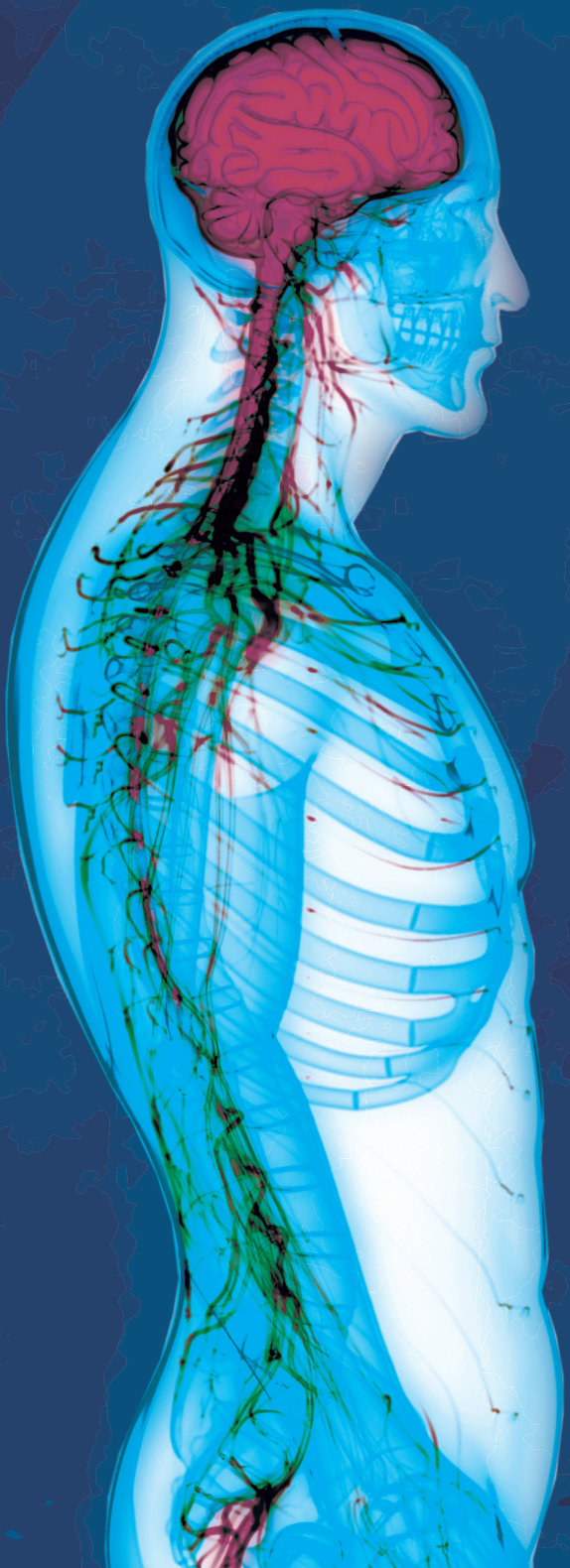
Supplemental file – NONMEM model code of final model

```
$SUBROUTINE ADVAN6 TOL9
$MODEL
COMP (CENTRAL,DEFDOSE)
COMP (COMP1)   ;M3G
COMP (COMP2)   ;M6G
COMP (PERIPH1) ; Peripheral cmt for parent
COMP (PERIPH2)  ; Peripheral cmt for parent
COMP (BUFFER)  ;m6g
COMP (BUFFER2) ;m6g
COMP (BUFFER3) ;m3g
COMP (BUFFER4) ;m3g
COMP (BUFFER5) ;m3g
COMP (BUFFER6) ;m3g
COMP (BUFFER7) ;m3g

$PK
TVCL1=THETA(1)
CL1=TVCL1*EXP(ETA(1))
TVV1=THETA(2)
V1=TVV1*EXP(ETA(2))
TVCL2=THETA(3)*(WT/98.5)**THETA(14)
CL2=TVCL2*EXP(ETA(3))
TVCL3=THETA(4)*(WT/98.5)**THETA(15)
CL3=TVCL3*EXP(ETA(4))
TVCL4=THETA(5)*(WT/98.5)**THETA(12)
CL4=TVCL4*EXP(ETA(5))
TVQ2=THETA(6)
Q2=TVQ2*EXP(ETA(6))
TVQ3=THETA(7)
Q3=TVQ3*EXP(ETA(7))
TVV5=THETA(8)*(WT/98.5)**THETA(13)
V5=TVV5*EXP(ETA(8))
TVV2=V1*THETA(9)
V2=TVV2*EXP(ETA(9))
V3=V2
TVV4=THETA(11)
V4=TVV4*EXP(ETA(11))
```

```
TVKTR=THETA(10)
KTR=TVKTR*EXP(ETA(10))
TVKTR2=THETA(16)*(WT/98.5)**THETA(17)
KTR2=TVKTR2*EXP(ETA(12))
K18=CL1/V1
K16=CL2/V1
K10=0.35*((CL1 + THETA(3)*(70/98.5)**THETA(14))/0.65)/V1 ;CL0/V1
K67=KTR
K73=KTR
K89=KTR2
K910=KTR2
K1011=KTR2
K1112=KTR2
K122=KTR2
K20=CL3/V2
K30=CL4/V3
K14=Q2/V1
K41=Q2/V4
K15=Q3/V1
K51=Q3/V5
S1=V1
S2=V2
S3=V3
S4=V4

ET1=ETA(1)
ET2=ETA(2)
ET3=ETA(3)
ET4=ETA(4)
ET5=ETA(5)
ET6=ETA(6)
ET7=ETA(7)
ET8=ETA(8)
ET9=ETA(9)
ET10=ETA(10)
ET11=ETA(11)
```

```
$DES
DADT(1)=-(K18+K16+K10+K14+K15)*A(1)+K41*A(4)+K51*A(5)
DADT(2)=K122*A(12)-K20*A(2)
DADT(3)=K73*A(7)-K30*A(3)
DADT(4)=K14*A(1)-K41*A(4)
DADT(5)=K15*A(1)-K51*A(5)
DADT(6)=K16*A(1) -K67*A(6)
DADT(7)=K67*A(6) -K73*A(7)
DADT(8)=K18*A(1) -K89*A(8)
DADT(9)=K89*A(8) -K910*A(9)
DADT(10)=K910*A(9) -K1011*A(10)
DADT(11)=K1011*A(10) -K1112*A(11)
DADT(12)=K1112*A(11) -K122*A(12)

$ERROR
COM1=0
IF (CMT.EQ.1) COM1=1
COM2=0
IF (CMT.EQ.2) COM2=1
COM3=0
IF (CMT.EQ.3) COM3=1
Y1=F*(1+ERR(1)*(1-OBES)+ERR(4)*OBES)
Y2=F*(1+ERR(2)*(1-OBES)+ERR(5)*OBES)
Y3=F*(1+ERR(3)*(1-OBES)+ERR(6)*OBES)
Y=COM1*Y1+COM2*Y2+COM3*Y3
IPRED=F
IRES=DV-IPRED
DEL=0
IF(IPRED.EQ.0)DEL=1
IWRES=(1-DEL)*IRES/(IPRED+DEL)

$THETA
(0, 0.8)   ;CL1
(0, 5)     ;V1
(0, 0.15) ;CL2
(0, 0.15) ; CL3
(0, 0.15) ; CL4
(0, 0.9)   ; Q2
(0, 1.27) ; Q3
```

```
(0, 110)  ; V5
(0, 5,1000)          ; V2
(0, 0.158)           ; KTr
(0, 8)               ; V4
(-2, -1.02,20)       ; *CL4
(-0.9, 0.468,20)     ; *V5
(-2, -0.272,20)      ; *CL2
(-2, -1.08,20)       ; *CL3
(0, 1.64,1000)       ; ktr2 (m3g)
(-2,-0.5,20)         ; *KTR2

$OMEGA
0.08                 ;CL1
0 FIX                ;V1
0 FIX                ;CL2
0.4                  ;CL3
0 FIX                ;CL4
0 FIX                ;Q2
0 FIX                ;Q3
0 FIX                ;V5
0.0889               ;V2=V3
0.3   ;              KTR
0 FIX ;              V4
0 FIX ;              KTR2
0 FIX ;

$SIGMA
0.01; SIGMA1 parent
0.05
0.05
$SIGMA
0.1 ; SIGMA1 parent, obese
0.05
0.05
```



Section V

Summary, considerations and perspectives

Chapter 10

The impact of opioids on postoperative pain in different patient populations: summary, conclusions and perspectives

Summary and conclusions

The last decades it is increasingly recognized that acute as well as chronic postoperative pain is an important topic. With the increase in life expectancy and increase of the elderly population it is expected that the population of (chronic) pain patients will increase. In the Netherlands, nationwqide programs have been initiated to address postoperative pain, amongst others because pain is a quality indicator in Dutch hospitals[1]. Around 80% of patients undergoing surgery experience acute postoperative pain rated as moderate or severe[2]. Studies show that only half of postoperative patients experience adequate pain relief[3]. Multiple risk factors for the development of acute postoperative pain have been identified, for example younger age, female sex, anxiety, and use of preoperative analgesia[4]. In addition, acute postoperative pain is also a risk factor for the development of chronic postoperative pain. Chronic postoperative pain lasts 2 to 3 months after surgery and is beyond the healing of injured tissue and the related inflammatory processes[5,6]. The incidence of chronic postoperative pain varies widely, but it is estimated that 10 to 50% of the patients undergoing surgery develop chronic postoperative pain[5,7,8]. Chronic postoperative pain is variously defined and described, which probably plays a role in the wide variation in reported incidence. Type of surgery is also of importance, since especially surgical procedures where major nerves trespass the surgical field are associated with chronic pain[5]. Therefore, chronic pain is associated with a variety of surgical procedures such as amputation, breast surgery, thoracotomy, inguinal hernia repair, coronary artery bypass, and caesarean sections[5,9]. Risk factors identified for the development of chronic postoperative pain are acute postoperative pain, younger age, female gender, psychosocial factors such as anxiety, preceding pain and genetic susceptibility[5,6].

Pain and inadequate pain relief are a heavy burden for the patient and have an impact on the quality of life and performance of activities of daily living[8,10]. Moreover, this condition has also a high economic burden since in chronic pain patients unemployment rates and claims for incapacity benefit are high[11]. The optimal use and implementation of (inter)national guidelines for pain assessment and subsequent pain management and relief may decrease morbidity and mortality and increase quality of life in postoperative patients. Intraoperative and postoperative opioids play a major role in preventing and managing postoperative pain. Despite the extensive use of opioids for postoperative pain management, knowledge for optimal use in special patient populations is lacking.

This thesis aimed to contribute to the quality of postoperative pain management in different patient populations with the focus on opioid analgesia. In this chapter

the findings of the studies presented in this thesis are summarized and future perspectives are discussed.

Opioid analgesia in adult cardiac surgery patients

In *section II*, the focus is on adult cardiac surgery patients and on both acute and chronic postoperative pain. In adults, cardiac surgery belongs to the most frequently performed types of surgery worldwide with a known high risk on postoperative pain[12,13]. Patients after cardiac surgery with controllable pain, recover faster and have lower risk for complications[14]. Multiple studies suggest that the use of remifentanil, an ultra-short-acting and hyper potent opioid, is associated with an increase in acute and chronic postoperative pain when used during surgery[15,16]. In **chapter 2,** we present an overview of the literature on the associations of intraoperative remifentanil administration with acute postoperative pain, hyperalgesia, and chronic postoperative pain. From the studies that were identified, almost half found higher acute postoperative pain, higher postoperative analgesic requirements after intraoperative remifentanil use, or both. Coanaesthetics to some extent were found to influence this incidence, with studies using volatile agents (i.e. sevoflurane or nitrous oxide) reporting increased pain levels. Less evidence for increased postoperative pain was found when remifentanil was combined with total intravenous anaesthesia or a combination of anaesthetics. For chronic postoperative pain, only few studies were available and study design varied extensively. A potential association between the use of intraoperative use of remifentanil and chronic pain was found but no clear conclusions could be made. Further research with the primary goal to investigate the effect remifentanil infusion on acute and chronic postoperative pain was therefore needed. For this reason, a randomized controlled trial investigating the effect of remifentanil on acute and chronic postoperative pain was designed and the protocol is described in **chapter 3.** Patients received standardized anaesthesia with propofol and fentanyl boluses given at predetermined times and were randomized between remifentanil infusion and additional fentanyl boluses. In **chapter 4**, the results of this randomized controlled trial on the effect of remifentanil on acute and chronic postoperative pain 3, 6 and 12 months after surgery are reported. In this study, 126 adult patients undergoing cardiac surgery via sternotomy were included. Based on a self-report questionnaire, at 12 months after surgery there was no significant difference in incidence of chronic thoracic pain between the remifentanil and fentanyl groups (20% vs. 18%, respectively; p=0.817). At three months, however, significantly more patients in the remifentanil group reported chronic thoracic pain (51% vs. 33%; p=0.047). This effect was more pronounced in younger patients and in patients receiving a higher dose of

remifentanil (both $p<0.05$). In addition, in the first 24 and 48 hours after surgery, morphine consumption in the remifentanil group was significantly higher than in the fentanyl group (34.3 mg (interquartile range (IQR) 25.3 to 48.2) vs. 30.2 mg (IQR 19.2 to 38.1), p= 0.028; and 46.8 mg (IQR 33.8 to 59.2) vs. 39.0 mg (IQR 6.2 to 51.4), p=0.047, respectively). In conclusion, intraoperative use of remifentanil during cardiac surgery does not impact chronic postoperative pain one year after surgery. Nevertheless, remifentanil increases analgesic requirements and chronic postoperative pain until three months after surgery.

To investigate pain levels after cardiac surgery in a more objective manner, thermal detection and pain thresholds were measured in this randomized controlled trial of which the results were reported in **chapter 5**. Warm and cold detection and pain thresholds three days and 12 months after cardiac surgery were measured. The use of remifentanil, presence of postoperative chronic pain, age, opioid consumption and preoperative quality of life were tested as a predictor for altered pain sensitivity measured with thermal thresholds at 12 months after surgery. Both warm and cold detection and pain thresholds were not significantly different between the remifentanil and fentanyl groups three days as well as 12 months after surgery ($p>0.05$). No significant predictors for altered pain sensitivity were identified. We conclude that using quantative sensory testing we cannot confirm earlier reports of increased pain sensitivity one year after the use of remifentanil in this randomised study.

In this cohort of cardiac surgery patients, we also investigated potential genetic components of pain. **Chapter 6** describes the potential influence of *OPRM1* (mu-opioid receptor) and *COM*T (catechol-O-methyltransferase enzyme) polymorphisms in postoperative acute, chronic and experimental thermal pain. No association was found between COMT haplotype and other pain outcomes or OPRM1 polymorphisms and the different pain modalities. Patients in the fentanyl group with the COMT high-pain sensitivity haplotype required less postoperative morphine compared with the average-pain sensitivity haplotype (19.4 (16.5 to 23.0) vs. 34.6 (26.2 to 41.4); p=0.00768), but not to the low-pain sensitivity group (30.1 (19.1 to 37.7); p=0.13). In conclusion, COMT haplotype appears to explain a small part of the variability in acute postoperative pain in adult cardiac surgery patients.

Opioids after paediatric cardiac surgery

Section III focuses on the use of morphine in children after cardiac surgery. In children, morphine is commonly used for analgesia after cardiac surgery but

little is known about its analgesic efficacy in relation to plasma concentrations. Therefore, in **chapter 7** we report on the pharmacodynamics of morphine in children after cardiac surgery using repeated Time-to-Event (RTTE) modelling. In this study, data from a previous published study on morphine pharmacokinetics and morphine requirements in 35 children aged 3 to 35 months after cardiac surgery receiving morphine as loading dose (100 μg/kg) followed by continuous infusion (40 μg/kg/hr) were analysed[17]. Events were defined as rescue morphine bolus doses and/or increases in infusion rate as guided by validated pain scores (i.e. COMFORT-B). During the postoperative period (median 38 (IQR 23 to 46) hours), 130 events (median 4 (IQR 1 to 5) per patient) occurred, with the majority in the first 24h (107/130). Median morphine concentration during an event was 29.5 ng/ml (range 7 to 180 ng/ml). A RTTE model in which the hazard of rescue morphine decreased over time (half-life 18 hours; $p<0.001$) was found to describe the hazard for rescue events well. Counterintuitively, an increase in hazard for rescue morphine was seen at higher morphine concentrations (21.9% at 29.5 ng/ml; $p<0.001$). However, the confidence interval was wide, indicating that the actual influence of increased morphine concentration on the hazard could in fact be small. Still, morphine concentrations in this study are much higher compared to the previously suggested therapeutic range of 10 to 20 ng/ml. Although the evidence supporting this therapeutic range is limited, it was unexpected that rescue dosing was still required upon these high concentrations. The fact that 24% of the rescue morphine was administered within one hour of a previous dose, suggest that morphine is maybe not the ideal opioid to be used as rescue medication. Thus, in children after cardiac surgery receiving protocolized morphine infusions and rescue doses, we observed a significant number of rescue events. Rescue morphine was required at a wide range of morphine concentrations and further increase of the morphine concentration did not lead to a decrease in hazard. Future studies should focus on a multimodal approach using other opioids or other analgesics to treat breakthrough pain in children.

Pharmacokinetics of opioids in obese patients

In *section IV,* we focus on the obese patient population. As noted, the obese population is growing over the last decades. The increasing numbers will also result in an increase in the number of obese patients that undergo surgery and require treatment for postoperative pain.

First, in **chapter 8**, we present an overview of the literature about the influence of obesity on pharmacokinetic and pharmacodynamic parameters in adults. In this review, physiological changes associated with obesity are discussed. An overview

is provided on the alterations in absorption, distribution, drug metabolism and clearance in (morbid) obesity focusing on general principles that can be extracted from pharmacokinetic studies. Future research should focus on connecting obesity-related physiological changes with changes in pharmacokinetic and/or pharmacodynamics parameters and vice versa. In addition, efforts should focus on implementation of these model-derived dosing recommendations in clinical practice.

Second, in **chapter 9**, we present the pharmacokinetics of morphine in obese patients when compared to non-obese healthy volunteers. The clinical use of morphine is characterized by a large inter-individual variability in analgesic effect, in which the role of (morbid) obesity is unclear. The aim of this study was to investigate the influence of obesity on the pharmacokinetics of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) through a combined analysis in morbidly obese patients and non-obese healthy volunteers. Data from 20 morbidly obese patients [mean body mass index 49.9 kg/m^2 (range 37.6 to 78.6 kg/m^2) and weight 151.3 kg (range 112 to 251.9 kg)) and 20 healthy volunteers (mean weight 70.6 kg (range 58 to 85 kg)) were included. Morbidly obese patients received 10 mg of intravenous morphine after gastric bypass surgery, with additional morphine intravenous doses as needed. Healthy volunteers received an intravenous bolus of morphine of 0.1 mg/kg followed by an infusion of 0.030 mg/kg/h for 1 h. In morbidly obese patients, elimination clearance of M3G and M6G was decreased substantially compared with healthy volunteers ($p<0.001$). Regarding glucuronidation, only a slight decrease in the formation of M6G and a delay in the formation of M3G was found (both $p<0.001$). Obesity was also identified as a covariate for the peripheral volume of distribution of morphine ($p<0.001$). From this study, we can conclude that metabolism of morphine is not altered in morbidly obese patients. Morphine concentrations proved similar between the morbidly obese patients and non-obese patients, indicating that no weight-based dosing adjustments are necessary. However, decreased elimination of both M3G and M6G is evident, resulting in a substantial increase in exposure to these two metabolites. The clinical consequences of this findings are uncertain and are potentially only of interest upon prolonged administration of morphine.

Perspectives

In this section the results that were obtained in this thesis are discussed from a broader perspective. First, we will evaluate the use remifentanil in cardiac surgery in light of the results of section II of this thesis. Second, lessons to be learned from studies in obese and paediatric patients are outlined. Lastly, pain measures in

clinical pain studies and clinical practice are discussed.

Remifentanil in cardiac surgery

In *section II* of this thesis we have focused on the use of remifentanil during cardiac surgery. Toward the end of the 20th century, the number of cardiac surgery patients increased and surgery became more complicated with increasing age and comorbidities of these patients. The end of the "high-dose opioid anaesthesia" era started with the development of intravenous anaesthetic agents with rapid on- and offset, and was complete with the introduction of an ultra-short-acting opioid. Remifentanil is nowadays often used during cardiac surgery because of its favourable pharmacokinetic and pharmacodynamic properties[18]. Remifentanil is a short-acting, hyperpotent μ-opioid receptor agonist of which the clearance is independent of renal of hepatic function[19]. A systematic review on general anaesthesia and analgesia showed that, when compared with other intraoperative opioids, remifentanil was associated with clinical signs of deeper analgesia and anaesthesia, faster recovery (shorter extubation time), fewer respiratory events requiring naloxone and more frequent postoperative analgesic requirements[20]. In studies that evaluate fast-track cardiac anaesthesia with remifentanil, however, no superiority of remifentanil compared to sufentanil[21] or low-dose fentanyl[22] was found with regards to the time of recovery. Despite the vital use of opioids during surgery for preventing and treating peri- and postoperative pain, opioids are also associated with opioid induced hyperalgesia (OIH)[23,24]. Although OIH was first thought to be associated with all opioids, the strongest association was found with remifentanil[15]. OIH is demonstrated in animal models and human volunteers, but the clinical impact in patients is difficult to estimate since studies are diverse and sample sizes are small, as discussed in chapter 2[25]. Nevertheless, a systematic review showed a small but significant increase in acute postoperative pain and opioid consumption after (high) doses of remifentanil[15]. After four hours, a mean difference of 7.1 cm on a 100 cm scale (95% confidence interval (CI): 2.8 to 11.3) was found. More recently, an analysis of a large medical record database found similar outcomes with evidence of increased postoperative pain and opioid consumption in patients that underwent abdominal surgery and received remifentanil during surgery[26]. The pain score at arrival in the recovery area (NRS1) and the maximum pain score (NRSmax) during stay in the recovery area were both higher in the remifentanil group compared to the control group (mean NRS1 1.52 vs. 1.28; $p<0.001$; mean NRSmax 2.47 vs. 2.17; $p<0.001$). These results correspond with the findings presented in chapter 4; cardiac surgery patients that received remifentanil during surgery needed more morphine in the first 48 hours after

surgery to maintain acceptable pain scores (46.8 mg (IQR 33.8 to 59.2) vs. 39.0 mg (IQR 6.2 to 51.4), p=0.047). In conclusion, data show that remifentanil has a negative impact on acute postoperative pain, but absolute differences are small and potentially not of great clinical impact.

The number of studies that investigated the impact of the use of remifentanil on chronic postoperative pain are limited. In our hospital, an observational follow up study on 90 cardiac patients found that remifentanil was a risk factor for the development of chronic pain at 12 months in a dose related manner[27]. As reviewed in chapter 2, only three other studies evaluated long-term effects of remifentanil on pain outcome parameters, but they varied with regards to the type of surgery, the sample size, and the study design (Table 3, page 30). Recently, a secondary analysis of pain outcomes from a prospective, randomized, open-label trial that compared remifentanil and fentanyl on perioperative hyperglycemic response in cardiac surgery was published[28]. This is one of the few studies with prolonged follow up data available but has some important differences with our study in chapter 4. First, the recent study was not powered on postoperative pain but on hyperglycemic response. Second, patients in the remifentanil group received very high doses of remifentanil (median total cumulative dose of 11 mg of remifentanil; >80 μg/kg) whereas the fentanyl group received no remifentanil. In chapter 4, patients in the remifentanil group received a mean dose of 2.1 mg (25 μg/kg) remifentanil and also fentanyl (21 μg/kg). Similar to what we found in our study, patients in this recent study in the remifentanil group received more opioids directly after surgery. In contrast to the study results of chapter 4, postoperative chronic pain three months after surgery was not significantly different between the groups while after 6 and 12 months there were no differences on the incidence of chronic postoperative pain between the groups, which is in line with our results. Overall, the incidence of chronic postoperative pain in both groups during follow up (3, 6 and 12 months) was (much) higher compared to our study, which could be an explanation for the differences in results found in both studies after three months. For example, chronic postoperative pain after 3 months was present in 61% of patients in the fentanyl group versus 58% of patients in the remifentanil group (p=0.79), which is high compared to the results of chapter 4 in which 31% versus 51% of patients presented with chronic postoperative pain after three months, respectively (p=0.047).

Based on these results, it seems that there are no long term negative consequences of the use of remifentanil during cardiac surgery. On the other hand, our results in chapter 4 show that remifentanil has a negative impact on acute postoperative pain and potentially this effect can persist up to three months after surgery. The

question therefore is, is there an advantage of remifentanil that outweigh these (small) disadvantages on acute and chronic postoperative pain? The main advantage of remifentanil could be shorter time to extubation which could result in faster recovery and length in hospital stay[29]. Others state that the use of remifentanil results in increased hemodynamic stability during surgery[30] or in a decrease in the use of hypnotics and sedatives[31]. On the other hand, studies investigating fast-track cardiac surgery with remifentanil lack evidence for a superiority of remifentanil on these parameters[21,22]. A systematic review concludes that remifentanil does not seem to offer an advantage for lengthy, major interventions, but may be useful for selected situations[20].

We conclude that even if the use of remifentanil results in remifentanil induced hyperalgesia and has impact on postoperative pain, the clinical impact of this hyperalgesia is low and diminishes over time when given for cardiac surgery in the dosages described in chapter 4. Generally, the impact of remifentanil on postoperative pain after cardiac surgery is therefore low. At the same time, one of the post-hoc analyses of our study showed that patients with a high dose of remifentanil (≥ 1875 µg) and below the age of 65 year had a higher risk of postoperative pain at three months after surgery. This could be an argument to avoid high-dose remifentanil in younger patients.

As was stated at the beginning of this section, in the context of cardiac surgery, an opioid-based anaesthesia has been the cornerstone of perioperative management for decades. Due to global opioid concerns and an increased emphasis on enhanced recovery following cardiac surgery the concept of an opioid-free cardiac surgery is currently being explored using a multimodal analgesic management[32]. The wide range of availability of nonopioid analgesics (nonsteroidal anti-inflammatory drugs, acetaminophen, N-methyl-D-aspartate antagonists, alpha-2 agonists, local anaesthetics, gabapentinoids, and others) in combination with innovative regional analgesic techniques contributes to the feasibility of opioid-free or opioid-sparing (cardiac) surgery[33]. A meta-analysis of non-cardiac surgery studies has reported benefits with opioid-free anaesthesia, but the included studies were small and heterogenous[34]. A recent randomized study in 364 patients that underwent major or intermediate non-cardiac surgery showed that opioid-free surgery is not without consequences. The study was terminated early since patients in the opioid-free balanced anaesthesia with dexmedetomidine group had more postoperative hypoxemia, delayed extubation, prolonged PACU stay, and intraoperative bradycardia[35]. This study showed that opioid-free anaesthesia is not that easy to achieve. The data related to multimodal nonopioid interventions in cardiac surgical patients are limited. Grant et al. 2020 performed a study to assess the

association between nonopioid interventions employed as part of an enhanced recovery program for cardiac surgery and intraoperative opioid administration[36]. Patients undergoing cardiac surgery received 5 nonopioid interventions, including preoperative gabapentin and acetaminophen, intraoperative dexmedetomidine and ketamine infusions, and regional analgesia via serratus anterior plane block. These nonopioid interventions were associated with a reduction of intraoperative opioid administration but, low and ultralow intraoperative opioid use was not associated with significant differences in postoperative outcomes[36].

Summarizing, the field of opioid-free analgesia during surgery is growing due to increased focus on enhanced recovery programs and increasing rates of opioid prescriptions and opioid-related deaths worldwide[37]. The current incidence of postoperative pain remains high and multimodal analgesia could be beneficial for patients. Data of opioid-free analgesia in cardiac surgery patients is limited and future prospective studies are necessary to establish the role and advantages of opioid-sparing or opioid-free strategies in the setting of cardiac surgery.

Opiates in special patients populations; lessons learned.

Paediatric patients

In chapter 7 we focus on children as a special population that are treated with opiates. Regulatory and ethical guidelines for research in children are fairly restrictive which makes it more challenging to conduct clinical trials in this population[38]. In addition, the numbers of patients are smaller, age and weight varies widely and consent has to be obtained from parents. This makes pain research in children challenging and the progression in healthcare slow. Pain has an emotional load for both parents and children and possibly even for clinicians. Together with the task to minimize risk and/or harm in research, it is plausible that the traditional treatment strategy of postoperative pain in children is generally conservative and “step down”, i.e. start with high doses of analgesics and step down to lower doses or other less potent analgesics. From a pharmacological point of view, it is known that a higher dose does not always have an additional benefit on efficacy. This is underlined in chapter 7, where we found that at high morphine concentrations, there was no effect of additional rescue doses of morphine on the hazard for rescue events after paediatric cardiac surgery. Other studies show that it is also possible to use non-opioids as primary analgesic after surgery. The study of Ceelie et al. showed in a randomized controlled trial that infants who receive intravenous paracetamol as primary analgesic after major non-cardiac surgery that was ended with a single morphine loading dose at the end of surgery,

require the same amount of additional rescue morphine than those who receive a continuous morphine infusion[39]. This study shows that a "step up", i.e. primary analgesic of paracetamol with additional morphine, strategy for analgesics after surgery is also feasible in children. In this respect, it is important to highlight that in this study all infants received intravenous opioids during surgery, with a loading dose of morphine at the end of surgery. A recent study investigating the reduction, or replacement, of morphine by IV paracetamol in children (0 to 36 months old) after cardiac surgery will give more important information on this topic after cardiac surgery[40]. This study finished recently including 208 patients in four paediatric cardiac surgery centres and data are expected soon.

The results of the study described in chapter 7 also showed that need for rescue analgesia was required at a wide range of morphine concentrations (7 to 180 ng/ml). During an event, the median morphine concentration was 29.5 ng/ml and the majority of events (n = 111 (85%)) occurred above 20 ng/ml. This finding can have multiple explanations. First, the concentration-effect relation of morphine in the acute postoperative setting is possibly not strong which is reflected by the finding that patients with the highest concentrations do not experience the highest effect. Second, this could be also an effect of the difficulty for nurses to distinguish between pain and agitation. Over the last years, efforts are made to improve pain and sedation management with the implementation of standardized protocols resulting in more adequately sedated children[41]. Still, there is potential for improvement since under- and oversedation occur in 10 and 30% of the assessments in critically ill children admitted to the intensive care unit[42]. Recently, a study reporting on the same cohort of patients in chapter 7, found that of the patients that received midazolam as part of the analgesia and sedation protocol, only a marginal effect of midazolam concentrations on the COMFORT-B scores were found[43]. If this is a result of the combination of morphine and midazolam or the low midazolam dosages is uncertain. Still, both chapter 7 and this recent study, confirm that the optimal analgesic and sedation protocol for children after cardiac surgery has not yet been found. The recently finished study in children where rescue morphine is investigated next to IV paracetamol[40] could bring us a step closer to this goal by analysing rescue doses in this setting using the same methods as chapter 7 in which RTTE modelling was applied. In this study, where it is expected that some patients have only morphine rescue without a continuous infusion of morphine as they were randomized to the paracetamol group, data will be available of patients with low or absent morphine concentrations at time of an event. These data were not available for our analysis and would be of added value in the RTTE model.

In conclusion, worldwide there is a large variation in morphine dosing after cardiac surgery in children. Chapter 7 shows that morphine rescue on top of high-dose continuous infusion morphine does not lead to an additional effect on the hazard for rescue events after cardiac surgery. Future studies are planned to optimize the use of analgesics and sedatives in children after cardiac surgery.

Obese patients

In recent years, there has been a major increase in prevalence of overweight and obese patients[44]. With obesity, patients are more likely to undergo surgery since morbidity and mortality significantly increases[45]. Postoperative pain management in obese patients is challenging since patients have increased risk for opioid side effects[46,47] and PKPD parameters for drugs in obese patients could be altered as described in chapter 8. For example, acetaminophen (paracetamol) is a frequently used analgesic in the postoperative setting for postoperative pain management. The study of van Rongen et al. showed that both acetaminophen peak concentrations and area under the plasma concentration-time curves (AUCs) were substantially lower in morbidly obese patients[48]. Lower exposure results probably in lower effectiveness, but an increase in dose in these patients remains under debate since the role of earlier and greater formation of CYP2E1-mediated metabolites may contribute to acetaminophen hepatotoxicity in case higher dosages are given[49]. Based on these results, there is still room for optimizing the dose and possibly the efficacy of acetaminophen in obese patients.

In this thesis, we focused on morphine which is another frequently used analgesic after surgery. For morphine, there was limited information about the impact of morbid obesity on PK parameters. Therefore, in chapter 9, we studied morphine in morbidly obese patients that underwent bariatric surgery and compared the data to healthy volunteers. We found that the pharmacokinetics of morphine in obese patients versus healthy volunteers was not different which means, based on the PK of morphine, that an obese patient of 150 kg should receive a similar dose compared to a patient of 70 kg. We report also that a decreased elimination of both morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in obese patients is evident, resulting in a substantial increase in exposure to these two metabolites. Regarding the relevance of this finding, it has been suggested that M3G is responsible for side-effects and pain enhancement[50], while M6G has a potent analgesic action[51]. However, these effects have been debated as the effects were not established in clinical studies. M3G has much lower affinity for the opioid receptor compared to morphine or M6G with M6G concentrations being typically very low compared to M3G and morphine concentrations[52]. Both morphine

metabolites have a hydrophilic character which result in a lower penetration rate of the blood-brain barrier compared to morphine[53]. PK and PD studies after the administration of M6G itself show that M6G has potential analgesic activity, but lower compared to morphine[54,55]. Effect site concentrations 12 to 22 times greater than those of morphine are needed to obtain a similar analgesic effect for M6G[55]. For M3G, rat studies indicate that prolonged exposure to M3G may contribute to the side effects of morphine such as morphine-induced tolerance and opioid-induced hyperalgesia[56]. Therefore, the clinical impact of decreased clearance of morphine metabolites in morbidly obese patients that receive short term morphine for postoperative analgesia is not clear and is potentially only of interest when morphine is continuously administered over a prolonged period of time.

Besides the clinical impact of increased morphine metabolites in obese patients, the physiological changes underlying these increased metabolites could potentially be important for other drugs. The physiological explanation of decreased elimination of morphine glucuronides is found in the alterations in multidrug resistance proteins MRP2 and MRP3 as a result from (prolonged) obesity or non-alcoholic steatohepatitis (NASH)[57,58]. These transporters are responsible for the in- and efflux of molecules from hepatocytes to the bile and vice versa. Due to the challenges of both diagnosing the stage of NASH and quantifying alterations in liver transporters in patients, clinical studies to evaluate the precise impact of these transporters are difficult since liver biopsy is the gold standard but expensive and invasive[59]. Recently, a physiologically-based pharmacokinetic (PBPK) model was developed to predict morphine and morphine-3-glucuronide exposure in NASH by incorporating NASH-related changes in hepatic transporters[60]. Based on the assumptions in this PBPK model, this study shows that of the NASH-related physiological changes, NASH-mediated transporter alterations had the highest effect on M3G exposure with an increased area under the curve of 43%, while morphine exposure was not substantially altered[60]. These findings highlight the importance of NASH related transporter changes and are in line with the results of chapter 9. From these results regarding the impact of obesity on hepatic transporters, we anticipate that the PK of other drugs may be influenced. For example, mice studies suggest that MRP transporters are involved in the metabolism of anticancer agents such as methotrexate[61]. For this, more studies evaluating the influence of hepatic transporters and bile acid homeostasis on the PK of drugs in morbidly obese patients and after bariatric surgery are needed, which will ultimately also result in increased understanding of the pathophysiological changes associated with obesity. Regarding morphine, we conclude that there is no need to give a higher

dose of morphine or dose morphine per kilogram body weight in obese patients. In obese patients plasma concentrations of morphine glucuronides will be higher compared to non-obese weight patients but particularly upon short term use there is no evidence for clinical (side) effects of these concentrations.

Pain measures in clinical pain studies and clinical practice

Pain has been defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage" by the International association for the Study of Pain[62]. The experience of pain is a complex interaction among biological, psychological, behavioural and social-cultural factors[63]. Patients' self-reporting of their pain is regarded as the gold standard of pain assessment measurement. Despite increasing attention for pain over the years, there are still a lot of opportunities for improvements in postoperative pain management[2]. Pain research has a broad spectrum of outcome measures, many of which we have used in this thesis. The proper use and knowledge of these outcome measures is important to improve postoperative pain management, and therefore we here discuss the outcome measures used in this thesis.

Pain scales

In section II as well as in section III of this thesis, pain scales like numerical rating scale (NRS) and comfort behavioural (COMFORT-B) scale were used in a standardized pain protocol. In adults, it is common to use the NRS for pain intensity, which showed its validity in studies with pain provoking procedures and after analgesic treatment[64]. The COMFORT-B scale is a multifactorial pain scale that is validated for the use for postoperative pain in neonates and infants[65]. Still, certain aspects of these pain scales have to be taken into account when used in clinical studies.

First, if self-reported, patients must understand the basics of a 0 to 10 scale where the lowest score means "no pain" and the highest score the "worst pain imaginable" pain. It is acknowledged that better communication and patient assessment skills will help improve and tailor pain management[66]. A study in chronic low back pain patients illustrated that poor communication between physician and patients resulted in worse pain management. Over- and underestimation of pain related impairment by the physician resulted in lower treatment responses (resp. 71.7% and 24.3%)[67]. For daily clinical practice in hospitals, this underlines the need for pretreatment patient training by experienced health care providers about pain scales such as the NRS.

Second, how the NRS for measuring pain intensity in pain research is used may vary widely which could complicate the comparison of outcomes between studies or interventions. For example, pain assessment of acute pain after surgery can be executed at rest (static pain) or during mobilization (dynamic pain), but this is not always specified in study protocols and reports. Effective relief of dynamic pain facilitates patients' mobilization and therefore may have a positive effect on long-term outcome after surgery. Future studies therefore need to take both pain at rest vs. pain during mobilization into account[68]. In hindsight, in chapter 4 we should have assessed the NRS both in rest and during mobilization to be able to further optimize pain management in cardiothoracic surgery patients.

Another aspect of the NRS score as outcome measure is that multiple scores are needed to measure pain relief. Pain scales, like the NRS, are best used to measure pain at the moment of assessment, as memory of pain is usually not accurate and often coloured by changing context[69]. This makes timing of assessment of pain relief using NRS scores also important, but time consuming because every administration of analgesics needs evaluation. Therefore, the implementation of a standardized pain protocol with repetitive NRS scores is important since studies show that this improves postoperative outcomes[70,71]. In addition, education for nurses regarding pain and its treatment should receive continuous attention[71].

Finally, in order to relief the workload and administrative burden for nurses that record pain scores, self-assessment and recording of pain by patients could be further developed and studied. A study in oncology patients showed that a self-reporting bedside pain assessment tool provides a reliable and effective way of assessing pain[72]. Recently, a proof-of-concept study in the Netherlands showed that the majority of postoperative patients (90%) were able to correctly self-record their acute postoperative pain with a smartphone application and were positive (60%) about the ease of the recording[73]. This shows that this is a promising technical development which could save time for nurses while pain reporting and evaluation of effects of pain medication is facilitated. This field of self-reporting pain using electronic devices is also emerging in patients with chronic pain conditions[74].

Consumption of analgesics

In chapter 4, we used cumulative consumption of analgesics as pain outcome measurement after cardiothoracic surgery which was facilitated by the earlier implementation of a pain titration protocol several years ago[75]. In this study, the cumulative consumption of opioids could be used as measure for the effectiveness of the postoperative pain management because the NRS scores reported were similar between groups. In this setting, patients receiving intraoperative remifentanil

received significantly more morphine 48 hours after surgery compared to patients receiving intraoperative fentanyl, which implies that patients in the remifentanil group requested were in need of pain relief. Evaluation of the NRS values showing similar NRS values in both groups confirmed that the pain titration protocol was well implemented. The consumption of analgesics is of interest as clinical pain outcome measure because the administration of more analgesics not only reflects ineffectiveness of the current treatment for the individual of interest but could also result in more side effects as result of the increased dose. We emphasize that a prerequisite for the use of this measure is that a standardized pain protocol and adherence to this protocol is guaranteed.

Quantative Sensory Testing

Quantative sensory testing (QST) collectively refers to a group of procedures that assess the perceptual responses to systematically applied and quantifiable sensory stimuli[76]. QST is used as a tool for objective pain assessment in basic mechanistic studies, clinical studies for diagnostic and monitoring purposes and pharmacological studies to evaluate the efficacy of analgesics[77]. In chapter 5, we report thermal detection and pain thresholds in patients receiving remifentanil or fentanyl both three days and one year after cardiac surgery. No differences in detection and pain thresholds between remifentanil and fentanyl were found three days or one year after surgery and no prognostic factor for chronic postoperative pain QST was found. Despite the use of QST in experimental and clinical studies, its use in clinical practice for (predicting) acute postoperative pain seems limited. The main reason is that evidence for the use of QST in this area is conflicting[78]. This also applies for chronic postoperative pain as reviewed recently[79]. The most promising results are found in studies that evaluate the dynamic pain processing system using QST[79]. For example, measurement of diffuse inhibitory noxious control (DNIC) was of predictive value for chronic postoperative pain. DNIC occurs when the response from a painful stimulus is inhibited by another noxious stimulus. It gives a dynamic view of the pain processing system and reflects the "pain-inhibits-pain" paradigm[77,80]. Patients with preoperative impaired conditioned pain modulation or DNIC were found to have a greater likelihood of developing chronic postoperative pain[81,82]. Still, large replication studies are not available. Other reasons that QST has not made it to clinical practice are related to the fact that the standardized QST protocol is labour intensive, requires expensive equipment and highly trained operators to complete the tests and interpret the data[76]. It seems that QST protocols needs to become shorter and simpler to operate and to interpret to be more clinically useful in the future.

Measures to quantify chronic postoperative pain

Chronic postoperative pain is defined as pain that develops or increases in intensity after a tissue trauma (surgical or accidental) and persists beyond three months[83]. Severe chronic postoperative pain that has a negative impact on the patient's quality of life is has a prevalence of 2% to 15%, dependent on surgical procedure and definition of chronic pain[84]. In contrast to acute postoperative pain, which is often assessed by a one-dimensional pain scale such as the NRS, there are several assessment tools for chronic pain that are multidimensional. The assessment tools that are mostly used are the Brief pain Inventory and (short form) McGill Pain Questionnaire[69], on which the questionnaire used in chapter 4 of this thesis is also based. Still, there is a large variability in outcome measures used in clinical trials for chronic pain, which hinders the evaluation of the incidence of chronic pain its impact on quality of life and the efficacy of therapeutic interventions. Studies show that chronic pain after surgery remains common and is still unrecognized and underdiagnosed[83]. Internationally, an effort has been made to provide recommendations for interpreting clinical importance of treatment outcomes in clinical trials of the efficacy and effectiveness of chronic pain treatments[85]. There was a consensus that chronic pain clinical trials should assess outcomes representing six core domains: (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events, (6) participant disposition (e.g. adherence to the treatment regimen and reasons for premature withdrawal from the trial). It is recommended that two or more methods are to be used to evaluate the clinical importance of improvement or worsening for chronic pain clinical trial outcome measures[86]. In chapter 4 we used pain intensity, assessed by a 0 to 10 numerical rating scale and physical functioning, assessed by the (adapted) Brief Pain Inventory scale. In addition, a separate quality of life (short-form 12) questionnaire was used. Despite all these efforts internationally, the number of pharmacological intervention studies with prolonged follow up to evaluate impact on chronic postoperative pain is still low and mostly not conform the provided recommendations. In our opinion, decent measurements of quality of life before and after surgery is essential to measure clinical impact. The results of chapter 4 are an example why definition of chronic postoperative pain is of importance. Our results after three months showed that the intervention arm with remifentanil had more persistent postoperative pain compared to the fentanyl arm. Since we had also measurements after 6 and 12 months, we were able to report that this effect between groups disappeared over time. This emphasizes the importance of prolonged follow-up in chronic postoperative pain research to better estimate the clinical impact of new findings in the future.

To summarize, pain is an unpleasant and emotional experience, associated with actual or potential tissue damage[62]. It is a challenge to treat and prevent postoperative pain, especially in special patient populations where the optimal use of opioids is not thoroughly investigated. In this thesis we have extended the knowledge of opioids in three different populations: adult cardiac surgery patients, paediatric cardiac surgery patients and finally obese patients.

With the work presented in this thesis in adult cardiac surgery patients we show that remifentanil has impact on opioid consumption directly after surgery and on postoperative pain three months after surgery, while this effect diminishes over time and thus seems of low clinical impact. Detection and pain thresholds were not influenced by remifentanil nor by chronic pain in this population. Still, it could be argued that the use of remifentanil in some patients needs consideration since its advantages over other opioids are not that well established in the literature and according to our data, when used in younger patients and in a higher dose, remifentanil could give a potential additional risk on chronic postoperative pain.

In children that undergo cardiac surgery, morphine is the most frequently used opioid during and after surgery albeit at an enormous variation in dosing schemes between institutions[87]. This implicates that there is no consensus about an ideal dosing regime in this population and therefore we focused on morphine administered as continuous infusion with additional rescue morphine boluses as was standard of care. We found that rescue morphine was required at a wide range of morphine concentrations and that the hazard for rescue morphine was not decreasing with increasing morphine concentrations. This study does not show a strong relation between morphine concentration and efficacy in this setting where the number of rescue doses that was given was high. This questions a “step-down” analgesic approach that is often used in children after surgery, i.e. start with high doses of analgesics and step down to lower doses or other less potent analgesics. Future studies have to focus on a multimodal approach using other opioids or other analgesics to treat and prevent breakthrough pain in children.

In obese patients, we showed that there is no need for a dose increase of morphine based on its pharmacokinetics. The plasma clearance of morphine glucuronides in obese patients is decreased, which means that glucuronide concentrations could accumulated in obese patients upon prolonged administration of morphine but the clinical impact of this is probably low. What is of interest are the physiological changes in transporters that are causing this decrease in excretion clearance. Future studies evaluating the influence of hepatic transporters and bile acid homeostasis in morbidly obese patients and after bariatric surgery are needed to evaluate these changes and the impact on other drugs.

Concluding, pain is a complex puzzle among biological, psychological, behavioural and social-cultural factors. The high inter-individual variation in all these factors results in postoperative pain still being a major issue while the ultimate goal is to stay without pain after a surgical procedure. Therefore, the answer to the question: "Does it still hurt?" is: YES unfortunately. This thesis adds pieces to this complex puzzle by focusing on the use of opioids in three different patient populations.

Literature

1. Sommer, M. *et al.* The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur. J. Anaesthesiol.* 25, 267–74 (2008).
2. Gan, T. J., Habib, A. S., Miller, T. E., White, W. & Apfelbaum, J. L. Incidence, patient satisfaction, and perceptions of post-surgical pain: Results from a US national survey. *Curr. Med. Res. Opin.* 30, 149–160 (2014).
3. Apfelbaum, J. L., Chen, C., Mehta, S. S. & Gan, and T. J. Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. *Anesth. Analg.* 97, 534–540 (2003).
4. Yang, M. M. H. *et al.* Preoperative predictors of poor acute postoperative pain control: A systematic review and meta-analysis. *BMJ Open* 9, e025091 (2019).
5. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
6. Chapman, C. R. & Vierck, C. J. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *J. Pain* 18, 359.e1-359.e38 (2017).
7. Johansen, A., Romundstad, L., Nielsen, C. S., Schirmer, H. & Stubhaug, A. Persistent postsurgical pain in a general population: Prevalence and predictors in the Tromsø study. *Pain* 153, 1390–1396 (2012).
8. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
9. Richebé, P., Capdevila, X. & Rivat, C. Persistent Postsurgical Pain: Pathophysiology and Preventative Pharmacologic Considerations. *Anesthesiology* 129, 590–607 (2018).
10. Mongardon, N. *et al.* Assessment of chronic pain after thoracotomy: a 1-year prevalence study. *Clin. J. Pain* 27, 677–81 (2011).
11. Leadley, R. M., Armstrong, N., Lee, Y. C., Allen, A. & Kleijnen, J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. *J. Pain Palliat. Care Pharmacother.* 26, 310–25 (2012).
12. Roger, V. L. *et al.* Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 125, e2–e220 (2012).
13. Mueller, X. M. *et al.* Pain location, distribution, and intensity after cardiac surgery. *Chest* 118, 391–6 (2000).
14. Liu, S. S. & Wu, C. L. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. *Anesth. Analg.* 104, 689–702 (2007).
15. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
16. Kim, S. H., Stoicea, N., Soghomonyan, S. & Bergese, S. D. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front. Pharmacol.* 5, 108 (2014).
17. Valkenburg, A. J. *et al.* Pharmacodynamics and Pharmacokinetics of Morphine After Cardiac Surgery in Children With and Without Down Syndrome. *Pediatr. Crit. Care Med.* 17, 930–938 (2016).
18. Thompson, J. P. & Rowbotham, D. J. Remifentanil--an opioid for the 21st century. *Br. J. Anaesth.* 76, 341–343 (1996).

19. Westmoreland, C. L., Hoke, J. F., Sebel, P. S., Hug Jr, C. C. & Muir, K. T. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 79, 893–903 (1993).
20. Komatsu, R. *et al.* Remifentanil for general anaesthesia: a systematic review. *Anaesthesia* 62, 1266–1280 (2007).
21. Engoren, M., Luther, G. & Fenn-Buderer, N. A comparison of fentanyl, sufentanil, and remifentanil for fast-track cardiac anesthesia. *Anesth. Analg.* 93, 859–64 (2001).
22. Khanykin, B., Siddiqi, R., Jensen, P. F., Bigler, D. R. & Atroshchenko, G. V. Comparison of remifentanil and low-dose fentanyl for fast-track cardiac anesthesia: a prospective randomized study. *Heart Surg. Forum* 16, E324-8 (2013).
23. Angst, M. S. & Clark, J. D. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 104, 570–587 (2006).
24. Koppert, W. & Schmelz, M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract. Res. Anaesthesiol.* 21, 65–83 (2007).
25. De Hoogd, S. *et al.* Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. *Clin. J. Pain* 32, 726–735 (2016).
26. Niedermayer, S., Heyn, J., Guenther, F., Küchenhoff, H. & Luchting, B. Remifentanil for abdominal surgery is associated with unexpectedly unfavorable outcomes. *Pain* 161, 266–273 (2020).
27. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
28. Subramaniam, K., Ibarra, A., Ruppert, K., Mallikarjun, K. & Orebaugh, S. Intraoperative Remifentanil Infusion and Postoperative Pain Outcomes After Cardiac Surgery-Results from Secondary Analysis of a Randomized, Open-Label Clinical Trial. *J. Cardiothorac. Vasc. Anesth.* 35, 458–466 (2021).
29. Greco, M. *et al.* Remifentanil in cardiac surgery: a meta-analysis of randomized controlled trials. *J. Cardiothorac. Vasc. Anesth.* 26, 110–6 (2012).
30. Möllhoff, T. *et al.* Comparative efficacy and safety of remifentanil and fentanyl in 'fast track' coronary artery bypass graft surgery: a randomized, double-blind study. *Br. J. Anaesth.* 87, 718–26 (2001).
31. Patel, S. S. & Spencer, C. M. Remifentanil. *Drugs* 52, 417–27; discussion 428 (1996).
32. Choudhury, A., Magoon, R., Sahoo, S. & Sehgal, L. Opioid Free Cardiac Surgery: Opportunities and Obstacles. *J. Cardiothorac. Vasc. Anesth.* 34, 567–568 (2020).
33. Gabriel, R. A. *et al.* State of the art opioid-sparing strategies for post-operative pain in adult surgical patients. *Expert Opin. Pharmacother.* 20, 949–961 (2019).
34. Frauenknecht, J., Kirkham, K. R., Jacot-Guillarmod, A. & Albrecht, E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *Anaesthesia* 74, 651–662 (2019).
35. Beloeil, H. *et al.* Balanced Opioid-free Anesthesia with Dexmedetomidine versus Balanced Anesthesia with Remifentanil for Major or Intermediate Noncardiac Surgery. *Anesthesiology* 134, 541–551 (2021).
36. Grant, M. C. *et al.* Opioid-Sparing Cardiac Anesthesia: Secondary Analysis of an Enhanced Recovery Program for Cardiac Surgery. *Anesth. Analg.* 131, 1852–1861 (2020).

37. Fiore, J. F. *et al.* Preventing opioid prescription after major surgery: a scoping review of opioid-free analgesia. *Br. J. Anaesth.* 123, 627–636 (2019).
38. European Commission. Ethical considerations for clinical trials on medicinal products conducted with minors - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. (2017). Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf. (Accessed: 3rd May 2021)
39. Ceelie, I. *et al.* Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. *JAMA* 309, 149–54 (2013).
40. Zeilmaker-Roest, G. A. *et al.* Intravenous morphine versus intravenous paracetamol after cardiac surgery in neonates and infants: a study protocol for a randomized controlled trial. *Trials* 19, 318 (2018).
41. Ista, E., de Hoog, M., Tibboel, D. & van Dijk, M. Implementation of standard sedation management in paediatric intensive care: effective and feasible? *J. Clin. Nurs.* 18, 2511–20 (2009).
42. Vet, N. J. *et al.* Optimal sedation in pediatric intensive care patients: a systematic review. *Intensive Care Med.* 39, 1524–34 (2013).
43. Valkenburg, A. J. *et al.* Sedation With Midazolam After Cardiac Surgery in Children With and Without Down Syndrome: A Pharmacokinetic-Pharmacodynamic Study. *Pediatr. Crit. Care Med.* 22, e259–e269 (2021).
44. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet (London, England)* 387, 1377–1396 (2016).
45. Global BMI Mortality Collaboration *et al.* Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet (London, England)* 388, 776–86 (2016).
46. Lloret Linares, C. *et al.* Pharmacology of morphine in obese patients: clinical implications. *Clin. Pharmacokinet.* 48, 635–51 (2009).
47. Rose, D. K., Cohen, M. M., Wigglesworth, D. F. & DeBoer, D. P. Critical respiratory events in the postanesthesia care unit. Patient, surgical, and anesthetic factors. *Anesthesiology* 81, 410–418 (1994).
48. van Rongen, A. *et al.* Morbidly Obese Patients Exhibit Increased CYP2E1-Mediated Oxidation of Acetaminophen. *Clin. Pharmacokinet.* 55, 833–847 (2016).
49. A. van Rongen. The impact of obesity on the pharmacokinetics of drugs in adolescents and adults. (2016).
50. Lewis, S. S. *et al.* Evidence that intrathecal morphine-3-glucuronide may cause pain enhancement via toll-like receptor 4/MD-2 and interleukin-1beta. *Neuroscience* 165, 569–83 (2010).
51. Klimas, R. & Mikus, G. Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide. *Br. J. Anaesth.* 113, 935–44 (2014).
52. Chen, Z. R., Irvine, R. J., Somogyi, A. A. & Bochner, F. Mu receptor binding of some commonly used opioids and their metabolites. *Life Sci.* 48, 2165–71 (1991).

53. Bickel, U., Schumacher, O. P., Kang, Y. S. & Voigt, K. Poor permeability of morphine 3-glucuronide and morphine 6-glucuronide through the blood-brain barrier in the rat. *J. Pharmacol. Exp. Ther.* 278, 107–13 (1996).

54. Sverrisdottir, E. *et al.* A review of morphine and morphine-6-glucuronide's pharmacokinetic-pharmacodynamic relationships in experimental and clinical pain. *Eur. J. Pharm. Sci.* 74, 45–62 (2015).

55. Romberg, R. *et al.* Pharmacokinetic-pharmacodynamic modeling of morphine-6-glucuronide-induced analgesia in healthy volunteers: absence of sex differences. *Anesthesiology* 100, 120–133 (2004).

56. Blomqvist, K. J. *et al.* Morphine-3-glucuronide causes antinociceptive cross-tolerance to morphine and increases spinal substance P expression. *Eur. J. Pharmacol.* 875, 173021 (2020).

57. Ferslew, B. C. *et al.* Altered morphine glucuronide and bile acid disposition in patients with nonalcoholic steatohepatitis. *Clin. Pharmacol. Ther.* 97, 419–427 (2015).

58. Fisher, C. D. *et al.* Hepatic cytochrome P450 enzyme alterations in humans with progressive stages of nonalcoholic fatty liver disease. *Drug Metab. Dispos.* 37, 2087–2094 (2009).

59. Nalbantoglu, I. L. K. & Brunt, E. M. Role of liver biopsy in nonalcoholic fatty liver disease. *World J. Gastroenterol.* 20, 9026–37 (2014).

60. Sjöstedt, N., Neuhoff, S. & Brouwer, K. L. R. Physiologically-Based Pharmacokinetic (PBPK) Model of Morphine and Morphine-3-Glucuronide in Nonalcoholic Steatohepatitis (NASH). *Clin. Pharmacol. Ther.* (2020). doi:10.1002/cpt.2037

61. Kruh, G. D., Belinsky, M. G., Gallo, J. M. & Lee, K. Physiological and pharmacological functions of Mrp2, Mrp3 and Mrp4 as determined from recent studies on gene-disrupted mice. *Cancer Metastasis Rev.* 26, 5–14 (2007).

62. Merskey, H. & Bogduk, N. Part III: Pain Terms: A Current List with Definitions and Notes on Usage. in *Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy* 209–214 (1994).

63. Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N. & Turk, D. C. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol. Bull.* 133, 581–624 (2007).

64. Gilron, I. & Jensen, M. P. Clinical trial methodology of pain treatment studies: selection and measurement of self-report primary outcomes for efficacy. *Reg. Anesth. Pain Med.* 36, 374–81 (2011).

65. van Dijk, M. *et al.* The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. *Pain* 84, 367–377 (2000).

66. Müller-Schwefe, G. *et al.* Make a CHANGE: optimising communication and pain management decisions. *Curr. Med. Res. Opin.* 27, 481–8 (2011).

67. Mueller-Schwefe GHH; Ueberall MA. Pain intensity of patients with chronic low-back pain-induced restrictions to follow standardized rehabilitation programs are frequently underestimated by physicians and physiotherapists – results of a prospective German quality assurance program. *WIP Poster 2, Proc. World Inst. Pain Conf.*

68. Gilron, I., Carr, D. B., Desjardins, P. J. & Kehlet, H. Current methods and challenges for acute pain clinical trials. *Pain reports* 4, e647

69. Breivik, H. *et al.* Assessment of pain. *Br. J. Anaesth.* 101, 17–24 (2008).
70. van Gulik, L. *et al.* Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. *Eur. J. Anaesthesiol.* 27, 900–5 (2010).
71. Cui, C., Wang, L.-X., Li, Q., Zaslansky, R. & Li, L. Implementing a pain management nursing protocol for orthopaedic surgical patients: Results from a PAIN OUT project. *J. Clin. Nurs.* 27, 1684–1691 (2018).
72. Kim, E. B. *et al.* The effectiveness of a self-reporting bedside pain assessment tool for oncology inpatients. *J. Palliat. Med.* 15, 1222–33 (2012).
73. Thiel, B. *et al.* Patient reported postoperative pain with a smartphone application: A proof of concept. *PLoS One* 15, e0232082 (2020).
74. Bhattarai, P., Newton-John, T. R. O. & Phillips, J. L. Apps for pain self-management of older people's arthritic pain, one size doesn't fit all: A qualitative study. *Arch. Gerontol. Geriatr.* 89, 104062 (2020).
75. van Gulik, L. *et al.* Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. *Eur. J. Anaesthesiol.* 27, 900–905 (2010).
76. Cruz-Almeida, Y. & Fillingim, R. B. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Med.* 15, 61–72 (2014).
77. Arendt-Nielsen, L. & Yarnitsky, D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J. Pain* 10, 556–572 (2009).
78. Marcuzzi, A., Dean, C. M., Wrigley, P. J., Chakiath, R. J. & Hush, J. M. Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. *J. Pain Res.* 9, 599–607 (2016).
79. van Helmond, N. *et al.* Is Preoperative Quantitative Sensory Testing Related to Persistent Postsurgical Pain? A Systematic Literature Review. *Anesth. Analg.* 131, 1146–1155 (2020).
80. Yarnitsky, D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr. Opin. Anaesthesiol.* 23, 611–615 (2010).
81. Yarnitsky, D. *et al.* Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* 138, 22–28 (2008).
82. Wilder-Smith, O. H., Schreyer, T., Scheffer, G. J. & Arendt-Nielsen, L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: a pilot study. *J. Pain Palliat. Care Pharmacother.* 24, 119–28 (2010).
83. Schug, S. A. *et al.* The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain* 160, 45–52 (2019).
84. Fletcher, D. *et al.* Chronic postsurgical pain in Europe: An observational study. *Eur. J. Anaesthesiol.* 32, 725–34 (2015).
85. Turk, D. C. *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 106, 337–345 (2003).
86. Dworkin, R. H. *et al.* Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J. pain* 9, 105–21 (2008).
87. Zeilmaker-Roest, G. A. *et al.* An international survey of management of pain and sedation after paediatric cardiac surgery. *BMJ Paediatr. Open* 1, e000046 (2017).

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Chapter 11

Dutch Summary

Doet het nog steeds pijn? Perioperatieve pijnstilling met behulp van opiaten in verschillende patiëntenpopulaties.

Achtergrond

Pijn is een onplezierige sensorische en emotionele ervaring die gepaard gaat met feitelijke of mogelijke weefselbeschadiging[1]. Zowel acute als chronische pijn is een multidimensionaal en complex probleem dat fysiologische en biopsychosociale aspecten kent. Wereldwijd krijgt het onderwerp pijn de laatste jaren meer aandacht. Onderzoek laat zien dat de incidentie van acute postoperatieve pijn in het algemeen daalt over de jaren, maar ondanks deze daling blijft de incidentie aan de hoge kant[2]. In de Verenigde Staten geeft meer dan 80% van de postoperatieve patiënten aan dat ze acute postoperatieve pijn ondervinden. De meerderheid van deze patiënten geeft een score aan deze pijn van 'matig' tot 'ernstig'[3]. Andere studies laten zien dat slechts 50% van de patiënten adequate pijn ervaart na de operatie[4]. Postoperatieve pijn kan chronisch worden wanneer het langer dan twee tot drie maanden bestaat na de operatie en het onafhankelijk is van het helende weefsel of ontstekingsprocessen[5,6]. Het wordt geschat dat 10 tot 50% van de patiënten die een operatie ondergaat chronische postoperatieve pijnklachten kan krijgen[5,7,8].

Met deze aanzienlijke incidentiepercentages kan pijn nog steeds gezien worden als een groot maatschappelijk probleem. In Nederland zijn er landelijke initiatieven genomen om het probleem van postoperatieve pijn aan te pakken, onder andere omdat pijn is toegevoegd als kwaliteitsindicator voor de Nederlandse ziekenhuizen[9]. Pijn en inadequate pijnstilling zijn een zware last voor de patiënt, en dit heeft een grote impact op de kwaliteit van leven en bijvoorbeeld op het uitvoeren van dagelijkse activiteiten[8,10]. Het optimaliseren van pijnstilling en het optimaal inzetten van analgetica kan mogelijk leiden tot een verlaging van morbiditeit en mortaliteit en verhoogde kwaliteit van leven in postoperatieve patiënten. Opiaten behoren tot de meest gebruikte analgetica en zijn daarmee een hoeksteen van het postoperatieve pijnmanagement. Het perioperatief gebruik van opiaten is essentieel in het voorkomen en behandelen van acute en chronische pijn. Ondanks dat opiaten veelvuldig worden gebruikt zijn er nog steeds kennishiaten op het gebied van gebruik, optimale dosering en potentieel negatieve effecten. Dit geldt bijvoorbeeld in specifieke patiëntenpopulatie zoals volwassenen en kinderen na hartchirurgie of de morbide obese patiënten. Dit proefschrift beoogt een bijdrage te leveren aan de kennis over perioperatieve pijnmanagement in verschillende patiëntenpopulaties met de focus op opiaten.

Pijnstilling met opiaten in volwassen hartpatiënten

In sectie II ligt de focus op volwassen patiënten die een cardiothoracale ingreep ondergaan. In **hoofdstuk 2** van dit proefschrift wordt een literatuuroverzicht gepresenteerd van de studies die de associaties tussen het intraoperatief gebruik van remifentanil en acute postoperatieve pijn, hyperalgesie en chronische postoperatieve pijn hebben onderzocht. Bijna de helft van de geïncludeerde studies laten hogere acute postoperatieve pijnscores, hogere analgesie consumptie of beide zien na het gebruik van remifentanil. Het gebruik van andere anesthetica tijdens de operatie lijkt van invloed. Een voorbeeld hiervan zijn de dampvormige anesthetica waarbij de combinatie van sevofluraan met remifentanil hogere pijnscores laat zien in vergelijking tot de combinatie van remifentanil met intraveneuze anesthetica zoals propofol. Er zijn weinig publicaties beschikbaar op het gebied van chronisch postoperatieve pijn. De beschikbare studies waren niet opgezet met het primaire doel om het effect van remifentanil op de lange termijn te onderzoeken en verschilden in studieopzet waardoor een eenduidige conclusie op basis van deze studies niet getrokken kon worden. Op basis van deze heterogene studies met kleine patiëntenaantallen ontstaat de indruk dat intraoperatief gebruik van remifentanil het ontstaan van acute postoperatieve hyperalgesie kan beïnvloeden. De impact op chronische postoperatieve pijn is onduidelijk.

Om de invloed van remifentanil op acute en chronische postoperatieve pijn verder te onderzoeken is een gerandomiseerde, gecontroleerde studie opgezet. Dit studieprotocol is uiteengezet in **hoofdstuk 3** van dit proefschrift.

In **hoofdstuk 4** worden de resultaten gepresenteerd van deze gerandomiseerde en gecontroleerde studie naar de impact van remifentanil op acute en chronische postoperatieve pijn drie, zes en twaalf maanden na de operatie. In totaal werden er 126 patiënten geïncludeerd die een openhartoperatie ondergingen via sternotomie. Na twaalf maanden werd er geen significant verschil gevonden in incidentie van chronische thoracale pijn tussen de remifentanil- en fentanylgroepen (20% vs. 18%, p=0.817). Na drie maanden daarentegen, rapporteerden significant meer patiënten in de remifentanilgroep chronische thoracale pijn na de operatie (51% vs. 33%; p=0.047). Dit effect was meer uitgesproken bij jongere patiënten en bij patiënten die een hogere dosis remifentanil ontvingen. Daarnaast werd een significante verhoogde morfineconsumptie gezien in de remifentanilgroep in de eerste 24 en 48 uur na de operatie. Hieruit kan geconcludeerd worden dat het intraoperatief gebruik van remifentanil tijdens hartchirurgie geen impact heeft op de incidentie chronisch postoperatieve pijn één jaar na de operatie. Remifentanil verhoogt echter wel de behoefte aan analgetica direct na de operatie en verhoogt de kans op chronische pijn tot drie maanden na de operatie.

Om postoperatieve pijn na hartchirurgie op een meer objectievere manier te onderzoeken werden in deze gerandomiseerde studie ook detectie- en pijndrempels gemeten met behulp van koude en warme stimuli. Deze resultaten worden gerapporteerd in **hoofdstuk 5**. Warm en koude detectie- en pijndrempels werden preoperatief, drie dagen en twaalf maanden postoperatief gemeten. Verschillende variabelen zijn onderzocht op de voorspellende waarde ten aanzien van veranderende pijnsensitiviteit twaalf maanden na de operatie: het gebruik van remifentanil, aanwezigheid van chronische postoperatieve pijn, leeftijd, opiaatconsumptie en preoperatieve kwaliteit van leven. Zowel warme als koude detectie- en pijndrempels waren niet significant verschillend tussen de remifentanil en fentanyl groep drie dagen en twaalf maanden na de operatie. Er konden geen significante voorspellers voor veranderende pijngevoeligheid twaalf maanden na de operatie worden geïdentificeerd. Geconcludeerd werd dat één jaar na de operatie geen verschillen in pijngevoeligheid konden worden aangetoond met het meten van detectie- en pijndrempels.

In hetzelfde cohort van hartchirurgische patiënten werd ook onderzoek gedaan naar potentiële genetische componenten van pijn. **Hoofdstuk 6** beschrijft de potentiële invloed van *OPRM1* (mu-opioïde receptor) en *COMT* (catechol-O-methyltransferase enzym) polymorfisme in postoperatieve acute, chronische en experimentele thermale pijn. Er werd geen associatie gevonden tussen het COMT haplotype en andere pijnuitkomsten of OPRM1 polymorfismen en de verschillende pijnmodaliteiten. Patiënten in de fentanylgroep met het COMT 'hoge pijnsensitiviteit' haplotype hadden postoperatief minder opiaten nodig in vergelijking met het 'gemiddelde pijnsensitiviteit' haplotype. Deze resultaten leiden tot de conclusie dat in dit cohort van cardiothoracale patiënten de invloed van genetische variatie op postoperatieve pijn uitkomsten minimaal is, waarbij mogelijk alleen het COMT haplotype een klein deel van de variabiliteit in acute postoperatieve pijn in cardiothoracale volwassen patiënten kan verklaren.

Morfine na hartoperaties bij kinderen

In sectie III ligt de focus op het gebruik van morfine na hartoperaties bij kinderen. Morfine is de meest gebruikte pijnstiller rondom hartoperaties bij kinderen. Ondanks dat het veel gebruikt wordt is er slechts weinig bekend over de pijnstillende werking in relatie tot de plasmaconcentratie. In **hoofdstuk 7** worden de resultaten gerapporteerd van een farmacodynamische analyse van morfine toediening bij kinderen door gebruik te maken van herhaalde-eventmodellen. Hiervoor werden de data van een eerder gepubliceerde studie gebruikt[11]. In deze studie werden 35 kinderen (leeftijd 3 tot 35 maanden) geïncludeerd die een hartoperatie ondergingen

met daaropvolgend een morfinetoediening in een oplaaddosering (100 µg/kg) gevolgd door een continu-infuus (40 µg/kg/hr). Events werden gedefinieerd als extra morfine bolus doses en/of verhogingen van infusiesnelheid van het continue infuus van morfine. Extra giften van morfine werden gegeven op basis van het gestandaardiseerde pijnprotocol en pijnscores zoals de COMFORT-B. In totaal werden er 130 events (mediaan 4 (IQR 1 tot 5) per patiënt) geïdentificeerd die met name in de eerste 24 uur plaatsvonden (107/130). De mediane morfineconcentratie tijdens een event was 29.5 ng/ml (range 7 tot 180 ng/ml). Het model liet een daling van een verminderende behoefte aan extra morfine zien over tijd. Daarnaast liet het model ook een stijging zien van de kans op extra morfine injecties bij hogere morfineconcentraties. Het betrouwbaarheidsinterval van deze stijging is groot, wat deze bevinding onzeker maakt. De morfineconcentraties in deze studie zijn veel hoger vergeleken met de eerder gesuggereerde therapeutische range van 10 tot 20 ng/ml. Hoewel de wetenschappelijke onderbouwing voor deze range mager is, is het onverwachts dat er nog steeds events plaatsvinden bij deze hoge concentraties morfine. Aangezien 24% van de extra morfine werd gegeven binnen een uur van de voorgaande dosering kan het ook betekenen dat morfine mogelijk niet het meest ideale opiaat is om te gebruiken als 'rescue' medicatie. Toekomstige studies zouden moeten focussen op een multimodale aanpak met het gebruik van andere opiaten of andere pijnstillers om doorbraakpijn bij kinderen na hartchirurgie optimaler te kunnen behandelen.

Farmacokinetiek van opiaten in obese patiënten

In sectie IV wordt er gefocust op de (morbide) obese patiënten als zijnde een speciale patiëntpopulatie. De obese populatie groeit de laatste jaren wereldwijd en dit zal resulteren in een groeiend aantal operaties bij obese patiënten. Daarom is het belangrijk dat postoperatieve pijn in deze patiëntenpopulatie op de best mogelijke manier behandeld kan worden.

Allereerst is er in **hoofdstuk 8** een literatuuroverzicht gepresenteerd over de invloed van obesitas op de farmacokinetiek en dynamiek van geneesmiddelen bij volwassenen. Het effect van de fysiologische veranderingen die optreden bij (morbide) obesitas op geneesmiddelabsorptie, -verdeling, -metabolisme en -klaring worden besproken op basis van de beschikbare farmacokinetische studies. Toekomstige studies zouden meer de verbinding moeten maken tussen de fysiologische veranderingen bij obese patiënten en farmacokinetiek en dynamiek in plaats van een enkele dimensie te onderzoeken. Daarnaast blijft implementatie van doseeradviezen in de praktijk een punt van aandacht.

Het doel van **hoofdstuk 9** was om de farmacokinetiek van morfine en de actieve metabolieten bij morbide obese patiënten in kaart te brengen door deze te vergelijken met de kinetiek in gezonde vrijwilligers. Data van 20 morbide obese patiënten (gemiddelde BMI 49.9 kg/m^2, gemiddeld gewicht 151.3 kg) en 20 gezonde vrijwilligers (gemiddeld gewicht 70.6 kg) werden geïncludeerd. Bij de morbide obese patiënten bleek de eliminatieklaring van morfine-3-glucuronide (M3G) en morfine-6-glucuronide (M6G) substantieel verlaagd te zijn in vergelijking met de gezonde vrijwilligers. Met betrekking op de glucuronidatie van de metabolieten werd een minimale verlaging van formatie van M6G en een vertraging van de formatie van M3G gevonden. Obesitas werd ook als covariaat geïdentificeerd voor het perifere verdelingsvolume van morfine. Er kan geconcludeerd worden dat het metabolisme van morfine zelf niet anders is dan morbide obese patiënten in vergelijking met gezonde vrijwilligers. Dit betekent dat er geen op gewicht gebaseerde dosisaanpassingen gedaan hoeven te worden. Echter, de verlaagde eliminatieklaring van M3G en M6G is aanzienlijk en dit resulteert in een verhoogde blootstelling aan deze metabolieten. De klinische consequenties voor de patiënt zijn nog niet duidelijk en mogelijk alleen relevant bij langdurige morfinetoediening.

Perspectieven en conclusies

Tot slot worden in **hoofdstuk 10** de verkregen resultaten van de verschillende studies in deze thesis in een breder perspectief geplaatst. Eerst wordt gereflecteerd op de uitkomsten van de studies rondom het gebruik van remifentanil tijdens hartoperaties. Vervolgens wordt besproken wat de studies bij kinderen en obese patiënten ons kunnen leren en tot slot volgt een reflectie op de verschillende uitkomstmaten die in deze thesis zijn gebruikt om het effect op pijn te kwantificeren.

Allereerst wordt het gebruik van remifentanil tijdens hartchirurgie in volwassenen nader bekeken. Remifentanil wordt van alle opiaten het meest geassocieerd met opiaat geïnduceerde hyperalgesie[12]. Een negatief effect van remifentanil op pijnbeleving na de operatie wordt met name gezien in de acute periode na de operatie. Dit wordt ook in het literatuuroverzicht in hoofdstuk 2 geconcludeerd, hoewel studies divers zijn en het aantal proefpersonen in de studies klein. Recent is er daarentegen een studie rondom abdominale chirurgie gepubliceerd met veel grotere patiënten aantallen in vergelijking tot eerdere studies[13]. Geconcludeerd werd dat pijnscore bij aankomst (NRS1) op de recovery afdeling en de maximale pijnscore (NRSmax) beide verhoogd waren in de remifentanilgroep (gemiddelde NRS1 1.52 vs. 1.28; $p<0.001$; gemiddelde NRSmax 2.47 vs. 2.17; $p<0.001$). De resultaten uit hoofdstuk 4 zijn daarmee in overeenstemming; er wordt een verhoogde vraag naar opiaten direct na de operatie gezien in de remifentanilgroep.

Kortom, remifentanil lijkt een significante negatieve impact te hebben op acute pijn maar de absolute verschillen in pijnscores of cumulatief postoperatieve opiatengebruik zijn klein en waarschijnlijk niet van significante klinische impact.

Het aantal studies dat de invloed van remifentanil op chronisch postoperatieve pijn heeft onderzocht is beperkt. Een observationele follow-up studie in ons ziekenhuis laat zien dat remifentanil een risicofactor is voor het ontwikkelen op chronische pijn na twaalf maanden. Uit het onderzoek blijkt dat dit risico dosisafhankelijk lijkt[14]. In hoofdstuk 2 worden drie andere studies beschreven waarin de lange termijn effecten van remifentanil aan bod komen. Deze studies variëren aanzienlijk in opzet, omvang en de soort operatie die onderzocht werd. Naar aanleiding hiervan is een gerandomiseerde gecontroleerde studie opgezet (hoofdstuk 3) met als primair doel het effect van remifentanil versus fentanyl op de lange termijn te beoordelen. Recent zijn de secundaire eindpunten gepubliceerd van een studie met het primaire doel de impact van remifentanil en fentanyl op perioperatieve hyperglycemische respons te analyseren in hartchirurgie[15]. Hoewel deze studie een aantal overeenkomsten heeft met hoofdstuk 4 van deze thesis, zijn er ook belangrijke verschillen. Allereerst is de studie van Subramaniam et al. 2021 niet gepowerd op postoperatieve pijn maar op hyperglycemische respons. Ten tweede ontvingen de patiënten in de remifentanilgroep in deze studie geen additioneel fentanyl en kregen zij veel hogere doseringen remifentanil (mediaan cumulatieve dosis 11 mg; >80 μg/kg). In hoofdstuk 4 ontvingen patiënten in de remifentanilgroep een gemiddelde dosering van 2.1 mg (25 μg/kg) remifentanil en ook fentanyl (21 μg/kg). Ten aanzien van acute postoperatieve pijn laten beide studies een verhoogde opiatenconsumptie zien direct na de operatie. Op het gebied van chronische pijn na de operatie wordt in onze studie een significant verschil gevonden drie maanden na de operatie en geen verschil na zes en twaalf maanden. In de studie van Subramaniam et al. 2021 daarentegen werden geen verschillen gevonden drie, zes en twaalf maanden na de operatie. Een verklaring van dit verschil kan zijn dat de incidentie van chronische pijn (veel) hoger was op alle eindpunten in vergelijking tot onze studie. Ter illustratie, de studie van Subramaniam et al. 2021 vindt een incidentie van chronische postoperatieve pijn na drie maanden bij 61% van patiënten in de fentanylgroep versus 58% patiënten in de remifentanilgroep (p=0.79). In hoofdstuk 4 ligt de incidentie op 31% bij de fentanylgroep en 51% bij de remifentanilgroep (p=0.047). Samengevat; de gevonden resultaten van de impact van remifentanil op chronische pijn na hartchirurgie zijn divers. Toch laat hoofdstuk 4 zien dat er mogelijk wel nadelige effecten zijn tot aan drie maanden na de operatie. De vraag rijst dan of het voordeel om remifentanil te gebruiken tijdens hartchirurgie groter is dan de (kleine)

nadelen op acute en chronische pijn. Het voordeel van remifentanil zou met name een kortere extubatie tijd zijn, wat kan leiden tot sneller herstel en kortere ziekenhuisopname[16]. Daarnaast wordt ook gerapporteerd dat er een verhoogde hemodynamische stabiliteit gedurende operatie[17] en de verlaging van het gebruik van sedativa en hypnotica[18]. Deze voordelen worden echter niet gezien in studies waarin remifentanil niet-superieur wordt bevonden in fast-track hartchirurgie[19,20]. Een ander systematisch review concludeert dat remifentanil geen voordeel lijkt te hebben bij langdurige en grote interventies, maar wel bruikbaar kan zijn voor geselecteerde situaties[21].

In het huidige onderzoek wordt geconcludeerd dat de klinische impact van remifentanil op postoperatieve pijn na hartchirurgie beperkt is wanneer het wordt gebruikt zoals in het in hoofdstuk 4 beschreven regime. Daarnaast werd duidelijk dat er voor patiënten met een hoge dosis remifentanil (>1875 μg) en onder de leeftijd van 65 jaar een hoger risico bestaat op postoperatieve pijn drie maanden na de operatie. Deze bevinding kan meegenomen worden in de overweging om in de toekomst al dan niet remifentanil te gebruiken bij hartchirurgie.

Het is duidelijk dat opiaten al jaren de hoeksteen zijn van de anesthesie tijdens cardiothoracale chirurgie. Wereldwijd is er een groeiende aandacht voor versneld herstel na operaties in het algemeen. Daarnaast bestaan er zorgen over het verhoogde opiatengebruik en –misbruik. Dat maakt dat in toenemende mate behoefte is aan opiaatvrije anesthesie tijdens hartchirurgie[22]. Multimodale analgesie met medicatie anders dan opiaten (Non Steroidal Anti-Inflammatory Drugs, N-methyl-D-aspartaat antagonisten, alfa-2 agonisten, lokale anesthetica, gabapentinoïden en anderen) in combinatie met bijvoorbeeld innovatieve regionale anesthesietechnieken zouden hiervoor mogelijk ingezet kunnen worden[23]. Een meta-analyse van 23 studies waarin patiënten opiaatvrije anesthesie ontvingen bij operaties anders dan hartchirurgie liet zien dat deze techniek mogelijk voordelen heeft voor de patiënt[24]. De studies die dit onderzochten waren echter te klein en te heterogeen om harde conclusies te trekken. Een recente studie laat zien dat dat opiaatvrije anesthesie ook negatieve consequenties voor de patiënt kan hebben[25]. De studie is vroegtijdig gestopt vanwege het meer voorkomen van postoperatieve hypoxemie, vertraagde extubatie, intraoperatieve bradycardie en verlengde observatietijd. Dit kwam met name door de verhoogde dosering van de alternatieven pijnstillers die werden gebruikt bij de afwezigheid van opiaten. Grant et al. 2020 heeft een studie gepubliceerd waarin 5 interventies zonder opiaten tijdens of voor hartchirurgie geassocieerd waren met minder intra-operatief gebruik van opiaten[26]. Dit resultaat had geen negatieve maar ook geen positieve invloed op de postoperatieve uitkomsten.

Kortom, opiaatvrije anesthesie is een groeiend onderzoeksveld door het toegenomen misbruik en gebruik van opiaten en de focus op versneld herstel na (grote) operaties. De incidentie van postoperatieve pijn na hartchirurgie blijft hoog. Beschikbare data van opiaatvrije analgesie bij hartpatiënten zijn schaars en toekomstige studies moeten laten zien of dit ook daadwerkelijk voordelen voor de patiënt heeft.

In sectie III en IV van deze thesis krijgen speciale patiëntpopulaties de aandacht: kinderen na hartchirurgie en morbide obese patiënten. In hoofdstuk 7 wordt de farmacodynamiek van morfine bij kinderen na hartchirurgie uiteengezet om meer inzicht te krijgen in de pijnstillende werking van morfine in relatie tot plasmaconcentraties. De strenge regelgeving en ethische richtlijnen voor het uitvoeren van onderzoek bij kinderen maakt dat dit type onderzoek over in het algemeen uitdagend is. Daarnaast heeft pijn een emotionele waarde voor zowel ouders als kinderen, en mogelijk zelfs voor het behandelteam. Deze aspecten maken dat de traditionele strategie om pijn te behandelen bij kinderen over het algemeen conservatief is en het afbouwprincipe volgt. Dat wil zeggen dat gestart wordt met een hoge dosering en dit vervolgens wordt afgebouwd naar een lagere dosis of minder potente analgetica. Vanuit een farmacologisch oogpunt is het bekend dat een hogere dosis niet altijd meer effect betekent. Dit wordt ook duidelijk in hoofdstuk 7 waar gevonden wordt dat hogere morfineconcentraties geen effect heeft op de kans op het geven van extra morfineinjecties. Daarnaast was de concentratierange waarin morfine werd gegeven ten tijde van een 'rescue' event erg hoog. De huidige resultaten suggereren dat de concentratie-effect relatie van morfine in de acute postoperatieve situatie erg sterk is aangezien de patiënten met de hoogste concentratie niet het hoogste effect ervaren. Daarnaast lijkt morfine niet het ideale middel om deze momenten van pijn te behandelen aangezien een groot deel van de extra morfineinjecties dicht op een eerdere toediening zat. Deze resultaten kunnen een aanwijzing zijn dat het voor verpleegkundigen nog steeds moeilijk is om onderscheid te maken tussen sedatie en pijn. Er zijn toekomstige studies gaande[27] en nodig om het gebruik van analgetica en sedativa bij kinderen rondom hartchirurgie te kunnen optimaliseren.

Ondanks dat de (morbide) obese populatie wereldwijd elk jaar verder groeit, is de kennis rondom de farmacokinetiek van morfine bij deze populatie niet toereikend. In hoofdstuk 9 wordt de farmacokinetiek van morfine vergeleken van morbide obese patiënten met gezonde vrijwilligers. Hierbij wordt duidelijk dat morfine niet op gewicht gedoseerd hoeft te worden, maar dat de concentratie van de farmacologische metabolieten M3G en M6G kunnen gaan stapelen door verminderde eliminatieklaring bij morbide obese patiënten. In de literatuur wordt

meermaals aangegeven dat M3G verantwoordelijk zou zijn voor bijwerkingen en verergering van pijnklachten[28], terwijl M6G een pijnstillende werking zou hebben[29]. Deze effecten zijn echter nooit bevestigd in klinische studies. M3G heeft een veel lagere affiniteit voor de opiaatreceptor vergeleken met morfine of M6G[30]. Daarentegen zijn de concentraties van M6G weer veel lager vergeleken met de M3G en morfineconcentraties. Beide metabolieten hebben een hydrofiel karakter waardoor er minder penetratie is door de bloed-hersenbarrière[31]. De klinische impact van verlaagde eliminatieklaring van de morfinemetabolieten in morbide obese patiënten lijkt dus klein en is mogelijk alleen van belang wanneer er sprake is van continue morfinetoediening over een langere periode. De oorzaak van een verminderde eliminatieklaring bij obese patiënten is waarschijnlijk de fysiologische veranderingen die optreden bij patiënten die (langdurig) obees zijn of non-alcoholische steatohepatitis hebben. Studies laten zien dat er veranderingen optreden op het gebied van 'multidrug resistance proteins' MRP2 en MRP3[32,33]. Deze geneesmiddeltransporters zijn verantwoordelijk voor de in- en efflux van moleculen van de hepatocyten naar het gal en vice versa. Er zijn aanwijzingen in dierstudies dat er meer geneesmiddelen kunnen worden beïnvloed door deze geneesmiddeltransporters[34]. Dit vraagt om nader onderzoek.

Tot slot wordt er in hoofdstuk 10 een reflectie gegeven op de verschillende uitkomstmaten die in deze thesis zijn gebruikt om het effect op pijn te beschrijven. De gouden standaard bij het meten van pijn is nog altijd het rapporteren van pijn door de patiënt zelf op een gevalideerde pijnschaal. Studies laten zien dat bij het rapporteren van pijn op een visuele of numerieke schaal is voorlichting aan de patiënt belangrijk gebleken[35]. Betere communicatie en educatie helpt de patiënt een betere pijnbestrijding te krijgen en dit dient aandacht te krijgen in de dagelijkse praktijk. Daarnaast is de timing van het afnemen van een pijnscore belangrijk. In de literatuur worden vaak wisselende momenten gekozen waardoor het vergelijken van verschillende studies moeilijk is. Het is bijvoorbeeld belangrijk om statische pijnscores (in rust) en dynamische pijnscores (bij bewegen) af te nemen aangezien een snelle mobilisatie na een operatieve ingreep een positief invloed heeft op de lange termijn uitkomsten[36]. Achteraf gezien hadden we in hoofdstuk 4 hier ook beter onderscheid in kunnen maken om nog duidelijkere uitkomsten te krijgen. Een ander aandachtspunt is de implementatie van een gestandaardiseerd pijnprotocol met daarin afspraken over herhaaldelijke pijnmetingen. Het is gebleken dat dit postoperatieve uitkomsten verbeterd[37,38]. Een nadeel hiervan is dat dit arbeidsintensief kan zijn voor de verpleging. Recent is er een concept studie gepubliceerd waarin postoperatieve patiënten via een smartphone applicatie pijnscores zelf konden registreren[39]. Dit werd zowel door patiënt als verpleging positief ontvangen en is veelbelovend voor de toekomst.

Een andere veel gebruikte uitkomstmaat is de postoperatieve consumptie van pijnstillers, welke wij ook in hoofdstuk 4 hebben gerapporteerd. De consumptie van pijnstillers is van belang omdat het niet alleen een ineffectieve pijnbehandeling weerspiegelt maar ook van belang kan zijn in het kader van meer bijwerkingen van de extra doseringen pijnstillers. Indien deze uitkomstmaat wordt gebruikt in een klinische studie, is het van belang dat er een duidelijk gestandaardiseerd protocol is geïmplementeerd op de verpleegafdelingen zodat er kan worden afgeleid wat een verhoogde consumptie van pijnstillers na de operatie daadwerkelijk weerspiegelt. Zonder een dergelijk protocol is dit eindpunt moeilijk te interpreteren.

In hoofdstuk 5 wordt pijn geobjectiveerd met kwantitatieve sensorische testen (QST), wat een verzamelnaam is voor verschillende procedures waarin de perceptuele reactie op sensorische stimuli (warm, koud, druk) kwantificeerbaar gemaakt kan worden[40]. QST wordt gebruikt in wetenschappelijk onderzoek, maar ook in de praktijk bij het stellen van diagnoses of het evalueren van een pijnbehandeling[41]. In hoofdstuk 5 zien wij geen effect van de remifentanil of fentanyl op de gemeten pijndrempels. Daarnaast worden er geen voorspellende factoren gevonden voor een afwijkende pijn gevoeligheid. Ondanks het gebruik in experimentele en klinische studies blijft het gebruik van QST in de dagelijkse praktijk in relatie tot (het voorspellen van) postoperatieve pijn beperkt. Dit komt met name omdat er geen grote studies zijn waarin grote voordelen worden gevonden voor het meten van pijn of detectie drempels voor acute postoperatieve pijn[42] alsmede chronisch postoperatieve pijn[43]. De meest belovende resultaten worden gevonden in studies waarin gekeken wordt naar het dynamische pijn processen in het lichaam waar pijn modulatie plaatsvindt[43]. Dit kan bijvoorbeeld door het meten van diffuse noxische inhibitoire controle (DNIC). DNIC vindt plaats wanneer de reactie op een pijnlijke stimulus is geremd door een andere pijnlijke stimulus ('pijn remt pijn' paradigma)[41,44]. Patiënten met een verminderde preoperatieve DNIC score lijken meer risico te hebben op het ontwikkelen van chronische postoperatieve pijn[45,46]. Toch zijn er geen studies met grotere patiënten aantallen die deze bevindingen kunnen repliceren. Andere redenen dat QST niet veel gebruikt wordt in de klinische praktijk is dat het arbeidsintensief is, dure appratuur nodig is en getraind personeel nodig is om de test af te nemen en de data te interpreteren[40]. QST protocollen moeten korter en makkelijker worden om af te nemen en om te interpreteren om bruikbaarder te worden in de kliniek in de toekomst.

Chronische pijn is een belangrijke uitkomstmaat met een negatieve impact op kwaliteit van leven maar een hoge incidentie afhankelijk van soort operatie en de definitie van chronische pijn[47]. In tegenstelling tot acute pijn, welke vaak wordt gemeten met een één dimensionale schaal zoals de NRS, zijn er meerdere

instrumenten om chronische pijn te meten die multidimensionaal zijn[48]. Er is een grote variabiliteit in de gerapporteerde uitkomstmaten voor chronische pijn in klinische studies en dit maakt het moeilijk om de incidentie van chronische pijn in relatie tot kwaliteit van leven en therapeutische interventie te evalueren. Internationaal worden aanbevelingen gemaakt om uitkomstmaten in studies te homogeniseren maar tot nu toe blijft het aantal studies wat zich hier aan conformeert laag[49]. In onze ogen is het meten van kwaliteit van leven voor, en langere tijd na de operatie van belang om impact te meten voor de patiënt. Daarnaast is de lengte van follow-up ook belangrijk om de impact van chronische postoperatieve pijn te kunnen inschatten.

Samenvattend, hebben we in dit proefschrift getracht meer inzicht te krijgen in het perioperatieve gebruik van opiaten in verschillende patiëntenpopulaties. Hiertoe hebben we een prospectieve gerandomiseerde studie uitgevoerd in volwassenen die hartchirurgie ondergaan om de invloed van remifentanil op acute en chronische postoperatieve pijn te onderzoeken. Uit dit onderzoek kan geconcludeerd worden dat het intraoperatief gebruik van remifentanil tijdens hartchirurgie geen impact heeft op de incidentie chronisch postoperatieve pijn één jaar na de operatie. Desondanks, remifentanil verhoogt de behoefte aan analgetica direct na de operatie en chronische pijn tot drie maanden na de operatie. Patiënten met een jonge leeftijd welke een hoge dosering remifentanil krijgen lijken het meeste risico op het ontwikkelen van chronische pijn te hebben. De pijngevoeligheid, gemeten met behulp van detectie en pijndrempels, wordt niet beïnvloed door het gebruik van remifentanil. Daarnaast zijn er geen voorspellers geïdentificeerd voor een veranderde pijngevoeligheid na de operatie. Er zijn ook geen relevante aanwijzingen gevonden dat genetische factoren in dit cohort van patiënten een bijdrage leverden aan de variabiliteit in pijn.

In kinderen die hartchirurgie ondergaan laten we zien dat de kans op extra morfine niet daalt met hogere morfineconcentraties. Dit impliceert een matige concentratie-effect relatie van morfine bij kinderen direct na hartchirurgie. In de toekomst moet er misschien afgestapt worden van het principe dat er hoog gestart wordt met analgetica en vervolgens langzaam moet worden afgebouwd. Toekomstige studies moeten aantonen of dit mogelijk is en of multimodale analgesie een bijdrage kan leveren om het pijnbeleid bij kinderen na hartchirurgie te verbeteren.

In morbide obese patiënten hebben we laten zien dat er geen reden is om morfine te doseren op basis van lichaamsgewicht omdat de farmacokinetiek niet is gewijzigd ten opzichte van gezonde vrijwilligers. De plasmaconcentratie

van de morfine glucuronides zijn verhoogd in de morbide obese patiënten door een verlaagde eliminatieklaring. Dit betekent dat deze glucuronides kunnen accumuleren bij verlengde toediening maar de klinische impact is waarschijnlijk laag. Het zou interessant zijn om de fysiologische veranderingen die deze verlaagde eliminatieklaring hoogstwaarschijnlijk veroorzaken nader te onderzoeken om de invloed op andere geneesmiddelen te kunnen beoordelen.

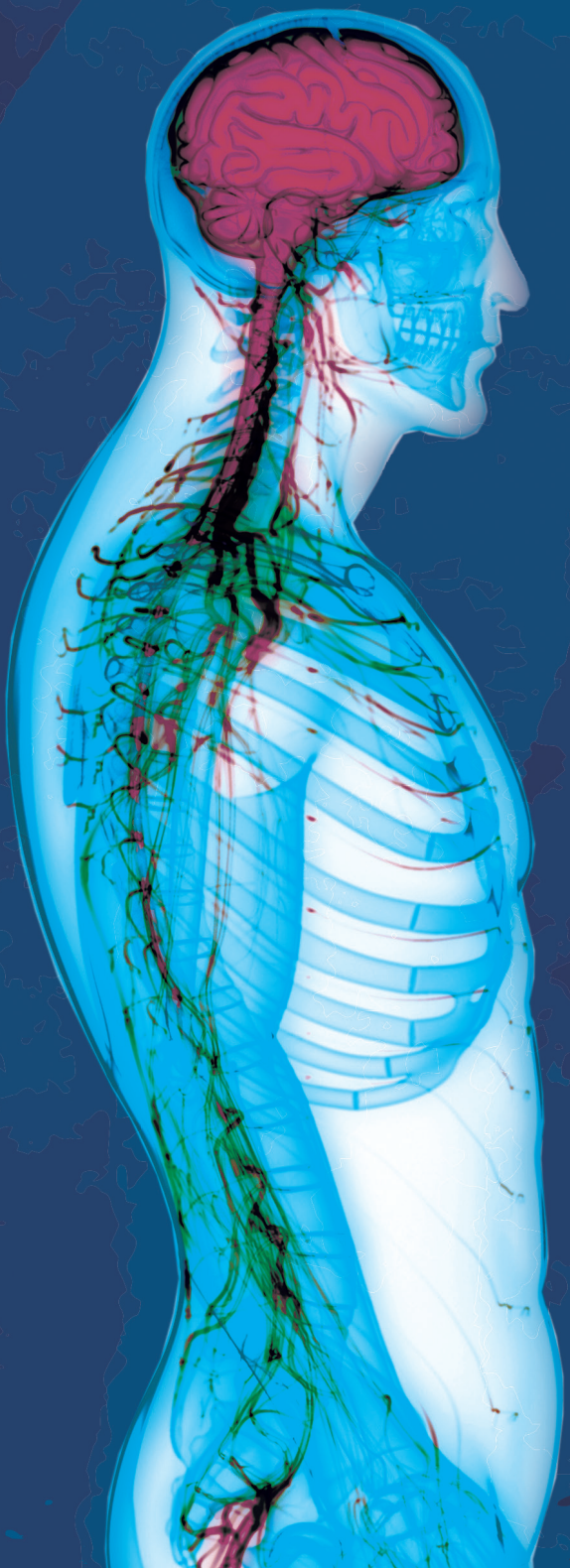
Concluderend, pijn is een complexe puzzel waarin biologische, psychologische, gedrags- en sociaal-culturele factoren een rol spelen. De hoge interindividuele variatie binnen deze factoren resulteren in het feit dat postoperatieve pijn nog steeds een belangrijke complicatie is na een operatie. Terwijl het doel eigenlijk is om postoperatieve pijn tot een minimum te beperken. Daarom is het antwoord op de vraag; “doet het nog steeds pijn?” Ja, helaas wel. Door in te zoomen op het perioperatieve gebruik van opiaten bij drie patiëntenpopulaties heeft dit proefschrift een aantal stukjes kunnen toevoegen aan deze complexe puzzel.

Literatuur

1. Merskey, H. & Bogduk, N. Part III: Pain Terms: A Current List with Definitions and Notes on Usage. in *Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy* 209–214 (1994).
2. Buvanendran, A. *et al.* The Incidence and Severity of Postoperative Pain following Inpatient Surgery. *Pain Med.* 16, 2277–83 (2015).
3. Gan, T. J., Habib, A. S., Miller, T. E., White, W. & Apfelbaum, J. L. Incidence, patient satisfaction, and perceptions of post-surgical pain: Results from a US national survey. *Curr. Med. Res. Opin.* 30, 149–160 (2014).
4. Apfelbaum, J. L., Chen, C., Mehta, S. S. & Gan, and T. J. Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. *Anesth. Analg.* 97, 534–540 (2003).
5. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
6. Chapman, C. R. & Vierck, C. J. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *J. Pain* 18, 359.e1-359.e38 (2017).
7. Johansen, A., Romundstad, L., Nielsen, C. S., Schirmer, H. & Stubhaug, A. Persistent postsurgical pain in a general population: Prevalence and predictors in the Tromsø study. *Pain* 153, 1390–1396 (2012).
8. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
9. Sommer, M. *et al.* The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur. J. Anaesthesiol.* 25, 267–74 (2008).
10. Mongardon, N. *et al.* Assessment of chronic pain after thoracotomy: a 1-year prevalence study. *Clin. J. Pain* 27, 677–81 (2011).
11. Valkenburg, A. J. *et al.* Pharmacodynamics and Pharmacokinetics of Morphine After Cardiac Surgery in Children With and Without Down Syndrome. *Pediatr. Crit. Care Med.* 17, 930–938 (2016).
12. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
13. Niedermayer, S., Heyn, J., Guenther, F., Küchenhoff, H. & Luchting, B. Remifentanil for abdominal surgery is associated with unexpectedly unfavorable outcomes. *Pain* 161, 266–273 (2020).
14. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
15. Subramaniam, K., Ibarra, A., Ruppert, K., Mallikarjun, K. & Orebaugh, S. Intraoperative Remifentanil Infusion and Postoperative Pain Outcomes After Cardiac Surgery-Results from Secondary Analysis of a Randomized, Open-Label Clinical Trial. *J. Cardiothorac. Vasc. Anesth.* 35, 458–466 (2021).
16. Greco, M. *et al.* Remifentanil in cardiac surgery: a meta-analysis of randomized controlled trials. *J. Cardiothorac. Vasc. Anesth.* 26, 110–6 (2012).
17. Möllhoff, T. *et al.* Comparative efficacy and safety of remifentanil and fentanyl in 'fast track' coronary artery bypass graft surgery: a randomized, double-blind study. *Br. J. Anaesth.* 87, 718–26 (2001).

18. Patel, S. S. & Spencer, C. M. Remifentanil. *Drugs* 52, 417–27; discussion 428 (1996).
19. Engoren, M., Luther, G. & Fenn-Buderer, N. A comparison of fentanyl, sufentanil, and remifentanil for fast-track cardiac anesthesia. *Anesth. Analg.* 93, 859–64 (2001).
20. Khanykin, B., Siddiqi, R., Jensen, P. F., Bigler, D. R. & Atroshchenko, G. V. Comparison of remifentanil and low-dose fentanyl for fast-track cardiac anesthesia: a prospective randomized study. *Heart Surg. Forum* 16, E324-8 (2013).
21. Komatsu, R. *et al.* Remifentanil for general anaesthesia: a systematic review. *Anaesthesia* 62, 1266–80 (2007).
22. Choudhury, A., Magoon, R., Sahoo, S. & Sehgal, L. Opioid Free Cardiac Surgery: Opportunities and Obstacles. *J. Cardiothorac. Vasc. Anesth.* 34, 567–568 (2020).
23. Gabriel, R. A. *et al.* State of the art opioid-sparing strategies for post-operative pain in adult surgical patients. *Expert Opin. Pharmacother.* 20, 949–961 (2019).
24. Frauenknecht, J., Kirkham, K. R., Jacot-Guillarmod, A. & Albrecht, E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis. *Anaesthesia* 74, 651–662 (2019).
25. Beloeil, H. *et al.* Balanced Opioid-free Anesthesia with Dexmedetomidine versus Balanced Anesthesia with Remifentanil for Major or Intermediate Noncardiac Surgery. *Anesthesiology* 134, 541–551 (2021).
26. Grant, M. C. *et al.* Opioid-Sparing Cardiac Anesthesia: Secondary Analysis of an Enhanced Recovery Program for Cardiac Surgery. *Anesth. Analg.* 131, 1852–1861 (2020).
27. Zeilmaker-Roest, G. A. *et al.* Intravenous morphine versus intravenous paracetamol after cardiac surgery in neonates and infants: a study protocol for a randomized controlled trial. *Trials* 19, 318 (2018).
28. Lewis, S. S. *et al.* Evidence that intrathecal morphine-3-glucuronide may cause pain enhancement via toll-like receptor 4/MD-2 and interleukin-1beta. *Neuroscience* 165, 569–83 (2010).
29. Klimas, R. & Mikus, G. Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide. *Br. J. Anaesth.* 113, 935–44 (2014).
30. Chen, Z. R., Irvine, R. J., Somogyi, A. A. & Bochner, F. Mu receptor binding of some commonly used opioids and their metabolites. *Life Sci.* 48, 2165–71 (1991).
31. Bickel, U., Schumacher, O. P., Kang, Y. S. & Voigt, K. Poor permeability of morphine 3-glucuronide and morphine 6-glucuronide through the blood-brain barrier in the rat. *J. Pharmacol. Exp. Ther.* 278, 107–13 (1996).
32. Ferslew, B. C. *et al.* Altered morphine glucuronide and bile acid disposition in patients with nonalcoholic steatohepatitis. *Clin. Pharmacol. Ther.* 97, 419–427 (2015).
33. Fisher, C. D. *et al.* Hepatic cytochrome P450 enzyme alterations in humans with progressive stages of nonalcoholic fatty liver disease. *Drug Metab. Dispos.* 37, 2087–2094 (2009).
34. Kruh, G. D., Belinsky, M. G., Gallo, J. M. & Lee, K. Physiological and pharmacological functions of Mrp2, Mrp3 and Mrp4 as determined from recent studies on gene-disrupted mice. *Cancer Metastasis Rev.* 26, 5–14 (2007).
35. Müller-Schwefe, G. *et al.* Make a CHANGE: optimising communication and pain management decisions. *Curr. Med. Res. Opin.* 27, 481–8 (2011).

36. Gilron, I., Carr, D. B., Desjardins, P. J. & Kehlet, H. Current methods and challenges for acute pain clinical trials. *Pain reports* 4, e647
37. van Gulik, L. *et al.* Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. *Eur. J. Anaesthesiol.* 27, 900–5 (2010).
38. Cui, C., Wang, L.-X., Li, Q., Zaslansky, R. & Li, L. Implementing a pain management nursing protocol for orthopaedic surgical patients: Results from a PAIN OUT project. *J. Clin. Nurs.* 27, 1684–1691 (2018).
39. Thiel, B. *et al.* Patient reported postoperative pain with a smartphone application: A proof of concept. *PLoS One* 15, e0232082 (2020).
40. Cruz-Almeida, Y. & Fillingim, R. B. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Med.* 15, 61–72 (2014).
41. Arendt-Nielsen, L. & Yarnitsky, D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J. Pain* 10, 556–572 (2009).
42. Marcuzzi, A., Dean, C. M., Wrigley, P. J., Chakiath, R. J. & Hush, J. M. Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. *J. Pain Res.* 9, 599–607 (2016).
43. van Helmond, N. *et al.* Is Preoperative Quantitative Sensory Testing Related to Persistent Postsurgical Pain? A Systematic Literature Review. *Anesth. Analg.* 131, 1146–1155 (2020).
44. Yarnitsky, D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr. Opin. Anaesthesiol.* 23, 611–615 (2010).
45. Yarnitsky, D. *et al.* Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* 138, 22–28 (2008).
46. Wilder-Smith, O. H., Schreyer, T., Scheffer, G. J. & Arendt-Nielsen, L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: a pilot study. *J. Pain Palliat. Care Pharmacother.* 24, 119–28 (2010).
47. Fletcher, D. *et al.* Chronic postsurgical pain in Europe: An observational study. *Eur. J. Anaesthesiol.* 32, 725–734 (2015).
48. Breivik, H. *et al.* Assessment of pain. *Br. J. Anaesth.* 101, 17–24 (2008).
49. Turk, D. C. *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 106, 337–345 (2003).



Section VI

Appendices

Curriculum vitae

Sjoerd de Hoogd was born on March 30th 1987 in 's-Gravenhage, The Netherlands. After his graduation in 2005 from the Adelbert College in Wassenaar, he studied Pharmacy at the Utrecht University. In 2012, he graduated with a Master in Pharmacy. After his graduation he started as a pharmacist in the VU University Medical Center, Amsterdam. In 2013, he started as PhD student at the Department of Clinical Pharmacy of the St. Antonius Hospital, Nieuwegein and the Division of Pharmacology of the Leiden Academic Centre for Drug Research (LACDR) under supervision of Professor Catherijne A.J. Knibbe and Professor Dick Tibboel. In 2015, he combined his PhD traineeship with a residency position in hospital pharmacy under mentorship of drs. M.M. Tjoeng, dr. E.M.W. van de Garde and Prof. dr. C.A.J. Knibbe. Sjoerd registered as a hospital pharmacist in 2019 and currently holds a position as a hospital pharmacist in the St. Antonius Hospital in Nieuwegein. Sjoerd currently lives in Utrecht together with Lisette and their two sons, Max en Teun.

List of publications

de Hoogd, S., Ahlers, S.J.G.M., van Dongen, E.P.A., Tibboel, D., Dahan, A., & Knibbe, C.A.J. (2014). Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials*, 15, 466.

de Hoogd, S., Ahlers, S.J.G.M., van Dongen, E.P.A., van de Garde, E.M.W., Hamilton-Ter Brake, T.A.T., Dahan, A., Knibbe, C.A.J. (2016). Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. *Clinical Journal of Pain*, 32(8), 726–735.

de Hoogd, S., Välitalo, P.A.J., Dahan, A., van Kralingen, S., Coughtrie, M.M.W., van Dongen, E.P.A., Knibbe, C.A.J. (2017). Influence of Morbid Obesity on the Pharmacokinetics of Morphine, Morphine-3-Glucuronide, and Morphine-6-Glucuronide. *Clinical Pharmacokinetics*, 56(12), 1577–1587.

de Hoogd, S., Ahlers, S.J.G.M., van Dongen, E.P.A., van de Garde, E.M.W., Daeter, E.J., Dahan, A., Knibbe, C.A.J. (2018). Randomized Controlled Trial on the Influence of Intraoperative Remifentanil versus Fentanyl on Acute and Chronic Pain after Cardiac Surgery. *Pain Practice*, 18(4), 443–451.

Smit, C., de Hoogd, S., Brüggemann, R.J.M., Knibbe, C.A.J. (2018). Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. *Expert Opinion on Drug Metabolism and Toxicology*, 14(3), 275–285.

de Hoogd, S., Valkenburg, A.J., van Dongen, E.P.A., Daeter, E.J., van Rosmalen, J., Dahan, A., Knibbe, C.A.J. (2019). Short- and long-term impact of remifentanil on thermal detection and pain thresholds after cardiac surgery. *European Journal of Anaesthesiology*, 36(1), 32–39.

Matic, M., de Hoogd, S., de Wildt, S.N., Tibboel, D., Knibbe, C.A.J., van Schaik, R. H. (2020). OPRM1 and COMT polymorphisms: implications on postoperative acute, chronic and experimental pain after cardiac surgery. *Pharmacogenomics*, 21(3), 181–193.

de Hoogd, S., Goulooze, S.C., Valkenburg, A.J., Krekels, E.H.J., van Dijk, M., Tibboel, D., & Knibbe, C.A.J. (2021). Postoperative breakthrough pain in paediatric cardiac surgery not reduced by increased morphine concentrations. *Pediatric Research*. [Epub ahead of print]

Nawoord – Acknowledgements

Op verschillende manieren hebben velen bijgedragen aan de totstandkoming van dit proefschrift. Allereerst wil ik mijn promotieteam bedanken. Catherijne, ik wil je bedanken voor de fijne samenwerking van de afgelopen jaren. Na onze overleggen kon ik weer met goede moed vooruit omdat jouw passie voor onderzoek en enthousiasme zo aanstekelijk is. Ik ben blij dat ik bij jou dit promotieonderzoek heb kunnen doen. Professor Tibboel, beste Dick, bedankt voor je klinische blik en fijne samenwerking. Beste Eric, mede dankzij jou kon ik mij als vreemde eend thuis voelen op het OK-complex tijdens de uitvoering van het onderzoek. Bedankt voor de prettige samenwerking en al je hulp!

Ik wil alle co-auteurs bedanken voor jullie discussies, expertise en input bij het tot stand komen van de manuscripten. In het bijzonder wil ik Bram Valkenburg, Pyry Välitalo en Bas Goulooze bedanken. Onze bijeenkomsten waarin de kennis van het modeleren werd gecombineerd met de klinische expertise waren leerzaam en productief. Ook wil ik Sabine Ahlers en de afdeling Anesthesiologie van het LUMC, in het bijzonder professor Dahan, bedanken voor de samenwerking en inspiratie bij het opzetten van de REFLECT studie.

Daarnaast wil ik alle collega's van de eenheid Farmacie van het St. Antonius bedanken voor de samenwerking, gezelligheid en ondersteuning! Gelukkig kunnen we deze fijne samenwerking voortzetten in mijn huidige rol als ziekenhuisapotheker. Een groot deel van mijn onderzoek heeft tijdens mijn opleiding tot ziekenhuisapotheker plaatsgevonden. Ik ben daarom ook mijn opleiders, Mathieu Tjoeng en Ewoudt van der Garde, dankbaar voor het vertrouwen en de flexibiliteit die mij altijd is gegeven.

Verder wil ik alle collega's van de afdeling Anesthesiologie, Intensive Care en Pijnbestrijding en Cardiothoracale Chirurgie van het St. Antonius ziekenhuis bedanken voor hun gastvrijheid op het OK/IC complex, samenwerking, inhoudelijke bijdrage en praktische hulp. Ook wil ik ook de anesthesiemedewerkers en verpleegkundigen van verschillende afdelingen bedanken voor hun praktische hulp en tijd tijdens de uitvoer van het onderzoek.

Tot slot wil ik graag mijn dierbare vrienden, familie bedanken voor de hulp, steun en liefde die ik de afgelopen jaren heb ontvangen. In het bijzonder mijn ouders, Marije en Gijs maar bovenal natuurlijk Lisette, op wie ik onvoorwaardelijk kan rekenen. Bedankt allemaal!