The influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs in adolescents and adults

Focus on propofol and nadroparin

Jeroen Diepstraten

The influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs in adolescents and adults

Focus on propofol and nadroparin

The research presented in this thesis was performed at the Department of Clinical Pharmacy of the St. Antonius Hospital Nieuwegein, The Netherlands and the Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA and the Department of Anaesthesiology, St Lucas Andreas Hospital, Amsterdam, the Netherlands.

Financial Support for the publication of the thesis was provided by the St. Antonius Hospital, the Department of Clinical Pharmacy of the St. Antonius Hospital, the Department of Anesthesiology, Intensive Care and Pain Management of the St. Antonius Hospital and the Dutch Society of Metabolic and Bariatric Surgery.

ISBN:	9789491356018
Cover Design & Layout:	MARLY VAN LIPZIG - (www.marlyvanlipzig.com)
Printed by:	Jubels bv – Amsterdam (www.jubels.nl)
Copyright:	The copyright of the articles that have been published are transferred to the respective journals

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden, op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker, volgens besluit van het College voor Promoties te verdedigen op donderdag 13 juni 2013 klokke 11.15 uur

door Jeroen Diepstraten, geboren te Eindhoven in 1979

Promotoren:	Prof. dr. C.A.J. Knibbe Prof. dr. A.A. Vinks *University of Cincinnati, Cincinnati, OH, USA*
Co-promotoren:	Dr. H.P.A. van Dongen Dr. B. van Ramshorst
Overige leden:	Prof. dr. L.P.H.J. Aarts Prof. dr. M. Danhof Prof. dr. H.J. Guchelaar Prof. dr. T. Hankemeier Prof. dr. M.M.R.F. Struys *Rijksuniversiteit Groningen*

Wer schaffen will, muß fröhlich sein.
Theodor Fontane

Table of contents

Section 01

Introduction and background

Introduction and outline

01

Obesity in adults, adolescents and children

Currently more than 13 % of the Dutch population is obese (Body Mass Index (BMI) > 30 kg/m^2) (1). Incidence of (morbidly) obese patients all over the world is rising as well (2-3). Besides, in 2008 childhood obesity affected 17% of the children and adolescents in the United States (4). If current trends persist, there will be 2.16 billion overweight (BMI > 25 kg/m^2) and 1.12 billion obese individuals worldwide in 2030 as compared to 388–405 million obese individuals in 2005 (5).

Extreme obese patients, morbidly obese patients (BMI > 40 kg/m^2), are reported to have various pathophysiological changes, such as an increased blood flow, cardiac output and oxygen consumption (6-7). In addition, morbidly obese patients suffer from increased risk for co-morbidities like diabetes type II and cancer (6). Due to these pathophysiological changes and co-morbidities, obese patients are more likely to utilize healthcare resources (8).

Dosing guidelines for most commonly used drugs in this population are not available due to the lack of studies providing adequate pharmacokinetic and pharmacodynamic data. Mostly the dose is rather based on clinical experience of the prescriber than on evidence based medicine. Serious problems may arise due to over- and underdosing, increasing adverse events and the risk of suboptimal efficacy, respectively. Therefore studies indentifying optimal body size descriptors for different drugs in order to define the dose in this special group of patients are urgently needed.

The influence of morbidly obesity on the pharmacokinetics and pharmacodynamics of propofol in adults and adolescents

For morbidly obese patients it is known that anaesthesia is not without risk. These patients are often difficult to intubate, are prone to desaturation due to altered pulmonary physiology and are known to have a different cardiac state (9-10).
Propofol, 2,6-di-isopropylphenol, is widely used for induction and maintenance of anaesthesia in both non-obese and obese patients as it has a rapid onset of action and fast recovery. The incidence of nausea and vomiting is the least of all anaesthetic agents (11). Propofol is a highly lipophilic drug which is protein-bound for 98%, mainly to albumin (12). While propofol clearance is mostly hepatic and for a small part extra-hepatic, it is known for being a high extraction drug (13). Pharmacokinetics of propofol in non-obese patients are characterized by a three-compartment model with a reported propofol clearance value of 1.4 to 2.2 L/min (14-15).
Propofols mechanism of action is not well defined but is probably due to enhance γ-aminobutyric acid (GABA)- mediated transmission (16). Propofol is rapidly redistributed and together with its high clearance from blood this leads to rapid recovery from anaesthesia (17). It has depressant effects on the cardiac contractility and causes reduction in venous and arteriolar systemic vascular resistance, resulting in a decrease in arterial blood pressure and a decrease of the pre- and afterload, respectively (18). In order to minimize the risk of side effects, optimal dosing of anaesthesia using propofol is needed.
Depth of propofol anaesthesia can be evaluated with Bispectral index (BIS) values, a derivative of the electroencephalographic (EEG) and therefore of brain activity of the cerebral cortex. BIS values varying from a dimensionless BIS value of 0 (complete cortical EEG suppression) to 100 (fully awake) (19). The BIS has been developed as a tool to measure the level of consciousness during anaesthesia and has benefits in comparison to clinical measures of anaesthesia, because it assesses sedation continuously and provides an objective, quantitative measure of the level of anaesthesia. The BIS has been approved to be used in the operating room for both children (20) and adults (21). As there are to date no dosing guidelines available for propofol anaesthesia in morbidly obese in both children and adults, effects of propofol have to be evaluated using both propofol concentrations and BIS values.

The influence of morbidly obesity on the pharmacodynamics of low molecular weight heparines

Despite significant advances in the prevention and treatment of venous thromboembolism events (VTE), pulmonary embolism is a common cause of hospital death (22), being responsible for approximately 150,000 to 200,000 deaths per year in the United States (23). Obesity is a known risk factor for VTE (24) with a relative risk for deep venous thrombosis of 2.50 (95% CI = 2.49 – 2.51) compared to non-obese patients (25). The relative risk for pulmonary embolism in hospitalized patients was more than two times higher in obese patients than in non-obese patients and even further increased in obese adolescents (26). Incidence of VTE after laparoscopic bariatric surgery for patients receiving thromboprophylactic therapy is relatively low with 0.9%. However, this risk increases to almost 3% 6 months after surgery (27).
Several derangements of normal haemostasis are thought to contribute to the prothrombotic state of obesity: enhanced platelet activity, procoagulant state, impaired fibrinolysis and activation of endothelial cells. The procoagulant state consists of increased tissue factor, fibrinogen, factor VII, factor VIII and thrombin generation (28). In contrast to non-obese patients, VTE is more difficult to diagnose as thoracic imaging often cannot be performed because of the weight limitations of the scanning equipment or otherwise the image quality is often poor (29).
Increased risk of VTE and difficult diagnosis makes optimal prophylactic therapy essential for this special group of patients. Low-molecular-weight heparines (LMWH) have been shown to substantially reduce the risk of VTE. LMWH contain fragments of heparin and have a molecular weight of 4 - 6 kDa and differ in their individual manufacturing processes and their in vitro potency (30). The major anticoagulant effect of LMWH is caused by binding to anti-thrombin (AT). Binding induces a conformational change in the molecule which accelerates its inhibitory activity on clotting factors Xa, IIa, IXa and XIIa. Compared to heparin, LMWH have a reduced ability to inactivate thrombin, because they consist of smaller fragments that cannot bind simultaneously to AT and thrombin (31) and less potent anti-factor IIa activity but have a stronger anti-factor Xa activity (31-32). Besides, LMWH have less effect on coagulation parameters, such as the activated partial thromboplastin time (32).
Nadroparin is a widely used LMWH in the Netherlands and is the standard drug for thrombotic prophylaxis in the St. Antonius Hospital, Nieuwegein. The ratio anti-factor Xa activity to anti-factor IIa activity for nadroparin is 2.5 - 4 : 1 compared to a ratio of 1:1 for heparin (32). Peak anti-factor Xa

activity of nadroparin are reached 3 - 5 h after subcutaneous administration with an elimination half-life of 8 - 10 h after subcutaneous injection in non-obese patients (30). Drug clearance of all LMWH is completely renal (30-31). Since it is not possible to measure LMWH levels directly, because it is a mixture of polysaccharides that includes biologically inactive species (33), and LMWH inhibit preferentially clotting factor Xa, anti-factor Xa assays have been developed and validated to determine the anticoagulant effect of LMWH (34). A standard curve is constructed by adding known amounts of LMWH to plasma and then adding a fixed amount of Xa. This results in the formation of an inactive antithrombin-Xa complex and residual Xa is measured using a chromogenic assay. The residual Xa activity is inversely proportional to the concentration of LMWH in the sample and may be quantitated from a calibration curve (35).
In comparison to heparin, LMWH have a more predictable dose-response relationship and therefore there is no need for routinely monitoring of anti-Xa levels (36). However for some special groups of patients; (morbidly) obese patients, patients with renal failure and pregnant patients, it can be justified as the dose-response relationship in these populations may be altered and these patients were excluded from clinical trials (34). For LMWH in general, the recommended prophylactic range in non-obese patients for anti-Xa levels 4 hours after administration is 0.2-0.5 IU/ml (37). Increased risk of bleeding has been observed for anti-Xa levels above 0.8 IU/ml (38). The guidelines of the American College of Chest Physicians suggest dosing adjustment of LMWH for very obese patients without clear dosing recommendations (24). Mostly a fixed dose of LMWH for thrombotic prophylaxis is given to non-obese patients and this dose is increased for a certain weight (based on BMI or total body weight) using a fixed amount. Using a fixed dose for thromboprophylaxis however could lead to underdosing and an increased risk for developing a thromboembolic event (31, 39). As there are to date no evidence based dosing guidelines available for LMWH prophylactic therapy in morbidly obese patients, clinical effects of LMWH have to be evaluated using anti-Xa levels as endpoint.

Body size descriptors for drugs in obesity

In order to develop evidence based dosing guidelines for morbidly obese patients, characterization of the influence of weight as covariate on variability between patients of pharmacokinetic and pharmacodynamic parameters of drugs starts often with population modelling. Covariate analysis involves the modelling of the distribution of the individual parameter estimates as a function of patient characteristics, pathophysiological factors, genetic/environmental factors and/or the concomitant use of other drugs, which may influence the pharmacokinetics and/or pharmacodynamics. The identification of predictive covariates for variability provides the scientific basis for rational and individualized dosing schemes. Different body size descriptors are available to characterize the influence of body weight on pharmacokinetic and pharmacodynamic parameters. Body mass index (BMI) is the international metric recommended to classify obesity, e.g. BMI higher than 40 kg/m2 is morbidly obese (3). However, BMI is not a measure of body composition; it is rather more of a descriptor of body shape as it cannot differentiate adipose tissue from muscle mass, with only an approximate relationship to excess body fat (40). Total body weight is mostly used to dose a drug however it is influenced by age, sex, height, muscles and obesity and therefore should be used with caution as body size descriptor of obesity. Lean body weight, as a measure of changes in body composition, is often suggested as an ideal metric for dosing in obese patients (41). The formula for estimation lean body weight was found to provide good predictive performance of the fat free mass measured with bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA) (42). This formula is not validated for children and therefore, recently, a new formula was developed by Peters et al. (43). However, it is unknown if these formulas are ideal body size descriptors in obese patients as pharmacokinetic and pharmacodynamic studies are lacking. It has been reported before in obese patients that metabolic pathways may be increased or decreased (44). Pharmacokinetic and pharmacodynamic studies are influenced by the metabolic pathways and properties of the drug and therefore there is no one body size descriptor that fits all drugs in obese patients.

Aims of the thesis

The aim of this thesis is to investigate the influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs and to develop a model-based approach to derive drug dosing algorithms for morbidly obese patients thereby focussing on propofol and low-molecular-weight heparin nadroparin.

Outline of the thesis

The influence of obesity on drug metabolism and elimination greatly differs per specific metabolic or elimination pathway. Chapter 2 provides an overview of clinical studies that reported drug clearance values in both obese and non-obese patients. Studies were classified according to their most important metabolic or elimination pathway.

The influence of morbidly obesity on the pharmacokinetics and pharmacodynamics of propofol in adults and adolescents
In order to describe the influence of excessive body weight on propofol in obese patients, we investigate the pharmacokinetics in both non-obese and morbidly obese patients and the pharmacodynamics in morbidly obese patients in Chapter 3 using Bispectral index (BIS) values as pharmacodynamic endpoint. As reports on the influence of perioperative remifentanil on the pharmacokinetics and pharmacodynamics of propofol are conflicting and for morbidly obese patients unexplored, in Chapter 4 morbidly obese patients receiving propofol-remifentanil anaesthesia and morbidly obese patients receiving propofol-epidural anaesthesia are compared. Given the developed PK PD model in Chapter 3, Chapter 5 addresses the validation of this model in clinical practice using BIS values as clinical endpoint. The subsequent chapter (Chapter 6), provides a pharmacokinetic model of propofol in morbidly obese adolescents as the prevalence of obesity is rising in younger patients. As the effect of weight gain can be due to aging and obesity, in Chapter 7 we perform a pharmacokinetic meta-analysis using data of both non-obese and morbidly obese adults, adolescents and children.

The influence of morbidly obesity on the pharmacodynamics of low molecular weight heparines
Chapter 8 was the starting point for investigating the influence of obesity on the pharmacodynamics of low molecular weight heparines (LMWH). It describes the pharmacodynamics of tinzaparin using anti-Xa levels as endpoint in a morbidly obese patient of 252 kg. As there is no consensus if and how the dose of LMWH needs to be adjusted in obese patients, we describe in Chapter 9 the current practice of thromboprophylaxis in obese surgical patients among surgeons in the Netherlands. Correlations between anti-Xa levels and different body size descriptors after a capped dose of 5,700 IU nadroparin in morbidly obese patients are studied in Chapter 10. Chapter 11 addresses the pharmacodynamics of nadroparin in both non-obese and morbidly obese patients using anti-Xa levels as pharmacodynamic endpoint.

As it is impossible to investigate all available drugs in morbidly obese patients using the method of Chapter 11, in Chapter 12 we extrapolate the PD model of nadroparin to another LMWH tinzaparin and compare these results with a reference model that was developed using a comprehensive covariate analysis of the tinzaparin data to provide the best description of these data based on statistical criteria.

Discussion and perspectives
Finally, the theme of this thesis is summarized and the potentials of pharmacokinetic and pharmacodynamic modelling in obese patients are discussed in Chapter 13.

References

1.RIVM. Nederland de Maat Genomen, 2009-2010. Bilthoven: RIVM2012.
2.Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009 Mar 28;373(9669):1083-96.
3.WorldHealthOrganisation. Obesity: Preventing and Managing the Global Epidemic. Geneva: World Health Organisation1997.
4.Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. Jama. 2010 Jan 20;303(3):242-9.
5.Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond). 2008 Sep;32(9):1431-7.
6.Kopelman PG. Obesity as a medical problem. Nature. 2000 Apr 6;404(6778):635-43.
7.Petersen VP. Body composition and fluid compartments in normal, obese and underweight human subjects. Acta Med Scand. 1957 Aug 13;158(2):103-11.
8.Ingelfinger JR. Bariatric surgery in adolesents. N Engl J Med. 2011 Oct 13;365(15):1365-7.
9.Sinha AC. Some anesthetic aspects of morbid obesity. Curr Opin Anaesthesiol. 2009 Jun;22(3):442-6.
10.Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. Br J Anaesth. 2000 Jul;85(1):91-108.
11.Sneyd JR, Carr A, Byrom WD, Bilski AJ. A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. Eur J Anaesthesiol. 1998 Jul;15(4):433-45.
12.Bryson HM, Fulton BR, Faulds D. Propofol. An update of its use in anaesthesia and conscious sedation. Drugs. 1995 Sep;50(3):513-59.
13.Al-Jahdari WS, Yamamoto K, Hiraoka H, Nakamura K, Goto F, Horiuchi R. Prediction of total propofol clearance based on enzyme activities in microsomes from human kidney and liver. Eur J Clin Pharmacol. 2006 Jul;62(7):527-33.
14.Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. Anesthesiology. 2000 Mar;92(3):727-38.
15.Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010 Apr 1;49(4):269-75.
16.Peduto VA, Concas A, Santoro G, Biggio G, Gessa GL. Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain. Anesthesiology. 1991 Dec;75(6):1000-9.
17.Reilly CS, Nimmo WS. New intravenous anaesthetics and neuromuscular blocking drugs. A review of their properties and clinical use. Drugs. 1987 Jul;34(1):98-135.
18.Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. Anaesthesia. 1985 Aug;40(8):735-40.
19.Vuyk J, Egberink EJ, Burm AG. [Bispectral analysis of the electroencephalogram: a new method for recording the level of consciousness during anaesthesia]. Ned Tijdschr Geneeskd. 2004 Jun 26;148(26):1276-80.
20.Sadhasivam S, Ganesh A, Robison A, Kaye R, Watcha MF. Validation of the bispectral index monitor for measuring the depth of sedation in children. Anesth Analg. 2006 Feb;102(2):383-8.
21.Monk TG, Weldon BC. Does depth of anesthesia monitoring improve postoperative outcomes? Curr Opin Anaesthesiol. 2011 Dec;24(6):665-9.
22.Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest. 1995 Oct;108(4):978-81.
23.Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Arch Intern Med. 2003 Jul 28;163(14):1711-7.
24.Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):381S-453S.
25.Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005 Sep;118(9):978-80.
26.Stein PD, Matta F, Goldman J. Obesity and pulmonary embolism: The mounting evidence of risk and the mortality paradox. Thromb Res. 2011 Nov 10.
27.Steele KE, Schweitzer MA, Prokopowicz G, Shore AD, Eaton LC, Lidor AO, et al. The long-term risk of venous thromboembolism following bariatric surgery. Obes Surg. 2011 Sep;21(9):1371-6.
28.Freeman AL, Pendleton RC, Rondina MT. Prevention of venous thromboembolism in obesity. Expert Rev Cardiovasc Ther. 2010 Dec;8(12):1711-21.
29.Hawley PC, Hawley MP. Difficulties in diagnosing pulmonary embolism in the obese patient: a literature review. Vasc Med. 2011 Dec;16(6):444-51.
30.Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis. 1996;26 Suppl 2:24-38.
31.Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3 Suppl):188S-203S.
32.Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. Anesth Analg. 1997 Oct;85(4):874-85.
33.Hainer JW, Sherrard DJ, Swan SK, Barrett JS, Assaid CA, Fossler MJ, et al. Intravenous and subcutaneous weight-based dosing of the low molecular weight heparin tinzaparin (Innohep) in end-stage renal disease patients undergoing chronic hemodialysis. Am J Kidney Dis. 2002 Sep;40(3):531-8.
34.Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost. 2004 Apr;2(4):547-50.
35.Gehrie E, Laposata M. Test of the month: The chromogenic antifactor Xa assay. Am J Hematol. 2011 Oct 14.
36.Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. J Thromb Haemost. 2004 Apr;2(4):551-4.
37.Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009 Jun;43(6):1064-83.
38.Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. Blood. 1991 Nov 1;78(9):2337-43.
39.Clark NP. Low-molecular-weight heparin use in the obese, elderly, and in renal insufficiency. Thromb Res. 2008;123 Suppl 1:S58-61.
40.Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004 Aug;58(2):119-33.
41.Han PY, Duffull SB, Kirkpatrick CM, Green B. Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther. 2007 Nov;82(5):505-8.
42.anmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
43.Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. Br J Anaesth. 2011 May;106(5):719-23.
44.Kotlyar M, Carson SW. Effects of obesity on the cytochrome P450 enzyme system. Int J Clin Pharmacol Ther. 1999 Jan;37(1):8-19.

Impact of obesity on drug metabolism and elimination in adults and children

02

Margreke J.E. Brill, Jeroen Diepstraten, Anne van Rongen,
Simone van Kralingen, John N. van den Anker, Catherijne A.J. Knibbe

Clin Pharmacokin. 2012(51): 277-304

Abstract

The prevalence of obesity in adults and children is rapidly increasing across the world. Several general (patho)physiological alterations associated with obesity have been described, but the specific impact of these alterations on drug metabolism and elimination and its consequences for drug dosing remains largely unknown.

In order to broaden our knowledge of this area, we have reviewed and summarized clinical studies that reported clearance values of drugs in both obese and non-obese patients. Studies were classified according to their most important metabolic or elimination pathway. This resulted in a structured review of the impact of obesity on metabolic and elimination processes, including phase I metabolism, phase II metabolism, liver blood flow, glomerular filtration and tubular processes.

This literature study shows that the influence of obesity on drug metabolism and elimination greatly differs per specific metabolic or elimination pathway. Clearance of cytochrome P450 (CYP) 3A4 substrates is lower in obese as compared with non-obese patients. In contrast, clearance of drugs primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT), glomerular filtration and/or tubular-mediated mechanisms, xanthine oxidase, N-acetyltransferase or CYP2E1 appears higher in obese versus non-obese patients. Additionally, trends indicating higher clearance values were seen for drugs metabolized via CYP1A2, CYP2C9, CYP2C19 and CYP2D6, while studies on high-extraction-ratio drugs showed somewhat inconclusive results. Very limited information is available in obese children, which prevents a direct comparison between data obtained in obese children and obese adults.

Future clinical studies, especially in children, adolescents and morbidly obese individuals, are needed to extend our knowledge in this clinically important area of adult and paediatric clinical pharmacology.

Introduction

Currently more than 30% of the US population is obese (Body Mass Index (BMI) >30 kg/m^2) (1-2), while approximately 5% have been reported to be morbidly obese (BMI > 40kg/m^2) (3). In Europe the prevalence of adult obesity ranges from 9-29% depending on the country (4) and increases every year. Also for children strong upward trends are observed. According to the national health and nutrition examination survey, conducted in 2007 – 2008, 17% of US children are obese(5). Upcoming economies, such as China and India, also show an alarming increase of obesity in both adults and children with more than 30% of Chinese adults being overweight (6). If current trends persist, there will be 2.16 billion overweight and 1.12 billion obese individuals worldwide in 2030 as compared with 388–405 million obese individuals in 2005 (7).

In view of this trend, it is important to understand the impact of obesity on drug metabolism and elimination and its consequences for drug dosing in the (morbidly) obese population. Obesity and morbid obesity are associated with several (patho)physiological changes that may influence the pharmacokinetics of drugs. Among other factors, obese patients have relatively more fat and less lean tissue per kilogram of total body weight than non-obese individuals (8-9). Blood volume is observed to be increased, particularly in the morbidly obese (10-11). In addition, studies have confirmed that obese patients suffer from low-grade inflammation (12), which is probably the underlying cause of the high prevalence of non-alcoholic steatohepatitis (NASH)(13-14). NASH has been reported to either increase or decrease drug metabolizing enzyme activity (15-18). The net effect of obesity on drug metabolism is also influenced by cardiac output and liver blood flow, both of which are shown to be increased in obese patients (19). Concerning renal function, a state of glomerular hyperfiltration similar to the condition seen in early-stage diabetic nephropathy and sickle cell disease has been reported in obese individuals (20-21). Until now, the influence of obesity on tubular processes has been unknown.

In summary, many (patho)physiologic alterations associated with obesity have been described in the literature, yet the impact of these alterations on specific drug metabolic and elimination pathways has not been clearly summarized. Numerous publications have described obesity-related alterations in all aspects of drug pharmacokinetics, including absorption, distribution, metabolism and elimination of drugs (9, 22-30). In addition, several publications have tried to provide practical guidelines for dosing in this population (9, 23-28). In recent publications the influence of obesity on drug metabolism and renal elimination was stated to be inconclusive and inconsistent, with drug clearance being the most important pharmacokinetic parameter for maintenance dosing regimens (9, 22, 24, 27, 30). In some cases, results from animal or in vitro studies have been used to fill the knowledge gaps (27, 30). So far, many pharmacokinetic studies have been performed in obese patients and these studies may represent a wealth of knowledge on clearance of specific drugs in obesity. In this review our goal was to order and sort pharmacokinetic studies by their primary drug metabolic or elimination pathway to gain insight into how these pathways change with obesity. Therefore, drugs representative for a specific pathway were included in the review, in order to generate knowledge on obesity-related changes in the most important metabolic and elimination pathways in humans. As such, this review provides insight into how obesity affects specific drug metabolism and renal elimination pathways in both obese adults and obese children, on the basis of results of pharmacokinetic studies in obese and non-obese individuals. For this purpose a direct comparison between drug clearance in obese and non-obese individuals is necessary: therefore clinical trials that included both obese and non-obese individuals were reviewed in this analysis.

Search Strategy and Selection Criteria

Approach

We studied individual drug metabolism and elimination processes by using drug clearance values as surrogate markers for these processes. To allow for direct comparisons between obese and non-obese individuals, clinical studies that investigated drug pharmacokinetics in both obese and non-obese patients were collected. The drugs reported in these clinical studies were categorized by their currently known rate-limiting clearance processes, and absolute clearance values were summarized in tables, which is an approach that has been applied before (29). In addition, weight-normalized clearance values were added to provide information on the weight-normalized changes in clearance values between non-obese and obese individuals. These weight-normalized clearance values were either directly extracted from the original publication or derived by dividing mean clearance by mean total body weight. As an alternative to total body weight, consideration was given to normalizing clearance values for lean body weight, as this parameter is often proposed as a body size descriptor for obese patients (27, 31). Unfortunately, this parameter was reported in only very few studies included in this review; therefore, it was not possible

to report clearance values adjusted for lean body weight.
Clearance processes were divided into metabolism and renal elimination. For drug metabolism, phase I metabolism, phase II metabolism and liver blood flow were considered. Drugs for which information about the rate-limiting cytochrome P450 (CYP) process was inconclusive were included in the Miscellaneous Phase I Metabolism section (section Other Phase I Metabolic Enzymes). For renal elimination, two processes involved in drug elimination by the kidneys were identified: glomerular filtration and tubular processes (tubular secretion and tubular reabsorption).

Inclusion criteria
Papers from the international peer reviewed literature reporting drug pharmacokinetics in obese and normal-weight adults or children were eligible for inclusion. Drugs were included if cleared by a specific metabolic or renal elimination pathway, as reported in international peer reviewed literature. This reference about the drugs main metabolic or elimination route was included in the tables.

Search terms and search results
The PubMed database was used for the search for papers in which the pharmacokinetics of a drug were studied in both an obese and non-obese population. The following search terms were used:

- (Clearance[All Fields] AND ("obesity"[MeSH Terms] OR "obesity"[All Fields])) AND (controls[All Fields] OR normal[All Fields] OR healthy[All Fields]), yielding 562 results on 2nd of March 2011.
- '[Substrate]' and 'obesity' and 'pharmacokinetics'. Substrates mentioned in Cytochrome P450 Drug Interaction Table were used(32). A total of 91 (CYP3A4), 10 (CYP2E1), 35(CYP2D6), 43(CYP1A2), 23 (CYP2C19), 14 (CYP 2C9), 1 (CYP 2C8), 7 (CYP2B6) papers of interest were found between March and May of 2011.
- '[Kidney process]' and 'obesity' and 'pharmacokinetics'. A total of 18 (glomerular), 5 (tubular secretion) and 2 (tubular reabsorption) papers of interest were found between May and June of 2011.

Additionally, references in the selected articles were checked for additional publications to include in this review.

Exclusion criteria
From studies investigating pharmacokinetics of drugs in both obese and non-obese patients, the following studies were excluded: studies on drugs for which the metabolic or renal elimination pathway was reported to be

miscellaneous, unknown or inconsistent, as concluded from peer reviewed literature; studies investigating endogenous substances (including insulin); pharmacodynamic studies; animal studies; case reports; and in vitro studies.

Drug metabolism

Drug metabolism predominantly occurs in the liver through enzymes responsible for the modification of functional groups (phase I reactions) and the conjugation of endogenous substituents to drugs to make them even more polar (phase II conjugation) (33).
In 90% of obese patients, histologically proven liver abnormalities as fatty infiltration are present (34). Non-alcoholic fatty liver disease (NAFLD) may range from simple liver steatosis without inflammation to NASH with active hepatic inflammation. NASH prevalence is difficult to assess, because the diagnosis can only be confirmed using a liver biopsy. However, it is estimated that up to 20% of the obese population and up to 50% of morbidly obese patients have NASH (35), and its incidence correlates with BMI (kg/m2) (36). While fatty infiltration of the liver may result in altered enzyme activity of phase I or II systems, this enzyme activity may also be subject to changes caused by other obesity-associated (patho)physiological changes such as the chronic state of inflammation (12, 16).
To describe the enzyme activity of phase I and II systems in obesity, we provide in this section an overview of clinical studies investigating drugs of which clearance is dependent on phase I or II reactions or liver blood flow and which were studied in both obese adults or children and non-obese adults or children in one report.

Phase I metabolisme
Phase I enzymes catalyse the modification of functional groups of a substrate (i.e. oxidation, reduction and hydrolysis), and the majority of these enzymes consist of CYPs. CYPs are predominantly located in the endoplasmatic reticulum of hepatocytes. Other sites include the gastro-intestinal tract, where significant amounts of gene expression of various CYP isoforms have been detected (37-38). CYP enzyme metabolism contributes to approximately 75% of all drug metabolism (39). In this section we provide an updated review of all studies that have investigated phase I-mediated drug clearance in both obese and non-obese patients in one report.
Cytochrome P450 (CYP) 3A4
CYP3A4 is involved in the phase I metabolism of approximately 50% of all drugs (40). In Table I, an overview of the studies comparing clearance

Table I *Cytochrome P450 (CYP) 3A4-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Taranabant (55)	n = 385 BMI 35.4 (3.8) kg/m²	n = 187 BMI 25 (3.2) kg/m²	0.5–8.0 mg PO	CL/F	22.4 (CV 44%) L/h	35.6 (CV 51%) L/h	NA	NA	(56)
Docetaxel (176)	n = 21 BMI >30 kg/m²	n = 130 BMI <30 kg/m²	55–100 mg/m² IV	CL	BMI 30–35 kg/m²: 46.1 (15) L/h	40.9 (15) L/h	NS	NA	(59)
Docetaxel (176)	n = 21 BMI >30 kg/m²	n = 130 BMI <30 kg/m²	55–100 mg/m² IV	CL	BMI >35 kg/m²: 42.3 (13) L/h	40.9 (15) L/h	NS	NA	(59)
Carbamazepine (45)	n = 18 TBW 111.4 (20) kg BMI 38.8 (6.0) kg/m²	n = 13 TBW 63.2 (8.3) kg BMI 22.4 (1.6) kg/m²	200 mg PO	CL	19.8 (1.2) mL/min	23.0 (1.3) mL/min	p = 0.07	0.18 vs 0.36 mL/min/kg	(51)
Carbamazepine (45)	n = 6 TBW 122 (8.4) kg BMI 42.5 (3.2) kg/m²	n = 6[d] TBW 92.2 (4.2) kg BMI 32.0 (1.4) kg/m²	200 mg PO	CL	20.4 (1.8) mL/min	31.6 (5.0) mL/min	p < 0.05	0.17 vs 0.34 mL/min/kg	(52)
ERBT (44)	n = 6 TBW >130% IBW	n = 18 Age 70–88[e] y	0.074 mmol	[14C] N-methyl erythromycin	Negative correlation between %IBW and ERBT		p = 0.001	NA	(41)
ERBT (44)	n = 5 TBW >130% IBW	n = 4 (hypertensive pts) Age 45–72[e] y	0.074 mmol	[14C] N-methyl erythromycin	Negative correlation between %IBW and ERBT		p < 0.001	NA	(42)
Midazolam (46)	n = 20 TBW 116.5 (7.6) kg	n = 20 TBW 65.7 (1.5) kg	5 mg IV, 10 mg PO	CL	472 (38) mL/min	530 (34) mL/min	NS	4.2 vs 8.1mL/min/kg	(48)
Triazolam (43)	n = 12 TBW 111.6 (12) kg	n = 12 TBW 63.8 (2.9) kg	1 mg PO	CL	340 (44) mL/min	531 (38) mL/min	p < 0.025	3.05 vs 8.32 mL/min/kg	(47)
Alprazolam (43)	n = 12 TBW 111.6 (12) kg	n = 12 TBW 63.8 (2.9) kg	0.5 mg PO	CL	66.4 (7.0) mL/min	88 (9.7) mL/min	NS	0.60 vs 1.38 mL/min/kg	(47)
Cyclosporine (43)	n = 10 TBW 89.7 (11) kg	n = 35 TBW 62.5 (8.4) kg	2.5 mg/kg IV and 14 m/kg PO (mg/kg)	CL	700 mL/min	780 mL/min	NS	7.80 vs 12.48 mL/min/kg	(50)
Cyclosporine (43)	n = 13 TBW 102.6 (4.4) kg (>125% IBW)	n = 38 TBW 67.8 (2.2) kg (≤125% IBW)	2.8 (2.0–3.3) mg/kg IV	CL	Lower CL		NS	CL in obese pts is halved when normalized for weight	(49)
Trazodone (57-58)	n = 23 112 (7) kg	n = 23 TBW 65 (2) kg	25 mg IV, 50 mg PO	CL	146 (10) mL/min	136 (8) mL/min	NS	1.30 vs 2.09 mL/min/kg	(177)
Alfentanil (53)	n = 6 TBW 123 kg	n = 7 TBW 64 kg	6838 vs 5990 µg	CL	179 mL/min	321 mL/min	p < 0.01	1.46 vs 5.02 mL/min/kg	(54)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP3A4 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c Body weight normalized clearance values were either taken from the reference or calculated using the mean clearance and mean body weight of the study group. Also see section Approach for calculation of weight-normalized clearance values.
d Same pts after weight loss.
e Values are expressed as range.
BMI = body mass index; CL = drug clearance; CL/F = oral clearance; CV = coefficient of variation; ERBT = erythromycin breath test; F = bioavailability; %IBW = percentage of ideal body weight; IV = intravenously; NA = not available; NS = not significant; PO = orally; t½ = elimination half-life; TBW = total body weight.

of CYP3A4-metabolized drugs in both obese and non-obese individuals is presented. The pharmacokinetics of ten CYP3A4 substrates in obese versus non-obese subjects have been reported, including alfentanyl, midazolam, triazolam, alprazolam, cyclosporine, carbamazepine, docetaxel, taranabant, trazodone and N-methyl-erythromycin.

As an in vivo probe of CYP3A4 activity, N-methyl-erythromycin, midazolam, triazolam, alprazolam and cyclosporine are widely applied (41-46). In this respect, it was reported that obesity was significantly associated with lower metabolism of [14C]-N-methyl-erythromycin, measured as exhaled $^{14}CO_2$ in both men and women (r^2= 0.91 and r^2 =0.90, respectively) (41-42), indicating reduced CYP3A4 metabolic activity. Similarly, triazolam clearance was significantly lower in obese patients (47). For midazolam (48), alprazolam (47) and cyclosporine (49-50), clearance values were reported to be lower in obese versus non-obese individuals, though this was not statistically significant, potentially because of the limited power of these studies.

A trend towards lower CYP3A4 activity associated with obesity was also found for other major CYP3A4-cleared drugs. Carbamazepine clearance in non-obese versus obese patients was only marginally higher (51). Upon major weight loss, carbamazepine clearance in six obese patients was significantly increased (52). As an explanation, it has been suggested that a fatty liver, as observed by abdominal ultrasound, may hinder carbamazepine metabolism either by inhibition of important biochemical reactions or by reduction in liver blood flow. After weight loss, ultrasound images showed a disappearance of fatty changes, in line with an increase in carbamazepine clearance. Clearance of alfentanil, which is also predominantly metabolized by CYP3A4 (53), was almost halved in obese as compared with non-obese patients (54). The pharmacokinetics of taranabant, primarily metabolized by CYP3A4 (55), were studied using data from 12 phase 1 clinical trials and one phase 2 study, including 385 obese individuals (BMI range 30-43 kg/m^2) (56). While the authors found a lower estimated oral clearance in obese individuals, they attributed this result to either increased protein binding or a decrease in CYP3A activity.

For two CYP3A4 substrates no difference in clearance was reported in obese versus non- obese patients. Trazodone, for which CYP3A4 is the major isoenzyme involved in the formation of its metabolite (57-58), showed no difference in clearance between obese and non-obese patients. Furthermore, docetaxel clearance values of adults patients were not significantly different between non-obese, obese or morbidly obese adults (59).

In studies of patients before and after gastric bypass surgery an increase in activity of CYP3A4 metabolism in obese individuals was reported. Cyclosporine requirement in patients after gastric bypass surgery was

significantly increased from 1.8 to 3.5 mg/kg/d (p=0.02,) in order to maintain similar cyclosporine trough levels (60). Similarly it was reported that higher, tacrolimus, sirolimus (CYP3A4 (61-62)) and mycophenolic acid (CYP3A4, CYP2C8 (63)) doses were needed in transplant recipients with a gastric bypass to ensure exposure similar to that in a non-bypass patient (64). In contrast, atorvastatin bioavailability 3 – 6 weeks after gastric bypass surgery was found to be both increased and decreased as compared with before surgery (65-66). The observations made in these gastric bypass studies seem to reflect an increase in CYP3A4-mediated clearance in after weight loss. However, these observations may also be explained by the surgical procedures or an increase in activity of CYP3A4 located in the intestines, both causing reduced absorption of oral drugs. Finally, it could be a combination of the factors mentioned. To our knowledge, no studies have investigated the oral bioavailability of CYP3A4 substrates in obese (gastric bypass) patients versus non-obese patients, and as such, we cannot distinguish between these factors.

In summary, 7 out of 13 studies presented in Table I show a significantly lower clearance of CYP3A4 substrates in obese patients and 4 studies show non-significantly lower absolute clearance values. Body weight-normalized clearance values, as depicted in Table I, show that drug clearance per kilogram body weight is halved in obese individuals. The underlying mechanism of impaired CYP3A4 metabolism and the potential consequences for CYP3A4 drug-drug interactions in obese patients are unclear and should be subjects of future research. Furthermore, it should be noted that the majority of patients included in these studies were mildly obese, while only a few morbidly obese patients (BMI >40 kg/m^2) were included. To date, the pharmacokinetics of CYP3A4-metabolized drugs have not been studied in obese children or adolescents.

CYP2E1

Although CYP2E1 metabolism represents only about 5% of phase I drug metabolism (39), the impact of obesity on CYP2E1 activity has been the subject of several studies, in which also a significant proportion of morbidly obese patients were included. Chlorzoxazone, enflurane, sevoflurane and halothane represent the four model drugs for CYP2E1 activity reviewed here, of which the results are summarized in Table II.

Chlorzoxazone pharmacokinetics were studied in several clinical trials, as this drug is a highly selective probe of CYP2E1 metabolism (67). In women, it was shown that morbid obesity is associated with increased 6-hydroxylation of chlorzoxazone, which is consistent with induction of CYP2E1 (68). For obese patients, with or without non-insulin-dependent diabetes mellitus, it was found that CYP2E1 activity was 40% higher as compared with non-

Table II *Cytochrome P450 (CYP) 2E1-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Chlorzoxazone (67)	n = 16 TBW 172 (104–273) kg BMI 60 (45–100) kg/m²	n = 16 TBW 59 (48–93) kg BMI 21 (18–26) kg/m²	750 mg PO	$CL_{unbound}/F$	27.5 (9–55) L/min	9.9 (3–49) L/min	p < 0.001	0.16 vs 0.17 L/min/kg	(18)
Chlorzoxazone (67)	n = 14 TBW 172 (104–273) kg BMI 59 (45–100) kg/m²	n = 14[d] TBW 145 (95–247) kg BMI 50 (41–98) kg/m²	750 mg PO	$CL_{unbound}/F$	26.8 (9–56) L/min	16.6 (8–45) L/min	p < 0.05	0.16 vs 0.11 L/min/kg	(18)
Chlorzoxazone (67)	n = 14 TBW 172 (104–273) kg BMI 59 (45–100) kg/m²	n = 14[e] TBW 118 (61–208) kg BMI 43 (22–82) kg/m²	750 mg PO	$CL_{unbound}/F$	26.8 (9–56) L/min	19.5 (8–50) L/min	NS	0.16 vs 0.17 L/min/kg	(18)
Chlorzoxazone (67)	n = 17 BMI 39 (1.4) kg/m²	n = 42 TBW within 20% IBW	500 mg PO	Metabolite/parent drug ratio	0.38 (0.1)	0.30 (0.2)	NS	NA	(67, 69)
	n = 13 (NIDD pts) BMI 37 (1.5) kg/m²	n = 42 TBW within 20% IBW	500 mg PO	Metabolite/parent drug ratio	0.45 (0.2)	0.30 (0.2)	p = 0.007	NA	(67, 69)
Chlorzoxazone (67)	n = 9 (women) BMI 35–50 kg/m² TBW 119 (16) kg	n = 9 (women) BMI 21–30 kg/m² TBW 72 (11) kg	250 mg PO	CL (parent)				6.2 (1.7) vs 4.2 (0.8) mL/min/kg (p=0.01)	(68)
				Fractional CL (6-OH metabolite)				4.0 (1.1) vs 2.52 (0.1) mL/min/kg (p=0.006)	(68)
Enflurane (70)	n = 26 TBW 128.4 (6.0) kg BMI 46.3 (1.7) kg/m²	n = 8 TBW 68.1 (1.2) kg BMI 22.9 (2.0) kg/m²	Similar MAC-hr (p > 0.05)	FL C_{max}	27.8 (2.0) µmol/L	17.0 (3.0) µmol/L	p < 0.01	0.27 vs 0.25 µmol/L/kg	(73)
Enflurane (70)	n = 24 TBW 127.6 (6.0) kg BMI 45.9 (1.7) kg/m²	n = 7 TBW 67.3 (1.2) kg BMI 23.6 (2.0) kg/m²	Similar MAC-hr	Mean FL C_{max}	28.0 (1.9) µmol/L	17.3 (1.3) µmol/L	p < 0.01	0.22 vs 0.26 µmol/L/kg	(74)
Sevoflurane (71)	n = 15 TBW 84.8 (2.7) kg BMI 29.3 (0.8) kg/m²	n = 16 TBW 63.8 (1.5) kg BMI 22.1 (0.4) kg/m²	Similar MAC-hr (p > 0.05)	All FL concentrations	Higher in obese pts		p < 0.001	NA	(75)
				Urinary FL excretion	Higher in obese pts (n = 8)		p < 0.001	NA	(75)
Sevoflurane (71)	n = 13 TBW 114 (8) kg BMI 41 (1) kg/m²	n = 10 TBW 73 (3) kg BMI 26 (1) kg/m²	Similar MAC-hr (p > 0.05)	FL C_{max}	49 µmol/L	42 µmol/L	NS	0.43 vs 0.58 µmol/L/kg	(76)
Halothane (72)	n = 17 TBW 125 (5) kg BMI 45 (1) kg/m²	n = 8 TBW 59 (5) kg BMI 22 (2) kg/m²	Similar MAC-hr (p > 0.05)	TFA serum concentration	At T = 1 and 3 h, significantly higher in obese pts		p < 0.05	NA	(77)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2E1 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d 6 wk post-weight-reducing surgery.
e 1 y post-weight-reducing surgery.
f Values are expressed as range.
BMI = body mass index; CL = clearance; CLunbound/F = oral clearance of unbound drug fraction; Cmax = maximum concentration; FL = ionic fluoride; %IBW = percentage of ideal body weight; MAC = minimum alveolar (anaesthetic) concentration; NA = not available; NIDD = non-insulin-dependent diabetes; NS = not significant; PO = orally; T = time; TBW = total body weight; TFA = trifluoro-acetic acid (metabolite of halothane) (72).

obese subjects (67, 69).
More recently, CYP2E1 activity in obesity was further studied by Emery et al. (18). Unbound oral clearance ($Cl_{unbound}$/F) of chlorzoxazone was approximately threefold higher in morbidly obese compared with non-obese individuals (p<0.001). Six weeks and 1 year post-weight-reducing surgery, chlorzoxazone Clunbound/F in patients was reduced. The authors suggest a causal relationship between the induction of CYP2E1 activity and hepatic fatty infiltration, based on liver biopsy assessment. They found a trend towards higher CLunbound/F with increasing severity of liver fatty infiltration or steatosis (p=0.06). More specifically they showed that CLunbound/F was significantly higher among subjects with steatosis involving >50% of hepatocytes, compared with those with steatosis in ≤ 50% of hepatocytes (p=0.02) (18).
Volatile anesthetics, including enflurane, sevoflurane and halothane, are partly metabolized by CYP2E1 as well. Ionic fluoride is formed by CYP2E1 oxidation of enflurane and sevoflurane, and therefore represents a reliable marker of CYP2E1 metabolism (70-71). A third volatile anesthetic, halothane, undergoes CYP2E1 biotransformation, which results in trifluoro-acetic acid (72). After a similar dose of enflurane maximal ionic fluoride concentrations were found to be significantly higher in obese compared with non-obese patients (73-74). A similar result was seen for sevoflurane in obese versus non-obese patients (75). A second sevoflurane study did not find a significant difference in ionic fluoride concentrations between obese and non-obese patients (76). After similar doses of halothane, significantly higher trifluoro-acetic acid concentrations in obese patients at 1 and 3 hours after dosing were found (77).
The studies summarized in Table II show a consistent and significant increase in clearance of different CYP2E1 substrates in obese as compared with non-obese subjects, indicating induction of CYP2E1 activity in obesity. When normalized for body weight, clearance values are more or less equal among obese and non-obese individuals, which indicates that CYP2E1 activity increases with body weight. As an explanation, liver fatty infiltration, which is expected to increase with increasing body weight may be the underlying cause of the CYP2E1 enzyme activity increase with body weight(18). In obese children, no studies on CYP2E1-metabolized drugs have been performed yet.
With regard to the higher CYP2E1 activity observed in obese patients, it can be anticipated that caution should be practiced when using paracetamol (paracetamol) in obese patients, as CYP2E1 catalyses the formation of the toxic metabolite N-acetyl-p-benzo-quinone imine (NAPQI). Two studies have looked into paracetamol pharmacokinetics in both obese and non-obese patients (78-79). Both studies are discussed in the Phase II metabolism

section, 90% of paracetamol is conjugated via phase II metabolism and only 5–10% of paracetamol is metabolized by CYP2E1 (80). Moreover, one study (79) did not report metabolites, but only paracetamol clearance values, while the other did not measure NAPQI or the metabolites formed after NAPQI (APAP-C or APAP-M) (78). Therefore, the above-stated warning may be considered somewhat speculative, and further studies are needed to assess the role of CYP2E1 in paracetamol metabolism and toxicity in both obese adults and children – in particular, given the importance of paracetamol in paediatric therapeutics.

CYP2D6
CYP2D6 metabolism represents about 10-15% of phase I drug metabolism in humans (40). The activity of this CYP isoform may differ greatly between individuals depending on its genetic polymorphisms (81-82). Two CYP2D6 substrates, dexfenfluramine and nebivolol, have been subjects of pharmacokinetic studies in obese and non-obese individuals, as shown in Table III.
For dexfenfluramine metabolism, there was a trend towards higher dexfenfluramine clearance and higher metabolite/parent ratio in obese versus non-obese subjects (83). Nebivolol clearance was significantly a higher in obese subjects as compared with non-obese individuals (84). As nebivolol clearance is relatively high (> 1 L/min), it may be more dependent on liver blood flow than on intrinsic CYP metabolism. However, as the CYP2D6 phenotype has been found to influence the clearance of nebivolol, it was included in this section (85).
In summary, these few studies indicate trends towards increased CYP2D6-mediated metabolism in obese versus non-obese patients.

CYP1A2
CYP1A2 metabolism represents a small part (~5%) of total phase I drug metabolism. Smoking has an inducing effect on CYP1A2 activity (86). Caffeine and theophylline have been indicated as CYP1A2-specific probes (87-88) and have been studied in obese versus non-obese populations by different research groups (Table IV).
In adults, caffeine clearance was not significantly different between non-smoking obese and non-smoking non-obese patients and between obese patients before and after weight loss (89). Two earlier caffeine studies in adult obese and non-obese subjects also did not show a significant difference in caffeine clearance (90-91).
In In children aged between 6 and 10 years, Chine et al. evaluated oxidative enzyme activity of CYP1A2, using the urinary metabolic ratio of caffeine metabolites (92). The authors observed non-significantly lower CYP1A2

Table III *Cytochrome P450 (CYP) 2D6-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Dex-fenfluramine (178)	n = 10 BMI 32.2 (2.9) kg/m²	n = 10 BMI 20.8 (2.0) kg/m²	30 mg PO	CL	43.9 (21) L/h	37.3 (11) L/h	NS	NA	(83)
Dex-fenfluramine (178)	n = 10 BMI 32.2 (2.9) kg/m²	n = 10 BMI 20.8 (2.0) kg/m²	30 mg PO	Parent/ metabolite ratio	2.29 (1.8)	2.05 (1.3)	NS	NA	(83)
Nebivolol (85)	n = 9 BMI 34.6 (5.6) kg/m² TBW 99 kg	n = 9 BMI 21.4 (2.6) kg/m² TBW 60 kg	0.073 mg/ kg IBW IV	CL	71.6 (17) L/h	51.6 (11) L/h	$p < 0.05$	0.72 vs 0.86 L/h/kg	(84)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2D6 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
BMI = body mass index; CL = clearance; IBW = ideal body weight; IV = intravenously; NA = not available; NS = not significant; PO = orally; TBW = total body weight.

enzyme activity in obese as compared with non-obese children.
Theophylline clearance showed a significant decrease in 16 obese women after a 6.2 (1.5) kg weight loss (93). In a study with 200 individuals, no significant difference in theophylline clearance between moderately obese and non-obese subjects was found (94). However, after correcting for the influence of smoking, higher total body clearance associated with obesity was found for a select group of young non-smoking subjects ($p<0.025$). In a third study, it was shown that theophylline clearance correlates with total body weight and not with ideal body weight (95).
In summary, trends of higher clearance values in obese as compared with non-obese patients indicate a slight increase in CYP1A2 activity. When corrected for body weight, clearance values showed both higher and lower clearance values for obese individuals as compared with non-obese subjects (Table IV).

CYP2C9

CYP2C9-mediated metabolism represents about 10% of phase I drug metabolism in humans. For this review, four CYP2C9 substrates (ibuprofen, phenytoin, glimepiride and glipizide) were identified and are presented in Table V.
Phenytoin and ibuprofen are widely accepted CYP2C9 substrates (96-97). Phenytoin and ibuprofen clearance showed a trend towards higher (98) and significantly (99) higher clearance in obese patients, respectively. Non-significantly higher CYP2C9 activity in obese subjects was also seen for glimepiride and glipizide. Glimepiride is metabolized primarily by CYP2C9 to the active M1 hydroxy metabolite, the cyclohexyl hydroxymethyl derivative (100). Glimepiride clearance of the parent drug and of the CYP2C9-dependent metabolite M1 were not significantly different in obese versus non-obese type-2 diabetes patients. However, the cumulative urine excretion of M1 over 24 hours post dose was 30% ($p<0.05$) higher in obese versus non-obese subjects, while both groups received equal doses (101). For glipizide (a CYP2C9 substrate (102)), clearance was slightly higher, which was not statistically different in obese as compared with non-obese subjects, though the difference in body weight was rather limited (103).
In summary, these studies indicate slightly increased CYP2C9-mediated clearance in obese as compared with non-obese patients. Body weight-normalized clearance values show a slight decrease in CYP2C9-mediated clearance per kilogram of total body weight (table V).

CYP2C19

CYP2C19 biotransformation is involved in approximately 5% of all phase I drug metabolism. As for CYP2D6 and CYP2C9, the activity of this isoform may

Table IV *Cytochrome P450 (CYP) 1A2-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Caffeine (87)	n = 9 (children) age 6–10[d] y TBW >95th %BMI	n = 16 (children) age 6–10 y TBW <84th %BMI	11.5 mg PO	Metabolic ratio	n = 7 5.4 (2.1)	n = 13 6.7 (1.7)	NS	NA	(92)
Caffeine (87)	n = 6 TBW 122 (8.4) kg BMI 42.5 (3.2) kg/m²	n = 6[e] TBW 92.2 (4.2) kg BMI 32.0 (1.4) kg/m²	200 mg PO	CL	113.7 (63) mL/min	135.7 (83) mL/min	NS	0.93 vs 1.47 mL/min/kg	(89)
Caffeine (87)	n = 14 TBW 110.4 (19) kg BMI 38.5 (5.8) kg/m²	n = 14 TBW 66.9 (13) kg BMI 22.6 (1.7) kg/m²	200 mg PO	CL	88.4 (47) mL/min	82.6 (34) mL/min	NS	0.80 vs 1.23 mL/min/kg	(89)
Caffeine (87)	n = 3 TBW 110 (27.5) kg	n = 3 TBW 74.0 (7.8) kg	5.83 mg/kg LBW PO	CL	355 (119) mL/min	219 (45) mL/min	NS	3.23 vs 2.96 mL/min/kg	(90)
Caffeine (87)	n = 16 TBW 110 (8) kg	n = 23 TBW 64 (3) kg	162 mg PO	CL	135 (14) mL/min	112 (12) mL/min	NS	1.22 vs 1.75 mL/min/kg	(91)
Theophylline (88)	n = 16 (women) TBW 102.8 (21) kg BMI 38.6 (7.8) kg/m²	n = 16 (women)[e] TBW 6.2 (1.5) kg	250 mg IV	CL	55 (14) mL/min	48 (13) mL/min	$p < 0.05$	0.54 vs 0.50 mL/min/kg	(93)
Theophylline (88)	n = 62 TBW 115–155%[d] IBW	n = 133 TBW <115% IBW	Various protocols	CL	62.9 (33) mL/h/kg IBW	55.5 (28) mL/h/kg IBW	NS	NA	(94)
Theophylline (88)	n = 5 TBW >155% IBW	n = 133 TBW <115% IBW	Various protocols	CL	59.7 (21) mL/h/kg IBW	55.5 (28) mL/h/kg IBW	NS	NA	Jusko et al. 1979(94)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP1A2 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
e Same pts after weight loss.
BMI = body mass index; CL = clearance; IBW = ideal body weight; %IBW = percentage of IBW; IV = intravenously; LBW = lean body weight; NA = not available; NS = not significant; PO = orally; TBW = total body weight.

Table V *Comparison of cytochrome P450 (CYP) 2C9-mediated clearance between obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Glimepiride (100)	n=14 T2D, 130 (36) kg	n=14 T2D 72.0 (10) kg	8 mg p.o.	Normalized CL	2.1 (0.1) L/h/1.73 m2	2.1 (0.8) L/h/1.73 m2	NS	NA	(101)
			8 mg p.o.	Cumulative M1 in 24h urine	130%	100%	p=0.043	NA	
Glipizide (102)	n=12 95.5 (17) kg	n=8 80.8 (10) kg	5 mg p.o.	CL	2.3 (1.0) L/h	2.0 (1.0) L/h	NS	0.024 vs 0.025 L/h/kg	(103)
Ibuprofen (179)	n=11 114 (11) kg 38.6 (3.3) kg/m^2	n=11 61 (3) kg 20.7 (0.5) kg/m^2	600 mg p.o.	CL	83 (4) mL /min	59 (4) mL /min	p<0.005	0.73 vs 0.97 mL/min/kg	(99)
Phenytoin (180)	n=14 124 kg 178% IBW	n=10 67 kg 92% IBW	300 mg i.v.	CLmetabolic	59 (10) mL /min	39 (3) mL /min	NS	0.48 vs 0.58 mL/ min/kg	(98)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2C9 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
BMI = body mass index; CL = clearance; %IBW = percentage of ideal body weight; IV = intravenously; M1 = M1 metabolite of glimepiride, cyclohexyl hydroxymethyl derivative; NA = not available; NS = not significant; PO = orally; T2DM = type 2 diabetes mellitus; TBW = total body weight.

Table VI *Cytochrome P450 (CYP) 2C19-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Diazepam (105)	n=17 101.1 (68-197) kg	n=17 60.4 (49-80) kg	7.5-15 mg i.v.	CL	38.1 (20-80) mL /min	27.3 (20-51) mL /min	p<0.025	0.38 vs 0.45 mL/min/kg	(106)
Desmethyl-diazepam (105)	n=12 105 (77-197) kg	n=12 67 (51-91) kg	10.3 mg p.o.	CL	13.2 (7-18) mL /min	13.4 (6-22) mL /min	NS	0.13 vs 0.20 mL/min/kg	(107)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a CYP2C19 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
CL = clearance; IV = intravenously; NS = not significant; PO = orally; TBW = total body weight.

largely differ depending on genetic polymorphisms (104). Only one clinical study, which is presented in Table VI, investigated the pharmacokinetics of CYP2C19 probes, i.e. diazepam and methyl diazepam (104-105). Diazepam clearance was higher in the obese group, and no difference in desmethyl diazepam clearance in obese versus non-obese individuals was found (106-107). Body weight-normalized clearance values show a slight decrease in CYP2C19-mediated clearance for obese individuals (Table VI).

Other phase I metabolic enzymes

Xanthine oxidase

Besides CYP enzymatic pathways, there is a wide variety of other enzymes contributing to phase I metabolism of drugs. However, often no appropriate substrate for a particular enzyme has been identified (108). We have identified two studies in children, investigating the pharmacokinetics of the xanthine oxidase-metabolized compounds mercaptopurine and caffeine (Table VII).

Mercaptopurine undergoes extensive biotransformation by xanthine oxidase (109). In children mercaptopurine clearance values were found to be higher in overweight or obese children as compared with non-obese children. In addition, a significant correlation between drug exposure and fat body mass, expressed by the weight/height percentile, was demonstrated (110).

Xanthine oxidase also mediates the biotransformation of the caffeine metabolite 1-methylxantine into 1-methyluric acid, which can be measured in urine. The metabolic ratio for xanthine oxidase, measured using the metabolites in urine, was higher in obese children than in non-obese children between 6 and 10 years of age (92). Obese children also showed elevated interleukin-6, C-reactive protein, and leptin levels, whereas adiponectin levels were decreased as compared with the non-obese children (92). It was suggested that these pro-inflammatory cytokines and adipokines upregulate xanthine oxidase gene expression and activity. Another explanation for the increase in xanthine oxidase activity may be the increase in liver volume associated with obesity.

In conclusion, xanthine oxidase-mediated clearance was significantly increased in obese versus non-obese children in both studies. To our knowledge, no studies on xanthine oxidase in adults have been performed.

Miscellaneous phase I metabolism enzymes

In addition to typical substrates for phase I drug metabolic enzymes, there are many other drugs that undergo hepatic biotransformation by a combination of phase I and phase II enzymes. As a result, even when the exact share of each involved enzyme is known, it is difficult to predict into what extent drug clearance will be affected in obese adults and children. In

Table VII *Other phase I (xanthine oxidase [XO])-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)	
Caffeine (87)	n = 9 (children) age 6–10[c] y TBW >95th %BMI	n = 16 (children) age 6–10[c] y TBW <84th %BMI	11.5 mg PO	Metabolic ratio of XO	n = 8 0.7 (0.06)	n = 16 0.6 (0.05)	p < 0.001	NA	(92)
6-mercapto-purine (109)	n = 9 (children) Age 4–14[c] y TBW >75th %BMI	n = 9 (children) Age 5–11[c] y TBW <75th %BMI	Similar doses	CL	206.9 (85) L/h	93.4 (30) L/h	p < 0.001	NA	(110)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as an XO probe was confirmed.
b Unless otherwise specified, mean values (standard deviation or range).
c Values are expressed as range.
BMI = body mass index; %BMI = BMI percentile (used in children); CL = clearance; NA = not available; PO = orally; TBW = total body weight; XO = xanthine oxidase.

Table VIII we have summarized all studies in obese and non-obese patients that have investigated the pharmacokinetics of drugs in which multiple enzymes are involved. Here we will only discuss antipyrine, while for the outcomes of other drugs, we refer to Table VIII.
Antipyrine (phenazone) is widely used as a model drug in the assessment of hepatic oxidative capacity in humans, as more than 99% of a given dose is excreted into urine as metabolites. The major metabolic routes are N-demethylation to norphenazone (CYP2C8, -2C9, -2C18, -1A2), 4-hydroxylation (CYP3A4, -1A2, -2B6) and 3-methylhydroxylation (CYP1A2, -2C9), which together account for 50% – 80% of the dose (111). Two antipyrine studies reviewed here did not find significantly different clearance values between the obese and non-obese patient groups (106, 112).
The outcomes of the antipyrine studies are representative for the general conclusion from the studies in Table VIII. In summary, 8 out of 13 studies did not show significantly different clearance values in obese versus non-obese subjects. Of the 5 studies that did find a difference in clearance values, obese clearance values were either higher (doxorubicin, ethinyl-estradiol and bisoprolol (113-115)) or lower (amiodarone and doxorubicinol (116-117)) as compared with clearance values in the non-obese group. Per kilogram of body weight, all clearance values were lower in obese as compared with non-obese individuals. The limited influence of obesity on these particular clearance values may in part be explained by compensating mechanisms among the different enzymatic pathways involved. However, it should be noted that the differences in body weight between the obese and non-obese subjects in all of the studies in Table VIII are relatively small. As this is a mixed group of drugs, it is difficult to generalize the results.

Summary of phase I metabolism
In summary, phase I enzymatic processes showed higher, lower or similar activity in obese as compared with non-obese subjects, depending on the enzymatic pathway. CYP3A4 mediated clearance was consistently lower, while CYP2E1-mediated clearance showed higher activity among obese versus non-obese adults. For CYP2E1, it has been demonstrated that an increase of CYP2E1-mediated clearance is correlated with both total body weight and the degree of liver steatosis, supporting the concept that liver fibrosis and inflammation associated with the increase in body weight are the underlying cause of increased CYP2E1 enzyme activity.
Clearance mediated by phase I metabolizing enzymes (CYP1A2, CYP2C9, CYP2C19 and CYP2D6) showed trends of higher clearance values in obese versus non-obese subjects, although in the majority of studies, this was not statistically significant, and the number of studies was limited. In contrast, CYP1A2 activity in children was non-significantly lower in obese versus non-obese children. Xanthine oxidase activity was significantly higher in obese as compared with non-obese children. Overall, the differences in body weight between obese and non-obese individuals wasere relatively small, and few or no morbidly obese patients were included in these studies.

Phase II metabolism

Phase II metabolic processes include glucuronide-, N-acetyl-, methyl-, gluthatione- and sulfate- conjugation of substrates. Uridine diphosphate-glucuronosyltransferase (UGT) enzymes catalyze the conjugation of various endogenous substances and exogenous compounds, and are by far the most important phase II processes for metabolism of drugs (~50%) (40).

Uridine Diphosphate Glucuronosyltransferase (UGT)
The human UGT superfamily is comprised two families (UGT1 and UGT2) and three subfamilies (UGT1A, UGT2A, and UGT2B). Many of the individual UGT enzymes are expressed not only in the liver but also in extrahepatic tissues, (including the gastrointestinal tract, adipose tissue and kidneys), where the extent of glucuronidation can be substantial (118). As the liver is the main UGT enzyme organ, it is suggested that liver disease or increased organ size, often co-occurring with (morbid) obesity, is somehow correlated with UGT activity. The expression of specific UGT enzymes in visceral and subcutaneous adipose tissue may also provide an explanation for increased UGT in activity in obesity (119).
Here we will discuss studies of four drugs that primarily undergo UGT conjugation, i.e. paracetamol, garenoxacin, oxazepam and lorazepam. The studies are summarized in Table IX. In contrast to CYP isoforms, individual UGT enzymes responsible for specific drug biotransformation processes were mentioned in an additional column of Table IX .
Paracetamol is extensively metabolized by UGT enzymes (120-121). In both adult men and women, significantly higher clearance values were found in obese compared with non-obese individuals (79). Between adolescents with and without NAFLD, no difference in total body weight-normalized clearance was found, indicating higher absolute clearance values in obese adolescents (78). Furthermore, the ratio of paracetamol/paracetamol-glucuronide metabolite in urine was significantly increased in obese adolescents, indicating increased UGT metabolism.
In a population pharmacokinetic analysis of garenoxacin (a major UGT substrate (122)), it was found that clearance values increased with total body weight. In the final pharmacokinetic model, an obesity factor (>130%

Table VIII *A combination of phase I- and phase II-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Voriconazole (181)	CYP2C19, 3A4, 2C9	n = 8 TBW 133 (105–155) kg BMI 46.2 (38–54) kg/m²	n = 14 TBW 76.9 (7.1) kg BMI 23.7 (1.9) kg/m²	200 mg	CL/F	13.4 (8.5–21) L/h	20.0 (14–26) L/h	NS	0.10 vs 0.26 L/h/kg	(182)
		n = 8 TBW 133 (105–155) kg BMI 46.2 (38–54) kg/m²	n = 14 TBW 76.9 (7.1) kg BMI 23.7 (1.9) kg/m²	300 mg	CL/F	10.1 (6.8–44) L/h	8.4 (3.9–13) L/h	NS	0.08 vs 0.11 L/h/kg	(182)
Ethynil estradiol (183-185)	CYP3A4, 1A2; UGT1A1c, 2C19	n = 15 BMI 33.5 (range 31–36) kg/m²	n = 13 BMI 22.4 (range 21–24) kg/m²	30 µg PO	AUC_{24}	1077 (750–1550) pg • h/mL	1414 (1040–1920) pg • h/mL	p = 0.04	NA	(114)
					C_{min}	31.5 (21–47) pg/mL at 24 h	34.2 (24–50) pg/mL at 24 h	NS	NA	
Levonorgestrel (186-187)	CYP3A4; minor: CYP2E1, 2C19, 2C9	n = 15 BMI 33.5 (range 31–36) kg/m²	n = 13 BMI 22.4 (range 21–24) kg/m²	150 µg PO	AUC	85.8 (62–119) ng • mL/mL	79.9 (45–142) ng • mL/mL	NS	NA	(114)
					C_{min}	2.6 (1.5–4.5) ng/mL at 24 h	2.5 (1.5–4.0) ng/mL at 24 h	NS	NA	
Amiodarone (188)	CYP3A4, 2C8	Total n = 23 BMI (obese pts) 25–31.4 kg/m²	Total n = 23 BMI (non-obese pts) <25 kg/m²	2.34 (0.68) mg/kg/d	CL		Decrease of 22.3% when BMI >25	p < 0.005	NA	(116)
Ifosfamide (189)	CYP3A, 2B	n = 4 TBW 76.8 (70.0–86.0) kg	n = 12 TBW 64.2 (48–77) kg	1.5 g/m² IV	CL	76.0 (65–92) mL/min	72.2 (53–189) mL/min	NS	0.99 vs 1.14 L/h/kg	(190)
Antipyrine (111, 191)	CYP1A2, 2B6, 2C8, 2C9, 2C18, 3A4	n = 20 TBW 110.4 (19) kg BMI 38.5 (5.8) kg/m²	n = 11 TBW 62.7 (8.7) kg BMI 22.3 (1.7) kg/m²	1 g PO	CL	39.3 (12) L/h	34.5 (7.0) L/h	NS	0.36 vs 0.55 L/h/kg	(112)
Antipyrine (111, 191)	CYP1A2, 2B6, 2C8, 2C9, 2C18, 3A4	n = 6 TBW 122.2 (21) kg BMI 42.5 (7.8) kg/m²	n = 6[e] TBW 92.3 (9.1) kg BMI 32.1 (3.0) kg/m²	1 g PO	CL	41.1 (12) L/min	47.7 (17) L/min	NS	0.34 vs 0.52 L/min/kg	
Antipyrine (111, 191)	CYP1A2, 2B6, 2C8, 2C9, 2C18, 3A4	n = 23 TBW 100.3 (59–197) kg	n = 25 TBW 62.5 (49–81) kg	20 mg/kg; maximum 2.0 g IV	CL	38.0 (21–72) mL/min	47.6 (18–103) mL/min	NS	0.38 vs 0.76 mL/min/kg	(106)
Bisoprolol (192)	CYP3A4, 2D6	n = 8 (women) TBW 91 (17) kg	n = 8 (women) TBW 51 (4) kg	Similar doses IV	CL	14.8 (1.4) L/h	12.8 (2.2) L/h	p < 0.05	0.163 vs 0.251 L/h/kg	(113)
Quinine (193)	CYP3A4, 2D6	n = 9 (Thai pts) TBW 96 (16) kg	n = 8 (Thai pts) TBW 57 (5) kg	600 mg PO	CL	85 (18) L/h	98 (33) L/h	NS	0.89 vs 1.72 L/h/kg	(194)
Glyburide (195)	CYP3A4, 2C9	n = 12 TBW 100.0 (23) kg BMI 36.0 (9.1) kg/m²	n = 8 TBW 73.3 (7.2) kg BMI 24.5 (2.0) kg/m²	20 mg daily dose PO	CL	3.26 (2.2) L/h	3.10 (2.0) L/h	NS	0.03 vs 0.04 L/h/kg	(196)

Table VIII *A combination of phase I- and phase II-mediated clearance in both obese and non-obese patients (pts) (continued).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Doxorubicin (197)	Various, including CYP3A4	n = 22 BMI >30 kg/m²	n = 77 BMI <30 kg/m²	40–75 mg/m² IV	CL	BMI 30–35 kg/m² (15 pts): 65.7 (17) L/h BMI >35 kg/m² (7 pts): 78.9 (27) L/h	63.6 (20) L/h	p = 0.045	NA	R(115)
Doxorubicin (197)	Various, including CYP3A4	n = 6 (children) age 1–21[d] y TBW 61.4 kg BMI >30% body fat	n = 16 (children) age 1–21[d] y TBW 39.6 kg BMI <30% body fat	Based on BSA	Doxorubicin CL	24.6 (2.5) L/h/m²	26.0 (6.0) L/h/m²	NS	NA	(117)
					Doxorubicinol CL	37.2 (15) L/h/m²	64.8 (35) L/h/m²	p = 0.033	NA	(117)

a The references mentioned with the substrate (first column) refer to literature in which the metabolic enzymes involved in the clearance of the drug are proposed.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
e Same pts after weight loss.
AUC = area under the concentration-time curve; AUC24 = AUC from 0 to 24 h; BSA = body surface area; CL = clearance; CL/F = oral clearance; Cmin = minimum concentration; CYP = cytochrome P450; IV = intravenously; M1 = M1 metabolite of glimepiride, cyclohexyl hydroxymethyl derivative; NA = not available; NS = not significant; PO = orally; T2D = type 2 diabetes; UGT = uridine diphosphate glucuronosyltransferase.

ideal body weight) used as a covariate for clearance significantly improved the model (123).

For both oxazepam and lorazepam, it was found that clearance values were significantly higher in obese as compared with non-obese control subjects (124). A determinant role of UGT in the metabolism of both compounds has been shown in the literature (120, 125). On the basis of the differences in oxazepam and lorazepam clearance values, the authors concluded that obesity is associated with an increased conjugating capacity and that this increase is in proportion to total body weight. It should be noted that many subjects in this study received more than one study drug, which may limit the interpretation of these results.

In conclusion, all studies show a significantly increased clearance in obese as compared with non-obese subjects. As a consequence, body weight-normalized clearance values were equal or only slightly lower for obese as compared with non-obese individuals, except for oxazepam clearance, which showed a significant increase in body weight-normalized clearance.

Other metabolic phase II routes

Apart from UGT, the pharmacokinetics of N-acetyltransferase (~5% of phase II drug metabolism) and glutathione S-transferase-metabolized drugs have been investigated in obese versus non-obese subjects. Caffeine, procainamide and busulfan have been indicated as substrates, as presented in Table X.

N-acetyltransferase is responsible for the N-acetylation of procainamide (126). Procainamide plasma clearance was slightly higher in obese as compared with non-obese adults, although this was non-significant (127). In obese children, a 5-fold increase in the metabolic ratio of the N-acetyltransferase pathway of caffeine was observed when compared with non-obese children (92), when only considering the slow-acetylator genotype.

For busulfan, both obese (BMI between 27 and 35 kg/m²) and severely obese patients (BMI > 35 kg/m²) showed significantly higher oral clearance values as compared with non-obese patients (128). Per kilogram of body weight, clearance was significantly lower in obese versus non-obese patients. This was confirmed in a more recent trial with busulfan in obese and non-obese adults (129). While CYP3A4 involvement is suggested (130), the glutathione S-transferase A1-1 isoform is the major and possibly determinant pathway of busulfan metabolism (131). In obese children (aged 0 – 21 years) busulfan clearance per kilogram of body weight after a test dose and a regular dose was lower than in non-obese children (132).

In conclusion, other type phase II-metabolized substrates show higher absolute clearance values in obese as compared with non-obese adults and

Table IX *Uridine diphosphate glucuronosyltransferase (UGT)-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 12 (NAFLD children) age 10–17[d] y BMI 34.0 (6.1) kg/m²	n = 12 (children) age 10–17[d] y BMI 26.2 (11) kg/m²	5 mg/kg up to 325 mg	Metabolite/parent drug ratio	Increased in obese pts		p = 0.028	NA	(78)
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 12 (NAFLD children) BMI 34.0 (6.1) kg/m²	n = 12 (children) BMI 26.2 (11) kg/m²	5 mg/kg up to 325 mg	CL				0.31 vs 0.31 L/kg/h (NS)	
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 7 (men) TBW 135 kg	n = 10 (men) TBW 71 kg	650 mg IV over 5 min	CL	484 mL/min	323 mL/min	p < 0.05	3.59 vs 4.55 mL/min/kg	(79)
Paracetamol (121)	UGT 1A9, 1A6, 2B15	n = 14 (women) TBW 88 kg	n = 11 (women) TBW 55 kg	650 mg IV over 5 min	CL	312 mL/min	227 mL/min	p < 0.05	3.55 vs 4.13 mL/min/kg	
Garenoxacin (122)	Sulfate conjugation of UGT	n = 196 TBW >130% IBW	n = 384 TBW <130% IBW	Various protocols	CL	Obesity (>130% IBW) was a covariate on CL		p < 0.00001	NA	(123)
Oxazepam (120)	UGT 1A9, 2B7, 2B15	n = 11 TBW 115 (13) kg	n = 11 TBW 60 (2.6) kg	30 mg PO	CL	156.8 (23) mL/min	50.4 (6.0) mL/min	p < 0.001	1.39 vs 0.82 mL/min/kg (p < 0.005)	(124)
Lorazepam (125)	Various, including UGT 2B15	n = 14 TBW 111.7 (10) kg	n = 14 TBW 62.8 (2.2) kg	2 mg IV	CL	102 (10) mL/min	62.9 (5.4) mL/min	p < 0.005	0.98 vs 1.00 mL/min/kg	(124)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as an UGT probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
BMI = body mass index; BSA = body surface area; CL = clearance; Cmin = minimum concentration; %IBW = percentage of ideal body weight; IV = intravenously; NA = not available; NAFLD = non-alcoholic fatty liver disease; NS = not significant; PO = orally; TBW = total body weight.

children, while weight-normalized clearance values were lower in obese as compared with non-obese patients.

Summary of phase II metabolism
For glucuronidation processes, all studies in Table IX show a significant increase in UGT biotransformation in obese as compared with non-obese subjects. Weight-normalized UGT clearance values were equal to or only slightly lower in obese as compared with non-obese patients. However, the number of studies with UGT-metabolized drugs is small. The underlying mechanism of this phenomenon remains unsolved, although NAFLD was demonstrated to be associated with higher paracetamol clearance values in adolescents (78).
N-Acetylation catalyzed by N-acetyltransferase shows a significant increase in obese children and a non-significant increase in adults. Glutathione transferase of busulfan in obese children and adults was lower in non-obese adults and children when normalized for body weight.

Liver blood flow

High-extraction-ratio drugs are rapidly metabolized and therefore sensitive to changes in liver blood flow, but are relatively insensitive to changes in enzyme activity and are thus a potential marker of liver blood flow. The influence of obesity on liver blood flow is not fully specified. NASH increases fat deposition in the liver, causing sinusoidal narrowing and altered functional morphology of the liver (133). In contrast, because of increased blood volume and cardiac output, liver blood flow is not necessarily reduced in obese subjects (19).
In Table XI, studies of eight high extraction ratio drugs in obese and non-obese subjects are summarized and include propofol, propanolol, labetalol, verapamil, lidocaine, fentanyl, sufentanil and paclitaxel.
Propofol is extensively metabolized by various UGT enzymes (118) and its clearance is limited by liver blood flow (134). Van Kralingen et al. (135) and Cortinez et al. (136) studied propofol pharmacokinetics in a wide range of body weights and found that total body weight as a covariate for clearance significantly improved the predictive performance of the population pharmacokinetic model.
Four different studies reported propranolol clearance values in obese versus non-obese patients. Three studies did not show altered clearance values between obese and non-obese patients (137-139), and one study found significantly lower propranolol clearance values in obese versus non-obese

patients (140). Propranolol clearance is strongly determined by liver blood flow as it approaches liver blood flow values (141). On the other hand, propranolol tends to decrease liver blood flow by ~20-30% by blocking the beta-adrenoreceptor, explaining the relative lower clearance value seen for propranolol compared with other drugs in Table XI (141).
Labetalol clearance in obese patients showed a trend towards being increased (138). For verapamil and lidocaine no difference in clearance between obese and non-obese was found (142-143). As lidocaine clearance is determined mainly by liver blood flow (144), the authors concluded that extreme total body weights did not change liver blood flow.
Sufentanil and fentanyl are predominantly metabolized by CYP3A4 (145), but their total clearance is mainly determined by liver blood flow (146-147). Sufentanil showed higher clearance values in obese versus non-obese patients: however, this difference was not statistically significant (148). The difference in body weight between the two groups studied was small (90 versus 74 kg). The pharmacokinetics of fentanyl were studied in a population with a wide range of total body weights, showing a non-linear positive correlation between total body weight and fentanyl clearance (149). Reported paclitaxel clearance values in obese and non-obese patients are extremely high (291 – 431 L/h), indicating liver blood flow-dependent clearance (150). Clearance values for paclitaxel in obese patients were higher than values of non-obese patients: however, this was not statistically significant (59).
In conclusion, only a few high-extraction-ratio drug studies in Table XI showed altered clearance values in obese versus non-obese adults. Body weight-normalized clearance values show a large decrease in clearance per kilogram. For instance, the clearance per kilogram values of propranolol and lidocaine are almost halved. A straightforward conclusion from these studies is complicated because of the heterogeneity of the drugs. Liver blood flow is about 2–2.5 L/min, while clearance values of some drugs listed in Table XI are less than 1 L/min, obscuring the justification of their role as a model drug for liver blood flow. When considering drugs with clearance values of more than 1.5 L/min (propofol, sufentanil and paclitaxel), all studies show higher clearances in obese patients. Propanolol was excluded from this comparison, as this drug shows high variability in drug clearance values among studies (Table XI). The observation of increased clearance is not statistically significant for sufentanil and paclitaxel, probably because of the small difference in total body weight in these studies. Unfortunately, the data from these studies did not allow comparison of weight-normalized clearance values.

Table X *Other phase II-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Metabolic enzymes	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
					Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Caffeine (87)	NAT2	n = 9 (children) age 6–10[d] y TBW >95% BMI	n = 16 (children) age 6–10[d] y TBW <84% BMI	11.5 mg PO	Metabolic ratio of NAT2	n = 6 1.01 (0.3)	n = 14 0.18 (0.1)	p < 0.01	NA	(92)
Procain-amide (92, 126, 178)	NAT2	n = 7 TBW 100.2 (17.3) kg	n = 7 TBW 68.4 (11.5) kg	300 mg IV	CL_{plasma}	51.7 (9.2) L/h	41.9 (14) L/h	p = 0.085	0.52 vs 0.61 L/h/kg	(127)
Busulfan (131)	GSTA1	n = 22 (children) age 0–21[d] y TBW >85% BMI	n = 29 (children) age 0–21[d] y TBW 25–85% BMI	Test dose 0.8 mg/kg IV	CL				3.2 vs 3.8 mL/min/kg (p = 0.1)	(132)
Busulfan (131)	GSTA1	n = 22 (children) age 0–21[d] y TBW >85% BMI	n = 29 (children) age 0–21[d] y TBW 25–85% BMI	2.9 vs 4.0 mg/kg IV	CL				3.1 vs 3.8 mL/min/kg (p = 0.03)	(132)
Busulfan (131)	GSTA1	n = 39 BMI 27–35 kg/m²	n = 71 BMI 18–26.9[d] kg/m²	0.8 mg/kg IBW, TBW or AIBW IV	CL				2.33 vs 2.63 mL/min/kg (p < 0.05)	(129)
Busulfan (131)	GSTA1	n = 11 BMI >35 kg/m²	n = 71 BMI 18–26.9[d] kg/m²	0.8 mg/kg IBW, TBW or AIBW IV	CL				1.88 vs 2.63 mL/min/kg (p < 0.05)	(129)
Busulfan (131)	GSTA1	n = 89 BMI 27–35[d] kg/m²	n = 173 BMI 18–27[d] kg/m²	0.4–1.8 mg/kg PO	CL/F	223 (53) mL/min	190 (45) mL/min	p < 0.001	2.56 vs 2.90 mL/min/kg (p < 0.01)	(128)
Busulfan (131)	GSTA1	n = 10 BMI >35 kg/m²	n = 173 BMI 18–27[d] kg/m²	0.4–1.8 mg/kg PO	CL/F	250 (47) mL/min	190 (45) mL/min	p = 0.001	2.30 vs 2.90 mL/min/kg (p < 0.01)	(128)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a NAT2 or GSTA1 probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
AIBW = adjusted ideal body weight; BMI = body mass index; %BMI = BMI percentile (used in children); CL = clearance; CL/F = oral clearance; GSTA1 = glutathione S-transferase A1; IBW = ideal body weight; IV = intravenously; NA = not available; NAFLD = non-alcoholic liver fatty disease; NAT2 = arylamine N-acetyltransferase type 2; PO = orally; TBW = total body weight.

Table XI *Liver blood flow-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Propofol (134)	n = 20 BMI 43 (6) kg/m² TBW 124 (20) kg	n = 44 BMI 25 (4) kg/m² TBW 74 (11) kg	Continuous infusion	CL	Individual clearance (L/min)= 2.22 • (70/TBW)$^{0.71}$	At 70 kg: 2.22 L/min	$p < 0.005$	NA	(135)
Propofol (134)	n = 27 TBW 82–169[d] kg	n = 24 TBW 44–122[d] kg	Continuous infusion	CL	Individual clearance (L/min)= 2.25 • (70/TBW)$^{0.75}$	At 70 kg: 2.25 L/min	$p < 0.01$	NA	(136)
Paclitaxel (198)	n = 14 BMI >30 kg/m²	n = 38 BMI <30 kg/m²	50–225 mg/m²	CL	383 (340–431) L/h	318 (291–347) L/h	NS	NA	(59)
Sufentanil (145-146)	n = 8 TBW 94.1 (14) kg	n = 8 TBW 70.1 (13) kg	4 µg/kg TBW IV	CL	1.99 (0.9) L/min	1.78 (0.5) L/min	NS	0.02 vs 0.03 L/min/kg	(148)
Propranolol (199)	n = 9 (normolipidaemic pts) BMI 35.6 (1.2) kg/m²	n = 18 BMI 24.0 (0.6) kg/m²	80 mg PO	CL/F	66.2 (22) L/h	73.1 (16) L/h	NS	NA	(137)
Propranolol (199)	n = 16 (hyperlipidaemic pts) BMI 35.6 (1.5) kg/m²	n = 18 BMI 24.0 (0.6) kg/m²	80 mg PO	CL/F	63.4 (21) L/h	73.1 (16) L/h	NS	NA	(137)
Propranolol (199)	n = 9 BMI 34.6 (5.6) kg/m² TBW 99 kg	n = 9 BMI 21.4 (2.6) kg/m² TBW 60 kg	0.108 mg/kg IBW	CL	46.2 (10.5) L/h	41.6 (6.8) L/h	NS	0.47 vs 0.69 L/h/kg	(138)
Propranolol (199)	n = 12 TBW 110.3 (20.4) kg	n = 12 TBW 66.7 (6.8) kg	8 mg IV	CL	57.5 (18) L/h	75.9 (15) L/h	$p < 0.01$	0.52 vs 1.14 L/h/kg	(140)
Propranolol (199)	n = 6 TBW 136.5 (36) kg	n = 6 TBW 66.8 (11) kg	10 mg IV	CL	780 (20) mL/min	780 (10) mL/min	NS	5.73 vs 11.67 mL/min/kg	(139)
Propranolol (199)	n = 6 TBW 136.5 (36) kg	n = 6 TBW 66.8 (11) kg	40 mg PO	CL	2.4 (0.2) L/min	2.8 (0.2) L/min	NS	0.02 vs 0.04 L/min/kg	(139)
Labetalol (200)	n = 9 TBW 99 (23) kg BMI 34.6 (5.6) kg/m²	n = 9 TBW 60 (11) kg BMI 21.4 (2.6) kg/m²	Mean 60.7–61.9 mg ($p > 0.05$)	CL	89.9 (11) L/h	81.5 (15) L/h	NS	0.91 vs 1.36 L/h/kg	(138)
Verapamil (201-202)	n = 12 (hypertensive pts) TBW 127 (8) kg	n = 11 (hypertensive pts) TBW 74 (4) kg	0.15 mg/kg; maximum 25 mg IV	CL	1.34 (0.2) L/min	1.25 (0.1) L/min	NS	0.01 vs 0.02 L/h/kg	(142)
Lidocaine (203)	n = 14 (men) TBW 124 (8) kg	n = 19 (men) TBW 69 (1) kg	25 mg IV	CL	1427 (120) mL/min	1346 (86) mL/min	NS	11.51 vs 19.51 mL/min/kg	(143)
Lidocaine (203)	n = 11 (women) TBW 96 (6) kg	n = 12 (women) TBW 59 (2) kg	25 mg IV	CL	1089 (83) mL/min	1162 (84) mL/min	NS	11.34 vs 19.69 mL/min/kg	(143)
Fentanyl (145, 204)	n = 10 TBW 117.3 (33) kg	n = 16 TBW 68.5 (9.5) kg	Bolus and infusion rate based on kg TBW	CL	986 (155) mL/min	718 (163) mL/min	$p < 0.001$	8.76 vs 10.48 mL/min/kg ($p < 0.025$)	(149)

a The references mentioned with the substrate (first column) refer to literature in which the drug is mentioned as a high-extraction-ratio drug.
b Unless otherwise specified, mean values (standard deviation or range).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
BMI = body mass index; CL = clearance; CL/F = oral clearance; IBW = ideal body weight; IV = intravenously; NA = not available; NS = not significant; PO = orally; TBW = total body weight.

Summary of liver blood flow
According to the results of propofol, sufentanil and paclitaxel studies, liver blood flow is likely to be increased in obese patients. However, only a few (very) high-extraction-ratio drugs have been studied and the difference in body weights between patients groups was limited for sufentanil and paclitaxel. To our knowledge, no studies have investigated the pharmacokinetics of high-extraction-ratio drugs in children.

Renal elimination

The kidneys are the primary organs involved in the elimination of drugs. The processes involved in drug elimination through the kidneys include glomerular filtration, tubular secretion and tubular reabsorption. The exact effect of obesity on these functions is not clear (25). Renal function seems to be affected as obese patients showed a 62% increase in the mean estimated glomerular filtration rate (eGFR) (151). This finding was observed, irrespective of the presence of hypertension by an increase of renal blood flow (152). Obesity is related to a state of glomerular hyperfiltration, which resembles that seen in early-stage diabetic nephropathy and sickle cell disease (20-21, 153). It has been argued that overweight may ultimately lead to end-stage renal disease because focal glomerular sclerosis and/or diabetic nephropathy have been observed in a small study in 17 morbidly obese patients who presented with proteinuria (154). In obese children it was found that the glomerular filtration rate increases with BMI (155). In contrast to obese adults, obese children showed a higher degree of albuminuria, a marker for glomerular dysfunction (156-157). Therefore, it was concluded that albuminuria indicates early renal glomerular dysfunction as a consequence of childhood obesity (156). However, obese children compared with non-obese children did not differ in their glomerular filtration rates as no overt changes in eGFR were detected (157).
The influence of obesity on renal tubular secretion and renal tubular reabsorption is not well known, and no objective clinical measure of these drug clearance pathways presently exists (151). Tubular dysfunction can be defined as the presence of at least two of the following criteria: nondiabetic glycosuria, urine phosphate wasting, hyperaminoaciduria, beta-2-microglobulinuria, and increased fractional excretion of uric acid (158-159). For obese children, an increased degree of beta-2-microglobulinuria, suggesting increased tubular dysfunction, has been described (156).
In this section, we will provide an overview of clinical studies investigating drugs that are primarily eliminated renally and were studied in both non-obese and obese adults and children.

Glomerular filtration

In Table XII, an overview of studies comparing clearance of drugs that are mainly excreted by glomerular filtration in obese and non-obese individuals is presented. These drugs include vancomycin, daptomycin, carboplatin, low-molecular-weight heparins and cimetidine.
Vancomycin clearance in morbidly obese patients is reported to increase with total body weight compared with non-obese patients (160). No significant increase of daptomycin clearance was described in obese patients with a mean total body weight of 114 kg (161). However, in patients with a higher mean total body weight (126 kg), significantly higher daptomycin clearance was reported (162). Carboplatin is mainly eliminated by glomerular filtration and partly by tubular secretion (163). Both a linear increase of carboplatin clearance with total body weight (164) and ideal body weight (165) have been described. A comparison of carboplatin clearance values between obese and non-obese patients showed no significant difference (59). The low-molecular-weight heparins enoxaparin, tinzaparin and dalteparin show higher total drug clearance in obese patients compared with non-obese patients (166-168). Studies on the influence of obesity on drug clearance mediated by glomerular filtration in obese children are very limited. In obese children, lower anti-Xa levels after the same dose of enoxaparin were reported, suggesting higher enoxaparin clearance in obese children (166). In contrast to these studies, total metabolic clearance of cimetidine was not altered in obese patients compared with non-obese patients (167).
In conclusion, the majority of these studies show higher clearance values with increasing body weights, indicating increased glomerular filtration in obese patients. Weight-normalized clearance values did not show a consistent trend for the influence of overweight on glomerular filtration, as normalized clearance values were either equal or lower in obese as compared with normal-weight patients.

Tubular secretion

Drugs that are (partly) eliminated by tubular secretion and have been investigated in obese patients are summarized in Table XIII and include procainamide, ciprofloxacin, cisplatin, topotecan and digoxin.

Table XII *Glomerular filtration-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Vancomycin (205)	n = 24 TBW 165 (46) kg	n = 24 TBW 68 (6) kg	TDM guided	CL	197 (77) mL/min	77 (22) mL/min	$p < 0.001$	1.19 vs 1.13 mL/min/kg	(160)
Daptomycin (206)	n = 7 TBW 114 (16) kg	n = 7 TBW 59 (6) kg	4 mg/kg based on TBW	CL	0.82 (0.21) L/h	0.73 (0.14) L/h	$p = 0.34$	0.43 vs 0.74 L/min/kg	(161)
Daptomycin (206)	n = 7 (obese pts) TBW 86 (9) kg	n = 12 TBW 64 (7) kg	4 mg/kg based on TBW	CL	0.86 (CV8%) L/h	0.72 (CV 6%) L/h	$p = 0.008$	10.07 vs 11.89 mL/h/kg	(162)
	n = 6 (morbidly obese pts) TBW 126 (17) kg				1.01 (CV 29%) L/h	0.70 (CV 34%) L/h	$p = 0.003$	7.82 vs 10.19 mL/h/kg	
Carboplatin (163)	n = 15 BMI >30 kg/m²	n = 218 BMI <30 kg/m²	Protocol based	CL	Related to adjusted IBW		No dose adjustment needed in obese pts	NA	(165)
Carboplatin (163)	n = 14 BMI >30 kg/m²	n = 64 BMI <30 kg/m²	Based on renal function	CL	6.48 L/h	5.88 L/h	$p = 0.37$	NA	(59)
Carboplatin (163)	n = 43 BMI >30 kg/m²	n = 285 BMI >18.5 kg/m² and <30 kg/m²	Based on renal function	CL	Increased with TBW		No dose adjustment needed in obese pts	NA	(164)
Enoxaparin (207)	n = 118 TBW 43–120[d] kg		1.0–1.5 mg/kg bid	CL	$CL = 0.3 \bullet CL_{CR}/70 + 0.42 \bullet LBW/55$ (kg)		$p < 0.001$	NA	(208)
Dalteparin (207)	n = 10 TBW 106 (22) kg	n = 10 TBW 70 (9) kg	Protocol based	CL	1.30 L/h	1.11 L/h	NS	0.74 vs 0.95 L/min/kg	(209)
Tinzaparin (207)	n = 425 TBW 37–151[d] kg		175 IU/kg od	CL	22% decrease in CL in L/h/kg in obese pts (BMI >30 kg/m²)			NA	(210)
Cimetidine (211)	n = 13 TBW 113 (9) kg	n = 16 TBW 64 (2) kg	200–300 mg IV	CL	616 (34) mL/min	579 (39) mL/min	NS	5.45 vs 9.05 mL/min/kg	(167)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a GFR probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Values are expressed as range.
bid = twice daily; BMI = body mass index; CL = clearance; CL_{CR} = creatinine clearance; CV%= coefficient of variation; GFR = glomerular filtration rate; IBW = ideal body weight; IV = intravenously; LBW = lean body weight; NA = not available; NS = not significant; od = once daily; TBW = total body weight; TDM = therapeutic drug monitoring.

Approximately 50% of administered procainamide is eliminated as unchanged drug by glomerular filtration and active tubular secretion (168). Renal procainamide clearance was shown to be higher in obese patients because of elevated tubular secretion, as no significant difference in 24-hour creatinine clearance was observed between obese and non-obese patients (127). Significantly higher clearance values were also reported for cisplatin and ciprofloxacin, which are eliminated by tubular secretion (59, 169-171). For both topotecan and digoxin, there was a trend towards higher drug clearance in obese patients, which is assumed to result from increased tubular secretion (59, 172). For tubular secretion, normalized clearance values per kilogram were equal or slightly lower in obese as compared with non-obese patients.
In conclusion, these studies indicate higher tubular secretion in obese as compared with non-obese individuals. To date, no information is available on the impact of obesity on the tubular secretion of drugs in children.

Tubular reabsorption

Studies on the influence of obesity on the tubular reabsorption of drugs are scarce (Table XIV). Tubular reuptake of lithium in obese patients was reported to be lower, as lithium clearance was significantly increased in obese patients and glomerular filtration did not differ between these obese and non-obese patients (173). In contrast, proximal tubular reabsorption of sodium in obese patients is reported to be increased because of glomerular hyperfiltration (174).

Summary of renal elimination
The reviewed studies show that clearance of renally eliminated drug is higher in obese patients because of increased glomerular filtration and tubular secretion. The influence of obesity on the tubular reabsorption is unknown, as there is a lack of evidence on this topic.

Discussion and conclusions

In this review, we have summarized the effects of obesity on drug metabolism and elimination. Studies that investigated pharmacokinetics of drugs in both obese and non-obese individuals were classified according to the drug's most important metabolic or elimination pathway. This allowed us to structurally review the influence of obesity on each individual metabolic or elimination pathway. Metabolic processes were subdivided into phase I metabolism, phase II metabolism and liver blood flow-dependent metabolism. Renal elimination was subdivided into glomerular filtration and tubular processes.
The reviewed studies show that the impact of obesity on drug metabolism and elimination differs greatly, depending on the metabolic or elimination pathway primarily involved in the handling of the investigated drug. In particular, CYP3A4-mediated drug elimination was found to be consistently lower, while UGT-, CYP2E1-, arylamine N-acetyltransferase type 2- and xanthine oxidase-mediated drug metabolism was consistently higher among obese as compared with non-obese subjects. Clearance mediated by phase I metabolizing enzymes CYP1A2, CYP2C9, CYP2C19 and CYP2D6 show trends towards higher clearance values in obese individuals.
Studies on drug clearance mediated by liver blood flow are somewhat inconclusive, although, on the basis of a few highly extracted drugs, an increase in liver blood flow can be noted in obese patients.
Regarding drug elimination, the reviewed studies show an increase of glomerular filtration and tubular secretion in obese patients. The influence of obesity on tubular reabsorption is unknown.
Many of the observed trends were also reflected in weight-normalized clearance values, which were halved (e.g. CYP3A4), almost equal (e.g. CYP2E1) or slightly decreased in obese as compared with non-obese individuals (e.g. CYP2C9 and tubular secretion). For other drug clearance pathways, trends in body weight-normalized clearance were not as pronounced (e.g. the glomerular filtration rate and CYP1A2). It should be emphasized that these body weight-normalized clearance values may provide information on quantitative differences in clearance values but do not explain the relationship between total body weight and drug clearance values.
The large number of studies included in this review shows that there is a substantial amount of information available on the impact of obesity on drug metabolism and elimination. However, in many of these studies, the difference in body weight between obese and non-obese subjects is rather small. More specifically, the obese subjects included in the reviewed studies are not as obese as the patients currently seeking medical care. From this perspective, information on drug metabolism and elimination in morbidly obese patients (BMI >40 kg/m^2) and super-obese patients (BMI >50 kg/m^2) is largely lacking and requires future research.
Regarding obesity in children, only five studies investigated pharmacokinetics of a drug in obese versus non-obese children, of which four were recently published (78, 92, 117, 132). Regarding renal elimination, no pharmacokinetic studies of obese versus non-obese children were found. Extrapolation of

Table XIII *Tubular secretion-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Procainamide (168)	n = 7 TBW 100 (17) kg	n = 7 TBW 68 (12) kg	300 mg IV	CL	4.19 (1.13) mL/min[d]	2.68 (0.85) mL/min[d]	0.05 > p > 0.02	0.04 vs 0.04 mL/min/kg	(127)
Ciprofloxacin (169)	n = 17 TBW 111 (20) kg	n = 11 TBW 72 (10) kg	400 mg IV	CL	638 mL/min	495 mL/min	p < 0.05	5.74 vs 6.88 mL/min/kg	(170)
Cisplatin (171)	n = 23 BMI <30 kg/m^2	n = 165 BMI <30 kg/m^2	50–100 mg/m^2	CL	60 L/h	53.3 L/h	p = 0.007	NA	(59)
Topotecan (212)	n = 21 BMI >30 kg/m^2	n = 108 BMI <30 kg/m^2	Protocol based	CL	21.7 L/h	19.6 L/h	p = 0.50	NA	(59)
Digoxin (213)	n = 13 TBW 100 kg	n = 16 TBW 65 kg	0.75 mg IV	CL	328 mL/min	278 mL/min	T-value 1.59 (NS)	3.28 vs 4.28 mL/min/kg	(172)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a tubular secretion probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
d Corrected for CLcr.
BMI = body mass index; CL = clearance; CLCR = creatinine clearance; IV = intravenously; NA = not available; NS = not significant; TBW = total body weight.

Table XIV *Tubular reabsorption-mediated clearance in both obese and non-obese patients (pts).*

Substrate (reference)[a]	Obese pts[b]	Non-obese pts[b]	Dose	Clearance					Reference
				Parameter	Obese pts[b]	Non-obese pts[b]	Significance	Weight normalized clearance (obese vs non-obese pts)[b,c]	
Lithium (214)	n = 10 TBW 110 (29) kg	n = 8 TBW 63 (7) kg	31.4 mEq	CL	33.9 (7.0) mL/min	23.0 (6.2) mL/min	p = 0.005	0.31 vs 0.37 mL/min/kg	(173)

a The references mentioned with the substrate (first column) refer to literature in which the appropriateness of the particular drug as a tubular reabsorption probe was confirmed.
b Unless otherwise specified, mean values (standard deviation).
c See section Approach for calculation of weight-normalized clearance values.
CL = clearance; mEq = milliequivalents; TBW = total body weight.

results from studies in obese adults to obese children is widely applied because often no clinical studies in obese children are available (24, 175). For the UGT mediated metabolism of paracetamol this may be justified, as paracetamol clearance in both adolescents (78) and adults (79) was increased. This strong similarity in results was not seen for other drugs that were studied in both adults and children such as caffeine (92). Moreover, the expression and activity of enzymatic pathways in children may be different compared with adults and are dependent on maturational status (age). In addition, obesity may influence the maturation process(es) itself, and the starting point of weight gain may also influence the maturation process(es), representing additional factors of variability in drug metabolism and elimination among obese adults and children. Taking this into consideration, extrapolation from adult observations may give false predictions of clearance values in children (and vice versa) and should be performed with care.

While it is impossible to study and assess the pharmacokinetics of every drug in obese subjects, future clinical trials should aim to quantify the impact of obesity on specific drug elimination pathways and on the underlying associated mechanisms (e.g. steatosis and inflammation). In this approach, study outcomes can be extrapolated to other drugs eliminated by the same pathway. This extrapolation can be achieved by using model drugs and within the context of a multidisciplinary research team including physicians, pharmacists, pharmacologists and pharmacometricians. Primarily, future research in this area should focus on individual metabolic and elimination pathways in adults and children that show increasing or decreasing trends in activity among obese versus non-obese individuals. As concluded from this review, these pathways include CYP3A4, CYP2E1, xanthine oxidase, UGT, N-acetyltransferase, glomerular filtration and tubular processes. Mainly, CYP3A4 deserves immediate research attention. Finally, particularly obese children and adolescents, and morbidly obese (BMI >40 kg/m^2) and super-obese patients (BMI >50 kg/m^2) should be included in these studies.

In conclusion, this systematic review of pharmacokinetic studies in obese and non-obese patients shows that the impact of obesity on drug metabolism and elimination greatly differs per drug metabolic or elimination pathway. However, the clinical trials reviewed here often only included overweight to moderately obese patients. As the prevalence of obesity and total body weights of both children and adults are still increasing and this trend will persist, future studies assessing the impact of morbid obesity on specific drug elimination pathways in both children and adults are warranted.

References

1. Centers for Disease Control and Prevention. 2009 [cited 2011 3 may 2011]; Available from: http://www.cdc.gov/obesity/data/trends.html.
2. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2008. Jama. Jan 20;303(3):235-41.
3. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 2006 Apr 5;295(13):1549-55.
4. IASO. International Association for the Study of Obesity.
5. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007-2008. Jama. 2010 Jan 20;303(3):242-9.
6. Jia WP, Wang C, Jiang S, et al. Characteristics of obesity and its related disorders in China. Biomed Environ Sci. 2010 Feb;23(1):4-11.
7. Kelly T, Yang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond). 2008 Sep;32(9):1431-7.
8. Cheymol G. Clinical pharmacokinetics of drugs in obesity. An update. Clin Pharmacokinet. 1993 Aug;25(2):103-14.
9. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. Clin Pharmacokinet. 2000 Sep;39(3):215-31.
10. Alexander JK, Dennis EW, Smith WG, et al. Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. Cardiovasc Res Cent Bull. 1962 Winter;1:39-44.
11. Zavorsky GS. Cardiopulmonary aspects of obesity in women. Obstet Gynecol Clin North Am. 2009 Jun;36(2):267-84, viii.
12. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005 May;115(5):1111-9.
13. Guzzaloni G, Grugni G, Minocci A, et al. Liver steatosis in juvenile obesity: correlations with lipid profile, hepatic biochemical parameters and glycemic and insulinemic responses to an oral glucose tolerance test. Int J Obes Relat Metab Disord. 2000 Jun;24(6):772-6.
14. Wree A, Kahraman A, Gerken G, et al. Obesity affects the liver - the link between adipocytes and hepatocytes. Digestion. 2011;83(1-2):124-33.
15. Fisher CD, Lickteig AJ, Augustine LM, et al. Hepatic cytochrome P450 enzyme alterations in humans with progressive stages of nonalcoholic fatty liver disease. Drug Metab Dispos. 2009 Oct;37(10):2087-94.
16. Donato MT, Lahoz A, Jimenez N, et al. Potential impact of steatosis on cytochrome P450 enzymes of human hepatocytes isolated from fatty liver grafts. Drug Metab Dispos. 2006 Sep;34(9):1556-62.
17. Donato MT, Jimenez N, Serralta A, et al. Effects of steatosis on drug-metabolizing capability of primary human hepatocytes. Toxicol In Vitro. 2007 Mar;21(2):271-6.
18. Emery MG, Fisher JM, Chien JY, et al. CYP2E1 activity before and after weight loss in morbidly obese subjects with nonalcoholic fatty liver disease. Hepatology. 2003 Aug;38(2):428-35.
19. Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. J Clin Anesth. 2005 Mar;17(2):134-45.
20. Marik P VJ. The obese patient in the ICU. Chest. 1998;113:492-8.
21. Darbari DS, Neely M, van den Anker J, et al. Increased clearance of morphine in sickle cell disease: implications for pain management. J Pain. 2011 May;12(5):531-8.
22. Jain R, Chung SM, Jain L, et al. Implications of obesity for drug therapy: limitations and challenges. Clin Pharmacol Ther. 2011 Jul;90(1):77-89.
23. Abernethy DR, Greenblatt DJ. Drug disposition in obese humans. An update. Clin Pharmacokinet. 1986 May-Jun;11(3):199-213.
24. Mulla H, Johnson TN. Dosing dilemmas in obese children. Arch Dis Child Educ Pract Ed. 2010 Aug;95(4):112-7.
25. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet. 2010;49(2):71-87.
26. Ingrande J, Lemmens HJ. Dose adjustment of anaesthetics in the morbidly obese. Br J Anaesth. 2010;105(S1):16-23.
27. Morrish GA, Pai MP, Green B. The effects of obesity on drug pharmacokinetics in humans. Expert Opin Drug Metab Toxicol. 2011 Mar 22.
28. Abernethy DR, Greenblatt DJ. Pharmacokinetics of drugs in obesity. Clin Pharmacokinet. 1982 Mar-Apr;7(2):108-24.
29. Kotlyar M, Carson SW. Effects of obesity on the cytochrome P450 enzyme system. Int J Clin Pharmacol Ther. 1999 Jan;37(1):8-19.
30. Edelman AB, Cherala G, Stanczyk FZ. Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review. Contraception. 2010 Oct;82(4):314-23.
31. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004 Aug;58(2):119-33.
32. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table version 5.0. Indiana University School of Medicine; 2007 [cited 2011 May 4 2011]; Available from: http://medicine.iupui.edu/clinpharm/ddis/table.asp.

33.Williams RT. Detoxication Mechanisms: The Metabolism and Detoxication of Drugs,Toxic Substances, and Other Organic Compounds. 2nd ed. London: Chapman and Hall; 1959.
34.Moretto M, Kupski C, Mottin CC, et al. Hepatic steatosis in patients undergoing bariatric surgery and its relationship to body mass index and co-morbidities. Obes Surg. 2003 Aug;13(4):622-4.
35.Silverman JF, O'Brien KF, Long S, et al. Liver pathology in morbidly obese patients with and without diabetes. Am J Gastroenterol. 1990 Oct;85(10):1349-55.
36.Harnois F, Msika S, Sabate JM, et al. Prevalence and predictive factors of non-alcoholic steatohepatitis (NASH) in morbidly obese patients undergoing bariatric surgery. Obes Surg. 2006 Feb;16(2):183-8.
37.Thorn M, Finnstrom N, Lundgren S, et al. Cytochromes P450 and MDR1 mRNA expression along the human gastrointestinal tract. Br J Clin Pharmacol. 2005 Jul;60(1):54-60.
38.Lindell M, Karlsson MO, Lennernas H, et al. Variable expression of CYP and Pgp genes in the human small intestine. Eur J Clin Invest. 2003 Jun;33(6):493-9.
39.Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol. 2008 Jan;21(1):70-83.
40.Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science. 1999 Oct 15;286(5439):487-91.
41.Hunt CM, Westerkam WR, Stave GM, et al. Hepatic cytochrome P-4503A (CYP3A) activity in the elderly. Mech Ageing Dev. 1992 Jun;64(1-2):189-99.
42.Hunt CM, Watkins PB, Saenger P, et al. Heterogeneity of CYP3A isoforms metabolizing erythromycin and cortisol. Clin Pharmacol Ther. 1992 Jan;51(1):18-23.
43.Ohno Y, Hisaka A, Suzuki H. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. Clin Pharmacokinet. 2007;46(8):681-96.
44.Watkins PB. The role of cytochromes P-450 in cyclosporine metabolism. J Am Acad Dermatol. 1990 Dec;23(6 Pt 2):1301-9; discussion 9-11.
45.Kerr BM, Thummel KE, Wurden CJ, et al. Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. Biochem Pharmacol. 1994 Jun 1;47(11):1969-79.
46.Streetman DS, Bertino JS, Jr., Nafziger AN. Phenotyping of drug-metabolizing enzymes in adults: a review of in-vivo cytochrome P450 phenotyping probes. Pharmacogenetics. 2000 Apr;10(3):187-216.
47.Abernethy DR, Greenblatt DJ, Divoll M, et al. The influence of obesity on the pharmacokinetics of oral alprazolam and triazolam. Clin Pharmacokinet. 1984 Mar-Apr;9(2):177-83.
48.Greenblatt DJ, Abernethy DR, Locniskar A, et al. Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology. 1984 Jul;61(1):27-35.
49.Yee GC, Lennon TP, Gmur DJ, et al. Effect of obesity on cyclosporine disposition. Transplantation. 1988 Mar;45(3):649-51.
50.Flechner SM, Kolbeinsson ME, Tam J, et al. The impact of body weight on cyclosporine pharmacokinetics in renal transplant recipients. Transplantation. 1989 May;47(5):806-10.
51.Caraco Y, Zylber-Katz E, Berry EM, et al. Carbamazepine pharmacokinetics in obese and lean subjects. Ann Pharmacother. 1995 Sep;29(9):843-7.
52.Caraco Y, Zylber-Katz E, Berry EM, et al. Significant weight reduction in obese subjects enhances carbamazepine elimination. Clin Pharmacol Ther. 1992 May;51(5):501-6.
53.Kharasch ED, Russell M, Mautz D, et al. The role of cytochrome P450 3A4 in alfentanil clearance. Implications for interindividual variability in disposition and perioperative drug interactions. Anesthesiology. 1997 Jul;87(1):36-50.
54.Bentley JB, Finley JH, Humphrey LR, et al. Obesity and Alfentanil Pharmacokinetics. Anesth Analg. 1983;62:251.
55.Reddy VB, Doss GA, Karanam BV, et al. In vitro and in vivo metabolism of a novel cannabinoid-1 receptor inverse agonist, taranabant, in rats and monkeys. Xenobiotica. 2010 Sep;40(9):650-62.
56.Li XS, Nielsen J, Cirincione B, et al. Development of a population pharmacokinetic model for taranabant, a cannibinoid-1 receptor inverse agonist. AAPS J. 2010 Dec;12(4):537-47.
57.Rotzinger S, Fang J, Baker GB. Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources. Drug Metab Dispos. 1998 Jun;26(6):572-5.
58.Mihara K, Otani K, Suzuki A, et al. Relationship between the CYP2D6 genotype and the steady-state plasma concentrations of trazodone and its active metabolite m-chlorophenylpiperazine. Psychopharmacology (Berl). 1997 Sep;133(1):95-8.
59.Sparreboom A, Wolff AC, Mathijssen RH, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol. 2007 Oct 20;25(30):4707-13.

60.Marterre WF, Hariharan S, First MR, et al. Gastric bypass in morbidly obese kidney transplant recipients. Clin Transplant. 1996 Oct;10(5):414-9.
61.Boni J, Leister C, Burns J, et al. Pharmacokinetic profile of temsirolimus with concomitant administration of cytochrome p450-inducing medications. J Clin Pharmacol. 2007 Nov;47(11):1430-9.
62.Kamdem LK, Streit F, Zanger UM, et al. Contribution of CYP3A5 to the in vitro hepatic clearance of tacrolimus. Clin Chem. 2005 Aug;51(8):1374-81.
63.Picard N, Cresteil T, Premaud A, et al. Characterization of a phase 1 metabolite of mycophenolic acid produced by CYP3A4/5. Ther Drug Monit. 2004 Dec;26(6):600-8.
64.Rogers CC, Alloway RR, Alexander JW, et al. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin Transplant. 2008 May-Jun;22(3):281-91.
65.Skottheim IB, Jakobsen GS, Stormark K, et al. Significant increase in systemic exposure of atorvastatin after biliopancreatic diversion with duodenal switch. Clin Pharmacol Ther. 2010 Jun;87(6):699-705.
66.Skottheim IB, Stormark K, Christensen H, et al. Significantly altered systemic exposure to atorvastatin acid following gastric bypass surgery in morbidly obese patients. Clin Pharmacol Ther. 2009 Sep;86(3):311-8.
67.Lucas D, Ferrara R, Gonzalez E, et al. Chlorzoxazone, a selective probe for phenotyping CYP2E1 in humans. Pharmacogenetics. 1999 Jun;9(3):377-88.
68.O'Shea D, Davis SN, Kim RB, et al. Effect of fasting and obesity in humans on the 6-hydroxylation of chlorzoxazone: a putative probe of CYP2E1 activity. Clin Pharmacol Ther. 1994 Oct;56(4):359-67.
69.Lucas D, Farez C, Bardou LG, et al. Cytochrome P450 2E1 activity in diabetic and obese patients as assessed by chlorzoxazone hydroxylation. Fundam Clin Pharmacol. 1998;12(5):553-8.
70.Kharasch ED, Thummel KE, Mautz D, et al. Clinical enflurane metabolism by cytochrome P450 2E1. Clin Pharmacol Ther. 1994 Apr;55(4):434-40.
71.Kharasch ED. Biotransformation of sevoflurane. Anesth Analg. 1995 Dec;81(6 Suppl):S27-38.
72.Reichle FM, Conzen PF. Halogenated inhalational anaesthetics. Best Pract Res Clin Anaesthesiol. 2003 Mar;17(1):29-46.
73.Miller MS, Gandolfi AJ, Vaughan RW, et al. Disposition of enflurane in obese patients. J Pharmacol Exp Ther. 1980 Nov;215(2):292-6.
74.Bentley JB, Vaughan RW, Miller MS, et al. Serum inorganic fluoride levels in obese patients during and after enflurane anesthesia. Anesth Analg. 1979 Sep-Oct;58(5):409-12.
75.Higuchi H, Satoh T, Arimura S, et al. Serum inorganic fluoride levels in mildly obese patients during and after sevoflurane anesthesia. Anesth Analg. 1993 Nov;77(5):1018-21.
76.Frink EJ, Jr., Malan TP, Jr., Brown EA, et al. Plasma inorganic fluoride levels with sevoflurane anesthesia in morbidly obese and nonobese patients. Anesth Analg. 1993 Jun;76(6):1333-7.
77.Bentley JB, Vaughan RW, Gandolfi AJ, et al. Halothane biotransformation in obese and nonobese patients. Anesthesiology. 1982 Aug;57(2):94-7.
78.Barshop NJ, Capparelli EV, Sirlin CB, et al. Acetaminophen pharmacokinetics in children with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr. 2011 Feb;52(2):198-202.
79.Abernethy DR, Divoll M, Greenblatt DJ, et al. Obesity, sex, and acetaminophen disposition. Clin Pharmacol Ther. 1982 Jun;31(6):783-90.
80.Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol. 2002;40(1):3-20.
81.May DG. Genetic differences in drug disposition. J Clin Pharmacol. 1994 Sep;34(9):881-97.
82.van den Anker JN. Developmental pharmacology. Dev Disabil Res Rev. 2010;16(3):233-8.
83.Cheymol G, Weissenburger J, Poirier JM, et al. The pharmacokinetics of dexfenfluramine in obese and non-obese subjects. Br J Clin Pharmacol. 1995 Jun;39(6):684-7.
84.Cheymol G, Woestenborghs R, Snoeck E, et al. Pharmacokinetic study and cardiovascular monitoring of nebivolol in normal and obese subjects. Eur J Clin Pharmacol. 1997;51(6):493-8.
85.Lefebvre J, Poirier L, Poirier P, et al. The influence of CYP2D6 phenotype on the clinical response of nebivolol in patients with essential hypertension. Br J Clin Pharmacol. 2007 May;63(5):575-82.
86.Schrenk D, Brockmeier D, Morike K, et al. A distribution study of CYP1A2 phenotypes among smokers and non-smokers in a cohort of healthy Caucasian volunteers. Eur J Clin Pharmacol. 1998 Jan;53(5):361-7.
87.Rostami-Hodjegan A, Nurminen S, Jackson PR, et al. Caffeine urinary metabolite ratios as markers of enzyme activity: a theoretical assessment. Pharmacogenetics. 1996 Apr;6(2):121-49.

88.Rasmussen BB, Brosen K. Theophylline has no advantages over caffeine as a putative model drug for assessing CYPIA2 activity in humans. Br J Clin Pharmacol. 1997 Mar;43(3):253-8.
89.Caraco Y, Zylber-Katz E, Berry EM, et al. Caffeine pharmacokinetics in obesity and following significant weight reduction. Int J Obes Relat Metab Disord. 1995 Apr;19(4):234-9.
90.Kamimori GH, Somani SM, Knowlton RG, et al. The effects of obesity and exercise on the pharmacokinetics of caffeine in lean and obese volunteers. Eur J Clin Pharmacol. 1987;31(5):595-600.
91.Abernethy DR, Todd EL, Schwartz JB. Caffeine disposition in obesity. Br J Clin Pharmacol. 1985 Jul;20(1):61-6.
92.Chine M, Schwarzenberg SJ, Johnson LA. Altered xanthine oxidase and N-acetyl transferase activity in obese children. Br J Clin Pharmacol. 2011 Mar 8.
93.Zahorska-Markiewicz B, Waluga M, Zielinski M, et al. Pharmacokinetics of theophylline in obesity. Int J Clin Pharmacol Ther. 1996 Sep;34(9):393-5.
94.Jusko WJ, Gardner MJ, Mangione A, et al. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. J Pharm Sci. 1979 Nov;68(11):1358-66.
95.Blouin RA, Elgert JF, Bauer LA. Theophylline clearance: effect of marked obesity. Clin Pharmacol Ther. 1980 Nov;28(5):619-23.
96.Gonzalez FJ, Idle JR. Pharmacogenetic phenotyping and genotyping. Present status and future potential. Clin Pharmacokinet. 1994;26(1):59-70.
97.He SM, Zhou ZW, Li XT, et al. Clinical drugs undergoing polymorphic metabolism by human cytochrome P450 2C9 and the implication in drug development. Curr Med Chem. 2011;18(5):667-713.
98.Abernethy DR, Greenblatt DJ. Phenytoin disposition in obesity. Determination of loading dose. Arch Neurol. 1985 May;42(5):468-71.
99.Abernethy DR, Greenblatt DJ. Ibuprofen disposition in obese individuals. Arthritis Rheum. 1985 Oct;28(10):1117-21.
100.Langtry HD, Balfour JA. Glimepiride. A review of its use in the management of type 2 diabetes mellitus. Drugs. 1998 Apr;55(4):563-84.
101.Shukla UA, Chi EM, Lehr KH. Glimepiride pharmacokinetics in obese versus non-obese diabetic patients. Ann Pharmacother. 2004 Jan;38(1):30-5.
102.Tan B, Zhang YF, Chen XY, et al. The effects of CYP2C9 and CYP2C19 genetic polymorphisms on the pharmacokinetics and pharmacodynamics of glipizide in Chinese subjects. Eur J Clin Pharmacol. 2010 Feb;66(2):145-51.
103.Jaber LA, Ducharme MP, Halapy H. The effects of obesity on the pharmacokinetics and pharmacodynamics of glipizide in patients with non-insulin-dependent diabetes mellitus. Ther Drug Monit. 1996 Feb;18(1):6-13.
104.Flockhart DA. Drug interactions and the cytochrome P450 system. The role of cytochrome P450 2C19. Clin Pharmacokinet. 1995;29 Suppl 1:45-52.
105.Bertilsson L, Henthorn TK, Sanz E, et al. Importance of genetic factors in the regulation of diazepam metabolism: relationship to S-mephenytoin, but not debrisoquin, hydroxylation phenotype. Clin Pharmacol Ther. 1989 Apr;45(4):348-55.
106.Abernethy DR, Greenblatt DJ, Divoll M, et al. Alterations in drug distribution and clearance due to obesity. J Pharmacol Exp Ther. 1981 Jun;217(3):681-5.
107.Abernethy DR, Greenblatt DJ, Divoll M, et al. Prolongation of drug half-life due to obesity: studies of desmethyldiazepam (clorazepate). J Pharm Sci. 1982 Aug;71(8):942-4.
108.Strolin Benedetti M, Whomsley R, Baltes E. Involvement of enzymes other than CYPs in the oxidative metabolism of xenobiotics. Expert Opin Drug Metab Toxicol. 2006 Dec;2(6):895-921.
109.Balis FM. Pharmacokinetic drug interactions of commonly used anticancer drugs. Clin Pharmacokinet. 1986 May-Jun;11(3):223-35.
110.Zuccaro P, Guandalini S, Pacifici R, et al. Fat body mass and pharmacokinetics of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. Ther Drug Monit. 1991 Jan;13(1):37-41.
111.Engel G, Hofmann U, Heidemann H, et al. Antipyrine as a probe for human oxidative drug metabolism: identification of the cytochrome P450 enzymes catalyzing 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine formation. Clin Pharmacol Ther. 1996 Jun;59(6):613-23.
112.Caraco Y, Zylber-Katz E, Berry EM, et al. Antipyrine disposition in obesity: evidence for negligible effect of obesity on hepatic oxidative metabolism. Eur J Clin Pharmacol. 1995;47(6):525-30.
113.Le Jeunne C, Poirier JM, Cheymol G, et al. Pharmacokinetics of intravenous bisoprolol in obese and non-obese volunteers. Eur J Clin Pharmacol. 1991;41(2):171-4.
114.Westhoff CL, Torgal AH, Mayeda ER, et al. Pharmacokinetics of a combined oral contraceptive in obese and normal-weight women. Contraception. 2010 Jun;81(6):474-80.
115.Rudek MA, Sparreboom A, Garrett-Mayer ES, et al. Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. Eur J Cancer. 2004 May;40(8):1170-8.
116.Fukuchi H, Nakashima M, Araki R, et al. Effect of obesity on serum amiodarone concentration in Japanese patients: population pharmacokinetic investigation by multiple trough screen analysis. J Clin Pharm Ther. 2009 Jun;34(3):329-36.
117.Thompson PA, Rosner GL, Matthay KK, et al. Impact of body composition on pharmacokinetics of doxorubicin in children: a Glaser Pediatric Research Network study. Cancer Chemother Pharmacol. 2009 Jul;64(2):243-51.
118.Kiang TK, Ensom MH, Chang TK. UDP-glucuronosyltransferases and clinical drug-drug interactions. Pharmacol Ther. 2005 Apr;106(1):97-132.
119.Tchernof A, Levesque E, Beaulieu M, et al. Expression of the androgen metabolizing enzyme UGT2B15 in adipose tissue and relative expression measurement using a competitive RT-PCR method. Clin Endocrinol (Oxf). 1999 May;50(5):637-42.
120.Court MH, Duan SX, Guillemette C, et al. Stereoselective conjugation of oxazepam by human UDP-glucuronosyltransferases (UGTs): S-oxazepam is glucuronidated by UGT2B15, while R-oxazepam is glucuronidated by UGT2B7 and UGT1A9. Drug Metab Dispos. 2002 Nov;30(11):1257-65.
121.Mutlib AE, Goosen TC, Bauman JN, et al. Kinetics of acetaminophen glucuronidation by UDP-glucuronosyltransferases 1A1, 1A6, 1A9 and 2B15. Potential implications in acetaminophen-induced hepatotoxicity. Chem Res Toxicol. 2006 May;19(5):701-9.
122.Hayakawa H, Fukushima Y, Kato H, et al. Metabolism and disposition of novel des-fluoro quinolone garenoxacin in experimental animals and an interspecies scaling of pharmacokinetic parameters. Drug Metab Dispos. 2003 Nov;31(11):1409-18.
123.Van Wart S, Phillips L, Ludwig EA, et al. Population pharmacokinetics and pharmacodynamics of garenoxacin in patients with community-acquired respiratory tract infections. Antimicrob Agents Chemother. 2004 Dec;48(12):4766-77.
124.Abernethy DR, Greenblatt DJ, Divoll M, et al. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med. 1983 Jun;101(6):873-80.
125.Chung JY, Cho JY, Yu KS, et al. Effect of the UGT2B15 genotype on the pharmacokinetics, pharmacodynamics, and drug interactions of intravenous lorazepam in healthy volunteers. Clin Pharmacol Ther. 2005 Jun;77(6):486-94.
126.Okumura K, Kita T, Chikazawa S, et al. Genotyping of N-acetylation polymorphism and correlation with procainamide metabolism. Clin Pharmacol Ther. 1997 May;61(5):509-17.
127.Christoff PB, Conti DR, Naylor C, et al. Procainamide disposition in obesity. Drug Intell Clin Pharm. 1983 Jul-Aug;17(7-8):516-22.
128.Gibbs JP, Gooley T, Corneau B, et al. The impact of obesity and disease on busulfan oral clearance in adults. Blood. 1999 Jun 15;93(12):4436-40.
129.Nguyen L, Leger F, Lennon S, et al. Intravenous busulfan in adults prior to haematopoietic stem cell transplantation: a population pharmacokinetic study. Cancer Chemother Pharmacol. 2006 Jan;57(2):191-8.
130.Buggia I, Zecca M, Alessandrino EP, et al. Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. GITMO (Gruppo Italiano Trapianto di Midollo Osseo). Anticancer Res. 1996 Jul-Aug;16(4A):2083-8.
131.Czerwinski M, Gibbs JP, Slattery JT. Busulfan conjugation by glutathione S-transferases alpha, mu, and pi. Drug Metab Dispos. 1996 Sep;24(9):1015-9.
132.Browning B, Thormann K, Donaldson A, et al. Busulfan Dosing in Children with BMIs >/=85% Undergoing HSCT: A New Optimal Strategy. Biol Blood Marrow Transplant. 2011 Feb 1.
133.Farrell GC, Teoh NC, McCuskey RS. Hepatic microcirculation in fatty liver disease. Anat Rec (Hoboken). 2008 Jun;291(6):684-92.
134.Al-Jahdari WS, Yamamoto K, Hiraoka H, et al. Prediction of total propofol clearance based on enzyme activities in microsomes from human kidney and liver. Eur J Clin Pharmacol. 2006 Jul;62(7):527-33.
135.van Kralingen S, Diepstraten J, Peeters MYM, et al. Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. Clin Pharmacokinet. 2011;accepted for publication.
136.Cortinez LI, Anderson BJ, Penna A, et al. Influence of obesity on propofol

pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth. 2010 Oct;105(4):448-56.
137. Wojcicki J, Jaroszynska M, Drozdzik M, et al. Comparative pharmacokinetics and pharmacodynamics of propranolol and atenolol in normolipaemic and hyperlipidaemic obese subjects. Biopharm Drug Dispos. 2003 Jul;24(5):211-8.
138. Cheymol G, Poirier JM, Carrupt PA, et al. Pharmacokinetics of beta-adrenoceptor blockers in obese and normal volunteers. Br J Clin Pharmacol. 1997 Jun;43(6):563-70.
139. Bowman SL, Hudson SA, Simpson G, et al. A comparison of the pharmacokinetics of propranolol in obese and normal volunteers. Br J Clin Pharmacol. 1986 May;21(5):529-32.
140. Cheymol G, Poirier JM, Barre J, et al. Comparative pharmacokinetics of intravenous propranolol in obese and normal volunteers. J Clin Pharmacol. 1987 Nov;27(11):874-9.
141. Routledge PA, Shand DG. Clinical pharmacokinetics of propranolol. Clin Pharmacokinet. 1979 Mar-Apr;4(2):73-90.
142. Abernethy DR, Schwartz JB. Verapamil pharmacodynamics and disposition in obese hypertensive patients. J Cardiovasc Pharmacol. 1988 Feb;11(2):209-15.
143. Abernethy DR, Greenblatt DJ. Lidocaine disposition in obesity. Am J Cardiol. 1984 Apr 1;53(8):1183-6.
144. Pea F, Licari M, Baldassarre M, et al. MEGX disposition in critically-ill trauma patients: subsequent assessments during the first week following trauma. Fundam Clin Pharmacol. 2002 Dec;16(6):519-25.
145. Tateishi T, Krivoruk Y, Ueng YF, et al. Identification of human liver cytochrome P-450 3A4 as the enzyme responsible for fentanyl and sufentanil N-dealkylation. Anesth Analg. 1996 Jan;82(1):167-72.
146. Gepts E, Shafer SL, Camu F, et al. Linearity of pharmacokinetics and model estimation of sufentanil. Anesthesiology. 1995 Dec;83(6):1194-204.
147. Koska AJ, 3rd, Romagnoli A, Kramer WG. Effect of cardiopulmonary bypass on fentanyl distribution and elimination. Clin Pharmacol Ther. 1981 Jan;29(1):100-5.
148. Schwartz AE, Matteo RS, Ornstein E, et al. Pharmacokinetics of sufentanil in obese patients. Anesth Analg. 1991 Dec;73(6):790-3.
149. Shibutani K, Inchiosa MA, Jr., Sawada K, et al. Accuracy of pharmacokinetic models for predicting plasma fentanyl concentrations in lean and obese surgical patients: derivation of dosing weight ("pharmacokinetic mass"). Anesthesiology. 2004 Sep;101(3):603-13.
150. Jiko M, Yano I, Okuda M, et al. Altered pharmacokinetics of paclitaxel in experimental hepatic or renal failure. Pharm Res. 2005 Feb;22(2):228-34.
151. Pai MP. Estimating the Glomerular Filtration Rate in Obese Adult Patients for Drug Dosing. Adv Chronic Kidney Dis. 2010 Sep;17(5):e53-e62.
152. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. Hypertension. 1995 Oct;26(4):610-5.
153. Marik P, Varon J. The obese patient in the ICU. Chest. 1998 Feb;113(2):492-8.
154. Kasiske BL, Crosson JT. Renal disease in patients with massive obesity. Arch Intern Med. 1986 Jun;146(6):1105-9.
155. Cindik N, Baskin E, Agras PI, et al. Effect of obesity on inflammatory markers and renal functions. Acta Paediatr. 2005 Dec;94(12):1732-7.
156. Csernus K, Lanyi E, Erhardt E, et al. Effect of childhood obesity and obesity-related cardiovascular risk factors on glomerular and tubular protein excretion. Eur J Pediatr. 2005 Jan;164(1):44-9.
157. Savino A, Pelliccia P, Giannini C, et al. Implications for kidney disease in obese children and adolescents. Pediatr Nephrol. 2011 Feb 11.
158. Post FA, Wyatt CM, Mocroft A. Biomarkers of impaired renal function. Curr Opin HIV AIDS. 2010 Nov;5(6):524-30.
159. Henegar JR, Bigler SA, Henegar LK, et al. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 2001 Jun;12(6):1211-7.
160. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol. 1998 Oct;54(8):621-5.
161. Pai MP, Norenberg JP, Anderson T, et al. Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. Antimicrob Agents Chemother. 2007 Aug;51(8):2741-7.
162. Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. J Clin Pharmacol. 2005 Jan;45(1):48-56.
163. Harland SJ, Newell DR, Siddik ZH, et al. Pharmacokinetics of cis-diammine-1,1-cyclobutane dicarboxylate platinum(II) in patients with normal and impaired renal function. Cancer Res. 1984 Apr;44(4):1693-7.
164. Schmitt A, Gladieff L, Lansiaux A, et al. A universal formula based on cystatin C to perform individual dosing of carboplatin

in normal weight, underweight, and obese patients. Clin Cancer Res. 2009 May 15;15(10):3633-9.
165. Ekhart C, Rodenhuis S, Schellens JH, et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer Chemother Pharmacol. 2009 Jun;64(1):115-22.
166. Lewis TV, Johnson PN, Nebbia AM, et al. Increased enoxaparin dosing is required for obese children. Pediatrics. 2011 Mar;127(3):e787-90.
167. Abernethy DR, Greenblatt DJ, Matlis R, et al. Cimetidine disposition in obesity. Am J Gastroenterol. 1984 Feb;79(2):91-4.
168. Karlsson E. Clinical pharmacokinetics of procainamide. Clin Pharmacokinet. 1978 Mar-Apr;3(2):97-107.
169. Drusano GL. An overview of the pharmacology of intravenously administered ciprofloxacin. Am J Med. 1987 Apr 27;82(4A):339-45.
170. Allard S, Kinzig M, Boivin G, et al. Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Ther. 1993 Oct;54(4):368-73.
171. Daley-Yates PT, McBrien DC. The mechanism of renal clearance of cisplatin (cis-dichlorodiammine platinum ii) and its modification by furosemide and probenecid. Biochem Pharmacol. 1982 Jul 1;31(13):2243-6.
172. Abernethy DR, Greenblatt DJ, Smith TW. Digoxin disposition in obesity: clinical pharmacokinetic investigation. Am Heart J. 1981 Oct;102(4):740-4.
173. Reiss RA, Haas CE, Karki SD, et al. Lithium pharmacokinetics in the obese. Clin Pharmacol Ther. 1994 Apr;55(4):392-8.
174. Chagnac A, Herman M, Zingerman B, et al. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. Nephrol Dial Transplant. 2008 Dec;23(12):3946-52.
175. Mortensen A, Lenz K, Abildstrom H, et al. Anesthetizing the obese child. Paediatr Anaesth. 2011 Mar 24.
176. Koolen SL, Oostendorp RL, Beijnen JH, et al. Population pharmacokinetics of intravenously and orally administered docetaxel with or without co-administration of ritonavir in patients with advanced cancer. Br J Clin Pharmacol. 2010 May;69(5):465-74.
177. Greenblatt DJ, Friedman H, Burstein ES, et al. Trazodone kinetics: effect of age, gender, and obesity. Clin Pharmacol Ther. 1987 Aug;42(2):193-200.
178. Haritos VS, Ching MS, Ghabrial H, et al. Metabolism of dexfenfluramine in human liver microsomes and by recombinant enzymes: role of CYP2D6 and 1A2. Pharmacogenetics. 1998 Oct;8(5):423-32.
179. Garcia-Martin E, Martinez C, Tabares B, et al. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clin Pharmacol Ther. 2004 Aug;76(2):119-27.
180. Kumar V, Wahlstrom JL, Rock DA, et al. CYP2C9 inhibition: impact of probe selection and pharmacogenetics on in vitro inhibition profiles. Drug Metab Dispos. 2006 Dec;34(12):1966-75.
181. Yanni SB, Annaert PP, Augustijns P, et al. In vitro hepatic metabolism explains higher clearance of voriconazole in children versus adults: role of CYP2C19 and flavin-containing monooxygenase 3. Drug Metab Dispos. 2010 Jan;38(1):25-31.
182. Pai MP, Lodise TP. Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother. 2011 Jun;55(6):2601-5.
183. Ebner T, Remmel RP, Burchell B. Human bilirubin UDP-glucuronosyltransferase catalyzes the glucuronidation of ethinylestradiol. Mol Pharmacol. 1993 Apr;43(4):649-54.
184. Palovaara S, Tybring G, Laine K. The effect of ethinyloestradiol and levonorgestrel on the CYP2C19-mediated metabolism of omeprazole in healthy female subjects. Br J Clin Pharmacol. 2003 Aug;56(2):232-7.
185. Yamazaki H, Shaw PM, Guengerich FP, et al. Roles of cytochromes P450 1A2 and 3A4 in the oxidation of estradiol and estrone in human liver microsomes. Chem Res Toxicol. 1998 Jun;11(6):659-65.
186. Stanczyk FZ, Roy S. Metabolism of levonorgestrel, norethindrone, and structurally related contraceptive steroids. Contraception. 1990 Jul;42(1):67-96.
187. Edelman A, Munar M, Elman MR, et al. Effect of Ethinyl estradiol/ Levonorgestrel combined oral contraceptive on the activity of Cytochrome P4503A in obese women. Br J Clin Pharmacol. 2012 Feb 2.
188. Ohyama K, Nakajima M, Nakamura S, et al. A significant role of human cytochrome P450 2C8 in amiodarone N-deethylation: an approach to predict the contribution with relative activity factor. Drug Metab Dispos. 2000 Nov;28(11):1303-10.
189. Brain EG, Yu LJ, Gustafsson K, et al. Modulation of P450-dependent ifosfamide pharmacokinetics: a better understanding of drug activation in vivo. Br J Cancer. 1998

Jun;77(11):1768-76.
190. Lind MJ, Margison JM, Cerny T, et al. Prolongation of ifosfamide elimination half-life in obese patients due to altered drug distribution. Cancer Chemother Pharmacol. 1989;25(2):139-42.
191. Walter-Sack I, Klotz U. Influence of diet and nutritional status on drug metabolism. Clin Pharmacokinet. 1996 Jul;31(1):47-64.
192. Horikiri Y, Suzuki T, Mizobe M. Pharmacokinetics and metabolism of bisoprolol enantiomers in humans. J Pharm Sci. 1998 Mar;87(3):289-94.
193. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. Clin Pharmacokinet. 1996 Apr;30(4):263-99.
194. Viriyayudhakorn S, Thitiarchakul S, Nachaisit S, et al. Pharmacokinetics of quinine in obesity. Trans R Soc Trop Med Hyg. 2000 Jul-Aug;94(4):425-8.
195. Zharikova OL, Fokina VM, Nanovskaya TN, et al. Identification of the major human hepatic and placental enzymes responsible for the biotransformation of glyburide. Biochem Pharmacol. 2009 Dec 15;78(12):1483-90.
196. Jaber LA, Antal EJ, Slaughter RL, et al. The pharmacokinetics and pharmacodynamics of 12 weeks of glyburide therapy in obese diabetics. Eur J Clin Pharmacol. 1993;45(5):459-63.
197. Joerger M, Huitema AD, Meenhorst PL, et al. Pharmacokinetics of low-dose doxorubicin and metabolites in patients with AIDS-related Kaposi sarcoma. Cancer Chemother Pharmacol. 2005 May;55(5):488-96.
198. Rahman A, Korzekwa KR, Grogan J, et al. Selective biotransformation of taxol to 6 alpha-hydroxytaxol by human cytochrome P450 2C8. Cancer Res. 1994 Nov 1;54(21):5543-6.
199. Masubuchi Y, Hosokawa S, Horie T, et al. Cytochrome P450 isozymes involved in propranolol metabolism in human liver microsomes. The role of CYP2D6 as ring-hydroxylase and CYP1A2 as N-desisopropylase. Drug Metab Dispos. 1994 Nov-Dec;22(6):909-15.
200. McNeil JJ, Louis WJ. Clinical pharmacokinetics of labetalol. Clin Pharmacokinet. 1984 Mar-Apr;9(2):157-67.
201. Hamann SR, Blouin RA, McAllister RG, Jr. Clinical pharmacokinetics of verapamil. Clin Pharmacokinet. 1984 Jan-Feb;9(1):26-41.
202. Echizen H, Eichelbaum M. Clinical pharmacokinetics of verapamil, nifedipine and diltiazem. Clin Pharmacokinet. 1986 Nov-Dec;11(6):425-49.
203. Zito RA, Reid PR. Lidocaine kinetics predicted by indocyanine green clearance. N Engl J Med. 1978 May 25;298(21):1160-3.
204. Oda Y, Mizutani K, Hase I, et al. Fentanyl inhibits metabolism of midazolam: competitive inhibition of CYP3A4 in vitro. Br J Anaesth. 1999 Jun;82(6):900-3.
205. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet. 1986 Jul-Aug;11(4):257-82.
206. Dvorchik B, Arbeit RD, Chung J, et al. Population pharmacokinetics of daptomycin. Antimicrob Agents Chemother. 2004 Aug;48(8):2799-807.
207. Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis. 1996;26 Suppl 2:24-38.
208. Barras MA, Duffull SB, Atherton JJ, et al. Modelling the occurrence and severity of enoxaparin-induced bleeding and bruising events. Br J Clin Pharmacol. 2009 Nov;68(5):700-11.
209. Yee JY, Duffull SB. The effect of body weight on dalteparin pharmacokinetics. A preliminary study. Eur J Clin Pharmacol. 2000 Jul;56(4):293-7.
210. Barrett JS, Gibiansky E, Hull RD, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. Int J Clin Pharmacol Ther. 2001 Oct;39(10):431-46.
211. Richards DA. Comparative pharmacodynamics and pharmacokinetics of cimetidine and ranitidine. J Clin Gastroenterol. 1983;5 Suppl 1:81-90.
212. Zamboni WC, Houghton PJ, Johnson RK, et al. Probenecid alters topotecan systemic and renal disposition by inhibiting renal tubular secretion. J Pharmacol Exp Ther. 1998 Jan;284(1):89-94.
213. Iisalo E. Clinical pharmacokinetics of digoxin. Clin Pharmacokinet. 1977 Jan-Feb;2(1):1-16.
214. Davis JM, Fann WE. Lithium. Annu Rev Pharmacol. 1971;11:285-302.

Section 02

The influence of morbidly obesity on the pharmacokinetics and pharmacodynamics of propofol in adults and adolescents

Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients

03

Simone van Kralingen*, Jeroen Diepstraten*, Mariska Y.M. Peeters,
Vera H.M. Deneer, Bert van Ramshorst, René J. Wiezer,
Eric P.A. van Dongen, Meindert Danhof, Catherijne A.J. Knibbe
both authors contributed equally

Clin Pharmacokin. 2011(50): 739-50
Comment in: Clin Pharmacokin. 2011(50): 751-3

Abstract

Background and objectives
In view of the increasing prevalence of morbidly obese patients, the influence of excessive total body weight (TBW) on the pharmacokinetics and pharmacodynamics of propofol was characterized in this study using bispectral index (BIS) values as pharmacodynamic endpoint.
Methods
A population pharmacokinetic and pharmacodynamic model was developed with the nonlinear mixed-effects modelling software NONMEM VI, on the basis of 491 blood samples from 20 morbidly obese patients (TBW range: 98 - 167 kg) and 725 blood samples of 44 lean patients (TBW range: 55 - 98 kg) from previously published studies. In addition, 2246 BIS values from the 20 morbidly obese patients were available for pharmacodynamic analysis.
Results
In a three-compartment pharmacokinetic model, TBW proved to be the most predictive covariate for clearance (CL) in 20 morbidly obese patients ($CL = 2.33\ L/min * (TBW/70)^{0.72}$). Similar results were obtained when the morbidly obese patients and 44 lean patients were analysed together ($CL = 2.22\ L/min * (TBW/70)^{0.67}$). No covariates were identified for other pharmacokinetic parameters. The depth of anaesthesia in morbidly obese patients was adequately described by a two-compartment biophase-distribution model with a sigmoid maximum possible effect (E_{max}) pharmacodynamic model (concentration at half-maximum effect (EC_{50}) 2.12 mg/L) without covariates.
Conclusion
We developed a pharmacokinetic and pharmacodynamic model of propofol in morbidly obese patients, in which TBW proved to be the major determinant for clearance, using an allometric function with an exponent of 0.72. For the other pharmacokinetic and pharmacodynamic parameters, no covariates could be identified.

Background

In Western countries, the prevalence of obesity is increasing, resulting in percentages of 20% in men and 25% in women in the US, respectively (1). The prevalence of morbidly obese patients is also rising (2-3). However, there have been a few studies on the influence of (morbid) obesity on the pharmacokinetics and pharmacodynamics of commonly used drugs (4-5). Therefore, systematic pharmacokinetic and pharmacodynamic studies in this special group of patients are urgently needed.

Propofol is widely used for induction and maintenance of anaesthesia in both lean and (morbidly) obese patients. There have been few reports focusing on the influence of excessive total TBW (TBW) on the pharmacokinetics of propofol. Servin et al. (6) originally used an adjusted TBW to dose propofol in morbidly obese patients, and upon pharmacokinetic analysis they observed a linear relationship between TBW and clearance. Schuttler and Ihmsen (7) found that propofol clearance depend on TBW, using an allometric equation with an exponent of 0.71; however, no morbidly obese patients were included in their study. Another study used simulations to propose lean body weight (LBW) as weight input for propofol dosing (8). More recently, it was reported that TBW was the size descriptor for all clearances and volume values of propofol in obese patients (9). While these conflicting reports on the pharmacokinetics of propofol may be a result of an unbalanced range in body weight and/or inclusion of only a limited number of morbidly obese patients in the analyses, there are still no reports available on the pharmacodynamics of propofol in morbidly obese patients.

Therefore, the aim of this study was to evaluate the pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients, using the Bispectral index (BIS) as a pharmacodynamic endpoint. For both the pharmacokinetics and pharmacodynamics, a systematic covariate analysis was performed using TBW, body mass index (BMI), ideal body weight (IBW) and LBW as weight covariates. For the pharmacokinetic analysis, data of 44 lean patients were available from previously published studies (10-11).

Methods

Patients

Twenty morbidly obese patients who were scheduled to undergo laparoscopic gastric banding or gastric bypass surgery were enrolled in a prospective study (ClinicalTrials.gov identifier NCT00395681). Patients were included if they were aged between 18 and 60 years, had an American Society of Anesthesiologists (ASA) physical status classification of II or III, had a BMI of over 40 kg/m^2 at inclusion, and normal renal and hepatic function as assessed by routine laboratory testing. All patients undergoing bariatric surgery were asked to lose weight preoperatively, as this has shown to improve the outcome. Therefore, patients were not excluded from the study as long as their BMI was higher than 35 kg/m^2 on the day of surgery and on the day of study. The exclusion criteria included pregnancy, breastfeeding, epilepsy and known allergy for propofol, soy bean oil or egg lecithin. The study protocol was approved by the hospitals ethics committee, and written informed consent was obtained from by each participating patient.

Forty-four lean patients had been enrolled earlier as part of two other studies; detailed information can be found in the references (10-11). Four patients from one of these studies (10) were excluded from the covariate analysis of the combined dataset of morbidly obese and lean patients, because there was no information available on the height of those patients.

Anaesthetic Procedure

All morbidly obese patients received standardized anaesthesia without premedication. Before induction, an antecubital infusion line, an indwelling arterial blood pressure line and leads for a three-lead ECG were installed, and a BIS electrode was placed on the patient's forehead. Patients were randomized to receive a bolus injection of propofol 200 mg or 350 mg over 60 seconds using total intravenous anaesthesia (TIVA) pump (Asena target-controlled infusion (TCI) and TIVA; Alaris Medical Systems) for induction of anaesthesia, together with 1% lidocaine 2 ml to avoid pain during injection (12). Thereafter, upon administration of fentanyl 250 µg and atracurium besilate 50 mg, the trachea was intubated and mechanical ventilation was initiated by the anaesthesiologist. Anaesthesia was maintained with a continuous infusion of 2% propofol at an initial infusion rate of 10 mg/h/kg TBW, which was started between 2 and 7 minutes after the propofol induction dose. Remifentanil was administrated 25 µg/h/kg IBW (13) and atracurium besilate at 0.3 mg/h/kg TBW, according to local practice. The propofol infusion rate was subsequently adjusted in order to keep BIS values between 40 and 60, the systolic arterial blood pressure between 80 and 160 mmHg, and the heart rate between 60 and 90 beats per minute. Propofol infusion rate adjustments of 50 – 150 mg/h could be made at the discretion of the anaesthesiologist, with no more than one infusion rate adjustment per 5 minutes. The remifentanil infusion rate was kept constant throughout the procedure, in order to rule out any influence of changes in remifentanil concentrations on BIS values or haemodynamic parameters.

In the previously published lean patient group, 24 female patients received a bolus injection of propofol 2.5 mg/kg for induction of anaesthesia, and anaesthesia was maintained with isoflurane (10). Another 20 lean intensive care patients received continuous propofol infusions for 2-5 days, with propofol doses based on the Ramsay six-point scale (11). In both previously published studies, no BIS values were available.

Blood sampling and analytical methods

In morbidly obese patients, arterial blood samples (2 mL) were collected at the following timepoints: at baseline prior to the start of the propofol bolus, approximately 1.5, 2.5 and 4 minutes after the propofol bolus; 3, 7, 15, 25 and 45 minutes after the start of the propofol infusion; just before and at 5 or 15 minutes after dose adjustment; just before discontinuation of the propofol infusion; and at 1, 3, 5, 7, 10, 20, 30, 60, 90, 120 and 150 minutes after the end of the infusion.

In one of previously published lean patients (10), arterial blood samples were collected at 1, 1.5, 2, 2.5, 3, 4, 5, 8, 11, 15, 20, 30, 45, 60, 90, 120, 150 and 180 minutes after the induction dose of propofol. In the other previously published study of lean patients (11), arterial blood samples were collected four times daily during propofol maintenance infusion for 2-5 days.

Whole-blood samples for propofol analysis were mixed thoroughly and stored at 4°C until analysis by high-performance liquid chromatography with fluorescence detection at 276 nm and 310 nm. With this method, the coefficients of variation for the intra-assay and inter-assay precision were less than 3.7% and 9.8%, respectively, over the concentration range from 0.05 to 5.0 mg/L, and the lower limit of quantification was 0.05 mg/L (14).

Data analysis and internal validation

The analysis was performed by means of non-linear mixed-effects modelling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD, USA) (15) with S-plus (version 6.2; Insightful software, Seattle, WA, USA) to visualize the data. Population pharmacokinetic and pharmacodynamic data were sequentially analysed by using the individual pharmacokinetic empirical Bayes estimates as input to the pharmacodynamic model. Discrimination between different models was made by comparison of the objective function value (OFV, i.e. -2 log likelihood (-2LL)). A p-value of < 0.005, representing a decrease of 7.9 in the OFV, was considered statistically significant. In addition, goodness-of-fit plots (observed versus individual-predicted concentration-time, observed versus population-predicted concentration-time, conditional weighted residuals versus time and conditional weighted residuals versus population-predicted concentration-time plots) were used for diagnostic purposes. 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 internal validity of the population pharmacokinetic and pharmacodynamic models was assessed by the bootstrap re-sampling method using 250 replicates (15). Parameters obtained with the bootstrap replicates were compared with the estimates obtained from the original data set.

Pharmacokinetic model

Log-transformed propofol concentration data were described by a three-compartment model (NONMEM VI, ADVAN11, TRANS4) parameterized in terms of the volume of distribution of the central compartment (V1), volume of distribution of the first peripheral compartment (V2) volume of distribution of the second peripheral compartment (V3), inter-compartmental clearance from the central compartment to the first peripheral compartment (Q2) inter-compartmental clearance from the central compartment to the second peripheral compartment (Q3), and clearance from the central compartment (CL) (Figure 1).

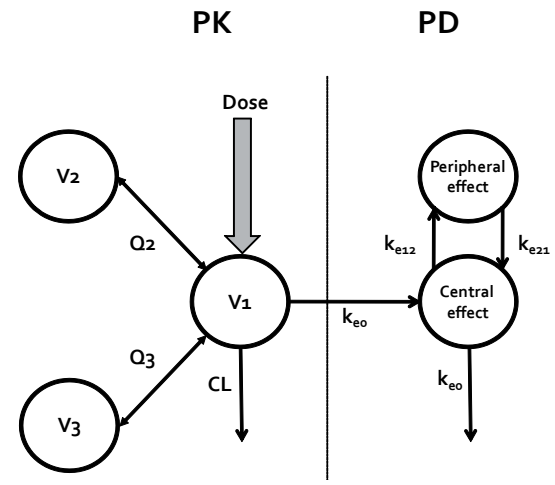


Figure 1 *Schematic representation of the pharmacokinetic and pharmacodynamic model for propofol, based on a three-compartment pharmacokinetic model parameterized using V1, V2, V3, CL, Q2 and Q3 and a two-compartment biophase-distribution model characterizing the pharmacodynamics using k_{e0}, k_{e12} and k_{e21}. The propofol concentration in the central effect-site compartment is responsible for the measured BIS values, as described using equation 4. BIS = bispectral index; CL = clearance from the central compartment; k_{e0} = first-order equilibrium constant linking the central pharmacokinetic compartment to the central effect-site compartment which equalsthe rate constant for drug loss from the central effect-site compartment; k_{e12} = rate constant from the central effect-site compartment to the peripheral effect-site compartment; k_{e21} = rate constant from the peripheral effect-site compartment to the central effect-site compartment; Q2 = inter-compartmental clearance from the central compartment to the first peripheral compartment; Q3 = inter-compartmental clearance from the central compartment to the second peripheral compartment; V1 = volume of distribution of the central compartment; V2 = volume of distribution of the first peripheral compartment; V3 = volume of distribution of the second peripheral compartment.*

The inter-individual value (post hoc value) of the parameters of the i^{th} individual was modelled by (equation 1):

$$\Theta_i = \Theta_{mean} * e^{\eta_i} \quad \text{(Eq. 1)}$$

where θ_{mean} is the population mean and η_i is a random variable with a mean of zero and variance of ω^2, assuming log-normal distribution in the population. The intraindividual variability, resulting from assay errors, model misspecifications and other unexplained sources, was best described with a proportional error model. This means for the j^{th} observed log-transformed propofol concentration of the ith individual, the relation (Y_{ij}) is described by equation 2:

$$Y_{ij} = \log C_{pred,ij} + \varepsilon_{ij} \quad \text{(Eq. 2)}$$

where C_{pred} is the predicted propofol concentration and ε_{ij} is a random variable with a mean of zero and variance of σ^2.

Biophase-Distribution and pharmacodynamic model

Concerning the biophase distribution, the delay in BIS values in relation to the propofol concentration in the central pharmacokinetic compartment was characterized on the basis of a hypothetical 'effect-site' compartment, which is an approach that has been applied previously for propofol-induced BIS values (16). In this approach, it is assumed that the rate of onset and offset of the observed effect is governed by the rate of propofol distribution to and from a hypothetical effect-site compartment. Under this interpretation, the effect-site compartment is linked to the blood compartment by a first-order equilibrium rate constant (k_{eo}), which equals a rate constant for drug loss (k_{eo}) from the effect-site compartment. Under the assumption that in equilibrium, the effect-site concentration equals the blood concentration, equation 3 can be used:

$$\frac{dC_e}{dt} = k_{e0} \cdot (C_b - C_e) \quad \text{(Eq. 3)}$$

where C_b is the blood concentration in the central pharmacokinetic compartment, C_e represents the effect-site concentration and k_{eo} is the first-order equilibration constant.

In addition to this previously applied one-compartment effect-site model, a two-compartment biophase-distribution model was also explored, in which distribution of propofol within the brain was represented by definition of a central effect-site compartment and a peripheral effect-site compartment. In this two-compartment biophase-distribution model, the rate constants from the central effect site to the peripheral effect site and from the peripheral effect site to the central effect site were k_{e12} and k_{e21}, respectively. This two-compartment effect-site model was parameterized in amounts, with the volume of the effect-site compartments set at 1. The full pharmacokinetic-pharmacodynamic model is depicted in Figure 1.

For the pharmacodynamic model, the values of the BIS were related to the propofol concentrations in the central effect-site compartment on the basis of the sigmoidal maximum possible effect (E_{max}) model (equation 4):

$$E = E_0 - \frac{E_{\max,i} \cdot C_{e,ij}^{\gamma}}{EC_{50,i}^{\gamma} + C_{e,ij}^{\gamma}} \quad \text{(Eq. 4)}$$

where E_o is the baseline BIS, $E_{max,i}$ is the E_{max} of propofol on the BIS in the ith individual, $C_{e,ij}$ is the individual-predicted propofol concentration in the central effect-site compartment in the i^{th} individual at the j^{th} timepoint, γ is the Hill coefficient representing the steepness of the concentration-response relation, and $EC_{50,i}$ is the propofol concentration (in mg/L) at half-maximum effect of the BIS in the i^{th} individual.

The interindividual variability (η_i) in the E_{max}, EC_{50} and k_{eo} was assumed to be log-normally distributed with a mean of zero and variance of ω^2 (equation 1). The residual error ε was best characterized by a proportional error model (equation 5):

$$Y_{ij} = E_{pred,ij} \cdot (1 + \varepsilon_{ij}) \quad \text{(Eq. 5)}$$

where Y_{ij} represents the observed Bispectral index in the i^{th} subject at the j^{th} time point.

Covariate analysis

Covariates were plotted independently against the individual post hoc parameter estimates of all pharmacokinetic and pharmacodynamic parameters and the conditioned weighted residuals to visualize potential relations. The following covariates were tested: TBW, BMI , IBW (17) and LBW (18), induction dose (200 versus 350 mg), sex, age, positive end-expiratory pressure, bilirubin level and renal function (serum creatinine levels). Covariates were tested using linear and allometric equations:

$$P_i = P_p \cdot \left(\frac{Cov}{Cov_{standard}}\right)^{z} \quad \text{(Eq. 6)}$$

where P_i and P_p represent individual and population parameter estimates, respectively; Cov represents the covariate; $Cov_{standard}$ represents a

Table I *Baseline characteristics of 20 morbidly obese patients and 44 lean patients (10-11).*

Parameter	Morbidly obese patients (mean (SD))	Lean patients (mean (SD))
Patients (n)	20	44
Sex (M / F)	4/16	16/28
Age (y)	45 (12)	52 (12)
TBW (kg)	124 (20)	74 (11)
IBW (kg)	61 (7)	63 (8)[a]
BMI (kg/m^2)	43 (6)	25 (4)[a]
LBW (kg)	60 (9)	45 (10)[a]

a = value for the 40 patients in whom height data were available.
BMI = body mass index; F = female; IBW = ideal body weight (17); LBW = lean body weight (18); M = male; SD = standard deviation; TBW = total body weight.

standardized (i.e. 70 kg for TBW) or median value of the covariate for the population; and z represents the exponential scaling factor, which was fixed at 1 for a linear function or an estimated value for an allometric equation. Potential covariates were separately entered into the model and statistically tested by use of the OFV and, if applicable, the 95% confidence interval of the additional parameter. When more than one significant covariate for the simple model was found, the covariate-adjusted model with the largest decrease in OFV was chosen as a basis to sequentially explore the influence of additional covariates with the use of the same criteria. Finally, after forward inclusion, a backward exclusion procedure was applied to justify the covariate. The choice of the covariate model was further evaluated as discussed above.

Simulations

On the basis of the final pharmacokinetic and pharmacodynamic model, simulations were performed to keep BIS values between 40 and 60 in morbidly obese patients ranging in TBW between 98 and 167 kg. In addition, BIS values were simulated using a linear dosing regimen (5 mg/kg/h) for these patients (19).

Results

Twenty morbidly obese patients were enrolled and 491 blood samples were available. From 44 lean patients, 725 blood samples were available (10-11). The morbidly obese patients had a mean TBW of 124 kg (range 98–167 kg) compared with 74 kg (range 55–98 kg) in the lean patients. All demographic characteristics of the morbidly obese patients and lean patients are provided in Table I.

Pharmacokinetics

A three-compartment pharmacokinetic model adequately described the time course of the propofol whole-blood concentrations in the morbidly obese patients. Exploratory plots of all tested covariates (see Methods, Covariate Analysis section) against individual post hoc parameter estimates of the simple model showed potential relations between the four weight-related covariates (TBW, LBW, IBW and BMI) and clearance. There were no relations between the explored covariates and other pharmacokinetic parameters. Subsequently, all four weight covariates were incorporated on clearance in the model and tested for significance (Table II). The analysis

Table II *Results of covariate analysis for the pharmacokinetic model of propofol in the dataset of morbidly obese patients and in the combined dataset of morbidly obese and lean patients.*

Model	Relationship of covariate with CL	No. of structural parameters	OFV	
			Morbidly obese	Morbidly obese and lean patients[a]
Simple	-	6	-643	-1557
LBW	$CL_i = CL_{pop} \bullet (LBW_i/55)$	6	-638	-1563
IBW	$CL_i = CL_{pop} \bullet (IBW_i/50)$	6	-640	-1543
BMI	$CL_i = CL_{pop} \bullet (BMI_i/23)^z$	7	-651	-1596
TBW	$CL_i = CL_{pop} \bullet (TBW_i/70)^z$	7	-653	-1599

a = 40 lean patients in whom height data were available.
BMI = body mass index; BMI_i = BMI of the i^{th} individual; CL = clearance from the central compartment; CL_i = CL in the i^{th} individual; CL_{pop} = population mean CL value; IBW = ideal body weight; IBW_i = IBW of the i^{th} individual;; LBW = lean body weight; LBW_i = LBW of the i^{th} individual; NA = not applicable; OFV = objective function value; TBW = total body weight; TBW_i = TBW of the i^{th} individual; z = allometric scaling factor.

showed that body weight TBW and BMI were the most predictive covariates for propofol clearance in morbidly obese patients (Table II).
For both the TBW model and the BMI model, the OFV was more than 7.9 points lower in comparison with the simple model ($p<0.005$). The diagnostic and individual plots of the TBW model proved to be superior to the simple model and the BMI model, particularly with respect to population-predicted concentrations. Therefore, the TBW model was chosen as the final model for morbidly obese patients, in which the equation for clearance was (equation 7):

$$CL_i = CL_{70\,kg} * (TBW_i/70)^z \qquad \text{(Eq. 7)}$$

where CL_i represents CL in the ith individual, $CL_{70\,kg}$ is the population mean CL value in an individual weighing 70 kg, TBW_i is the TBW of the i^{th} individual, 70 is the standard TBW in kilograms, and k is the allometric scaling factor, which was estimated to be 0.72. The pharmacokinetic parameters of the simple model and the final body weight model are shown in Table III. The stability of the final body weight TBW model was shown by the bootstrap analysis (Table III). In Figure 2A and 2B, the diagnostics of the final body weight TBW pharmacokinetic model in the 20 morbidly obese patients are shown.
For the analysis of both the dataset of the 20 morbidly obese patients and the dataset of the 44 lean patients from the previously published studies, a three-compartment pharmacokinetic model most adequately described the data. In Figure 3, the results of the covariate analysis are shown, with individual parameter estimates for clearance in the simple model without covariates versus the four tested weight covariates. For this covariate analysis, 40 lean patients were included instead of 44, as the height of four lean patients was not available. All four weight covariates were incorporated on clearance in the model and tested for significance (Table II). The covariate analysis showed that TBW was the most predictive covariate for propofol clearance in the combined dataset of morbidly obese patients and lean patients, which was similar to the results in the morbidly obese patients alone. In the final TBW model, which included all 20 morbidly obese patients and all 44 lean patients, the OFV decreased by 46 points ($p<0.001$), while the interindividual variability in clearance decreased by 33%, and diagnostic and individual plots of the TBW model improved in comparison with the simple model (Table III). Implementation of fixed exponents of 0.75 for clearance and 1 for volumes, as applied by Cortinez et al. (9), led to worse performance and an unstable model during bootstrap analysis, compared to the final TBW model. For the final TBW model in the 20 morbidly obese patients and all 44 lean patients, the equation for clearance was equation 7, where z was

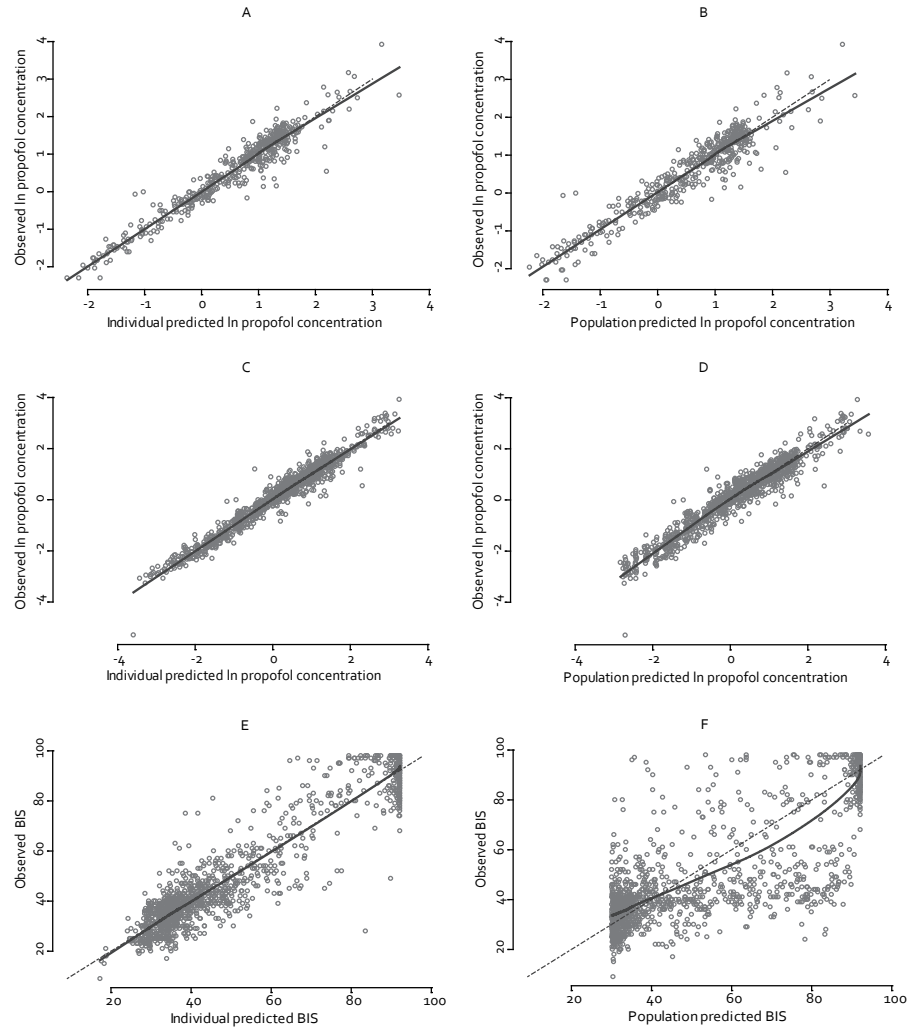


Figure 2 *Diagnostic plots of the final TBW pharmacokinetic model in 20 morbidly obese patients (A and B), the final TBW pharmacokinetic model in 20 morbidly obese patients and 44 lean patients (C and D), and the final pharmacodynamic model using BIS values in 20b morbidly obese patients (E and F), including observed versus individual predictions (A, C and E), and observed versus population predictions (B, D and F). BIS = bispectral index; ln = log-normal; TBW = total body weight. The solid line indicates the trend line, the dashed line represents the line of identity, x = y.*

Table III *Population pharmacokinetic parameters and their bootstrap values for the simple and final pharmacokinetic models for propofol in morbidly obese patients and in the combined dataset of morbidly obese and lean patients.*

Parameter	Morbidly obese patients[a]			Morbidly obese and lean patients[a]		
	Simple model	Final TBW model	Bootstrap final model	Simple model	Final TBW model	Bootstrap final model
Patients (n)	20	20	NA	64	64	NA
CL (L/min)	3.55 (8.8)	NA	NA	2.57 (3.8)	NA	NA
$CL_{70\,kg}$ (L/min)[b]	NA	2.33 (5.11)	2.29 (16.2)	NA	2.22 (2.8)	2.22 (3.3)
Z	NA	0.72 (10.8)	0.76 (36.7)	NA	0.67 (6.0)	0.67 (11.4)
V1 (L)	4.51 (13.0)	4.52 (10.1)	4.41 (14.4)	3.10 (8.3)	3.03 (9.3)	3.15 (11.9)
V2 (L)	22.1 (18.9)	22.2 (17.4)	22.5 (19.6)	5.48 (9.8)	5.34 (9.7)	5.61 (13.4)
V3 (L)	106 (12.6)	107 (12.3)	113 (20.4)	117 (7.6)	116 (7.6)	115 (7.8)
Q2 (L/min)	2.55 (14.3)	2.55 (15.1)	2.57 (14.8)	1.67 (7.6)	1.64 (7.0)	1.64 (9.7)
Q3 (L/min)	1.41 (15.5)	1.41 (14.0)	1.42 (15.2)	1.88 (4.8)	1.86 (5.0)	1.88 (5.6)
OFV	-643	-653	-677	-1726	-1772	-1760
Interindividual variability (%)						
CL	12.6 (36.1)	11.9 (29.7)	10.7 (39.7)	27.1 (14.0)	18.1 (13.5)	17.7 (19.2)
V1	45.0 (42.1)	44.7 (46.7)	50.5 (63.0)	44.5 (45.7)	44.5 (44.0)	47.4 (53.2)
V3	30.7 (46.9)	28.9 (47.3)	31.8 (106)	NA	NA	NA
Proportional intraindividual error (%)	29.4 (15.4)	29.4 (15.9)	29.0 (15.5)	27.9 (19.8)	31.9 (14.9)	27.5 (11.0)

a The data are expressed as mean [%CV] unless specified otherwise.
b $CL_i = CL_{70\,kg} \times (TBW/70)^z$.
CL = clearance from the central compartment; $CL_{70\,kg}$ *= population mean CL value in an individual weighing 70 kg;* CL_i *= CL in the* i^{th} *individual; CV = coefficient of variation; NA = not applicable; OFV = objective function value; Q2 = inter-compartmental clearance from the central compartment to the first peripheral compartment; Q3 = inter-compartmental clearance from the central compartment to the second peripheral compartment; TBW = total body weight; V1 = volume of distribution of the central compartment; V2 = volume of distribution of the first peripheral compartment; V3 = volume of distribution of the second peripheral compartment; z = allometric scaling factor in* $CL_i = CL_{70\,kg} \times (TBW/70)^z$.

Table IV *Population pharmacodynamic parameters for the one compartment effect-site model and two compartment biophase distribution model for propofol induced changes of the Bispectral index during induction, maintenance of and emergence from anesthesia in morbidly obese patients.*

Parameter	One-compartment effect-site model[a]	Final two-compartment biophase-distribution model[a]	Bootstrap final model[a]
E_o (value)	92.0 (1.0)	92.2 (1.0)	92.1 (1.0)
E_{max} (value)	60.3 (4.4)	62.1 (4.3)	62.1 (4.2)
EC_{50} (mg/L)	2.11 (4.6)	2.12 (4.6)	2.09 (5.1)
γ	6.63 (18.6)	8.76 (19.9)	9.16 (9.2)
k_{eo} (min^{-1})	0.089 (8.5)	0.095 (9.0)	0.097 (12.4)
k_{e12} (min^{-1})	-	0.050 (21.5)	0.050 (21.5)
k_{e21} (min^{-1})	-	0.049 (17.5)	0.047 (19.6)
OFV	9879	9712	9700
Interindividual variability (%)			
k_{eo}	39.7 (30.3)	36.6 (26.0)	46.8 (141)
EC_{50}	20.4 (33.6)	20.1 (36.4)	20.1 (39.0)
E_{max}	7.84 (27.6)	9.22 (43.6)	9.08 (40.5)
Proportional intraindividual error (%)	15.5 (9.75)	14.7 (11.4)	14.7 (12.0)

a The data are expressed as mean [%CV] unless specified otherwise.
γ = Hill coefficient; BIS = bispectral index; CV = coefficient of variation; E_o *= baseline BIS;* EC_{50} *= propofol concentration at half-maximum effect;* E_{max} *= maximum possible effect;* k_{e12} *= rate constant from the central to the peripheral effect-site compartment;* k_{e21} *= rate constant from the peripheral to the central effect-site compartment;* k_{eo} *= first-order equilibrium rate constant between plasma and the effect-site compartment; NA = not applicable; OFV= objective function value.*

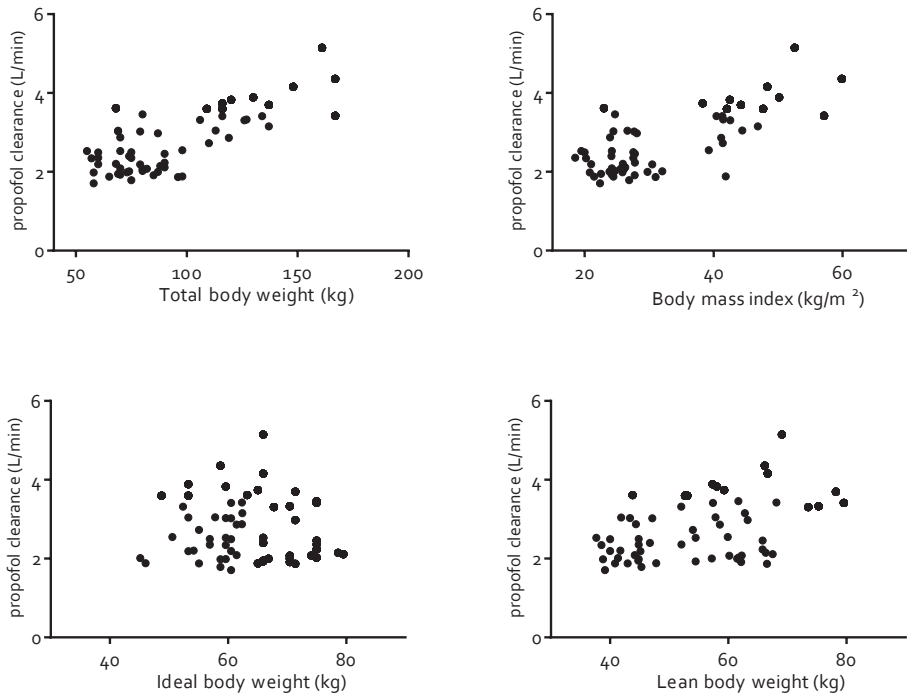


Figure 3 *Individual propofol clearance values versus TBW, BMI, IBW and LBW for the simple three-compartment pharmacokinetic model in 20 morbidly obese patients and 40 lean patients (n = 60). BMI = body mass index; TBW = total body weight; IBW = ideal body weight; LBW = lean body weight.*

estimated to be 0.67. Final diagnostic plots are shown in Figure 2C and 2D, and final pharmacokinetic parameter values are shown in Table III.
Bootstrap analysis of 250 replicates of the dataset of both the morbidly obese patients and the lean patients confirmed the stability of the model.

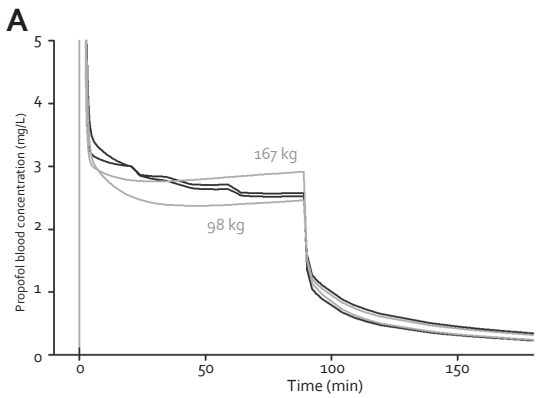
Pharmacodynamics
The pharmacodynamic dataset contained 2246 observed BIS values from the 20 morbidly obese patients. While a one-compartment effect-site model adequately described the BIS values over the time profiles of the patients, a two-compartment biophase-distribution model significantly improved the performance, which was reflected by a reduction in the OFV of 167 points ($p<0.001$). While the differences in concentrations in the central effect-site compartment are generally small during steady state, just after a rapid change in concentration in the central pharmacokinetic compartment, small changes can typically be observed in the conditional weighted residuals

versus time plots of the one-compartment effect-site model versus the two-compartment biophase-distribution model (data not shown). No covariates for the pharmacodynamics of propofol were found. Table IV shows the population parameters of the one-compartment effect-site model and the final two-compartment biophase-distribution model and the results of the bootstrap analysis of 250 replicates of the dataset of the 20 morbidly obese patients, confirming a stable E_{max} model. In Figure 2E and 2F, the diagnostics of the final pharmacodynamic model are shown.

Simulations
On the basis of the final pharmacokinetic and final pharmacodynamic model, simulations were performed aiming for BIS values between 40 and 60 for patients ranging in TBW between 98 and 167 kg. The results of the simulation exercise showed that, upon an induction dose of propofol 350 mg (12), the rate of the maintenance propofol infusion should be set to 7 mg/(70 kg * (TBW/70)$^{0.72}$)/h for 20 minutes, followed by 6.5 mg/(70 kg * (TBW/70)$^{0.72}$)/h for 20 minutes, 6 mg/(70 kg * (TBW/70)$^{0.72}$)/h during 20 minutes, and 5.5 mg/(70 kg * (TBW/70)$^{0.72}$)/h until the end of surgery, in order to achieve the desired BIS values. These BIS values can be expected provided that co-analgesia is achieved with remifentanil 25 µg/h times IBW (13) and predictive muscle relaxation is obtained using a continuous infusion of atracurium besilate.
Figure 4 shows blood propofol concentrations, propofol effect-site propofol concentrations and BIS values both with the model-based dosing regimen, as described above, and with a linear 5 mg/kg/h propofol dosing schedule in a 98 kg morbidly obese patient and in a 167 kg morbidly obese patient.

Discussion

In order to study the influence of morbid obesity on the pharmacokinetics and pharmacodynamics of propofol, a population pharmacokinetic-pharmacodynamic model was developed, in which clearance proved to scale with TBW, using an allometric function with an exponent of 0.72. While this allometric scaling factor of 0.72 in morbidly obese patients was fairly similar to the allometric scaling factor of 0.67 identified in both morbidly obese and lean patients, no other differences in pharmacokinetics or pharmacodynamics were identified.
It has been previously reported that variations in propofol clearance between patients are mainly influenced by TBW (6-7, 9). However, these studies evaluated only a limited number of obese (6-7) and morbidly obese patients (6-7, 9). In contrast to these findings, Han et al. suggested that LBW



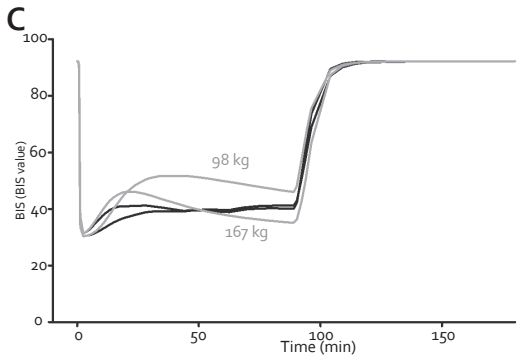


Figure 4 *Model-based predictions of blood propofol concentrations (A), effect-site propofol concentrations (B) and BIS values (C) upon a model-based dosing regimen (black lines) and a linear dosing regimen (grey lines) of propofol in a morbidly obese patient of 98 kg and a morbidly obese patient of 167 kg. The model-based dosing regimen consisted of an induction dose of propofol 350 mg, followed by 7 mg/(70kg * (TBW/70)$^{0.72}$)/h for the first 20 minutes, 6.5 mg/(70kg * (TBW/70)$^{0.72}$)/h for the following 20 minutes, 6 mg/(70kg * (TBW/70)$^{0.72}$)/h for the next 20 minutes, and 5.5 mg/(70kg * (TBW/70)$^{0.72}$)/h until the end of surgery. The linear dosing regimen consisted of an induction dose of propofol 350 mg, followed by 5 mg/kg/h throughout the entire procedure. BIS = Bispectral index; TBW = total body weight.*

is related to clearance of propofol and can therefore be used as a parameter for propofol dosing in obese patients (20). This suggestion was explored by McLeay et al. (8); however, their model was based on simulations and not supported by clinical data in (morbidly) obese patients. In our study in 20 morbidly obese patients and 40 lean patients, the patients' TBW, BMI, IBW and LBW were available and could be studied for their specific influence on any of the pharmacokinetic parameters. In morbidly obese patients, it was found that clearance correlated with TBW and BMI, with no significant difference between the two models in terms of the OFV. However, after analysing both the morbidly obese patient dataset and the lean patient dataset (range 55–167 kg), TBW proved to be superior to BMI as a covariate for clearance of propofol based on the basic goodness-of-fit plots together with the OFV (a decrease in the OFV of 3 points). As both Figure 3 and Table II demonstrate, IBW and LBW could not be identified as predictors of propofol clearance, despite the fact that there is great interest in LBW as a covariate for dosing based on theoretical principles (8, 20).

In morbidly obese patients, we found that the nature of the influence of TBW on clearance was best described by an allometric equation with an exponent of 0.72. This scaling factor was not significantly different from the scaling factor of 0.67 that we reported for the entire TBW range of lean and morbidly obese patients (55 - 167 kg). These results are in accordance with previously reported scaling factors of 0.71 in lean patients described by Schuttler et al. (7) and the fixed value of 0.75 in obese patients described by Cortinez et al. (9). More specifically, the clearance value of 2.22 L/min for a patient weighing 70 kg, as reported in our study, is in good agreement with the clearance of 2.25 L/min for a 70 kg person reported by Cortinez et al. (9). In our opinion, the nonlinearity in the relation between TBW and clearance is important to consider when dosing propofol in morbidly obese patients. In anaesthesia, medication is typically administered in milligrams per kilogram per hour, assuming a linear relation between TBW and clearance. While this dosing paradigm in milligrams per kilogram per hour may lead to overdosing in individuals at the upper TBW range, in this study we propose a nonlinear model-based dosing algorithm. Using this dosing regimen, the nonlinearity of the influence of TBW on clearance is accounted for and, as a result, a fixed dosing schedule (5.5–7 mg per (kg of TBW/70)$^{0.72}$ per hour) can be used for all patients ranging between 98 and 167 kg in TBW. While the proposed dosing regimen, together with the corresponding ABW, deserves further study in the TBW range that was included in this study (98–167 kg), it remains of interest to evaluate the extrapolation capacities of this function at higher TBW values than those that were included in the current study (e.g. >167 kg). It is emphasized that the proposed model-based dosing regimen is to be used in conjunction with full muscle relaxation and remifentanil co-

analgesia, as other co-medication may influence the pharmacokinetics and/or pharmacodynamics of propofol, resulting in lower or higher propofol infusion rates, despite the fact that the influence of TBW on propofol clearance remains the same.

Concerning the other pharmacokinetic parameters, there was a trend towards an increased V1 in morbidly obese patients compared with morbidly obese and lean patients together (4.52 L versus 3.03 L, respectively) (Table II). Previously, linear (6, 9) and allometric (7) relationships between TBW and the volume of distribution have been suggested. In our study, however, even though a large variability in individual values of the volume of distribution was found, incorporation of TBW as a covariate for the volume of distribution in the model did not result in significant improvement of the model according to the criteria described in the Methods section. It seems that larger datasets or different sampling schemes are needed to identify this influence or that factors other than TBW contribute to this large interindividual variability.

Besides the pharmacokinetics of propofol in morbidly obese patients we investigated the pharmacodynamics using the BIS as endpoint. As morbidly obese patients can be considered to suffer from chronic inflammation (21) and are reported to have a lower pain threshold (22), we hypothesized that differences in the pharmacodynamic effects of propofol in these patients compared with lean patients cannot be excluded. However, considering the pharmacodynamic parameters reported in morbidly obese patients in this study, it seems that the EC_{50} and k_{e0} are in accordance with previously reported pharmacodynamic parameters of propofol in lean patients (16, 23). We compared our results with literature values because no BIS data were available in our lean patients datasets for us to do a combined pharmacodynamic analysis on morbidly obese and lean patients. Instead, we studied the influence of TBW within the pharmacodynamic model of our morbidly obese patients, in which no significant covariates could be identified. On the basis of these results, and in the absence of other reports on the pharmacodynamic relation of propofol in morbidly obese patients, we conclude that there are no differences in sensitivity to the propofol effect, measured using the BIS, between lean and morbidly obese patients.

In the pharmacodynamic analysis, a two-compartment biophase-distribution model proved to be superior to a one-compartment effect-site model (a decrease in the OFV of 167 points). While a two-compartment biophase-distribution model has been previously reported for propofol in lean patients (23), plasma-effect-site equilibration is often assumed to be a mono-exponential first-order process (24). This assumption of a mono-exponential first-order process has been firmly adopted in pharmacokinetic and pharmacodynamic modelling, although it was reported as early as 1991 that this assumption appeared to be inadequate for amobarbital and alphaxalone and that a bi-exponential conductance function better described the data (25-26). An explanation for the two-compartment biophase-distribution function is re-distribution of the drug in the central nervous system. Although the differences between the two models are generally small during steady-state situations, just after a bolus injection and a large infusion rate change, differences between the models can be noted. As in to lean patients (23), a bi-exponential function was found to be superior to a one-compartment effect-site model in morbidly obese patients in this study.

The limitations of our study include the characteristics of the lean patient datasets, which were not fully comparable to those of the studied group of morbidly obese patients. One lean patient dataset was obtained in females receiving a single bolus dose of propofol and isoflurane for maintenance of anaesthesia (10), while the second lean patient dataset consisted of critically ill patients receiving a long-term infusion of propofol (11). Furthermore, our study in morbidly obese patients was performed during clinical practice, implying that substantial co-medication was given, which may have influenced the pharmacodynamic estimates. In particular, remifentanil and muscle relaxants are known to influence the pharmacodynamics of propofol, although the literature is conflicting on this issue (27-31). However, an advantage of this approach is that the resulting model-based dosing regimen can be used directly in clinical practice provided that the same anaesthetic protocol is applied. Another issue was the lack of external validation datasets. Furthermore, as a result of the BIS target of 40–60, a limited range of propofol concentrations and BIS values were obtained, resulting in under-studied BIS ranges, e.g. lower than 30. Further study is needed to describe the entire BIS range, although for clinical practice, the current dataset and derived model seems to be adequate.

On the basis of the results of the final pharmacokinetic and pharmacodynamic model of propofol in morbidly obese patients, a dosing schedule with specific rates in milligrams per kilogram per hour with use of an adjusted body weight ($70\ kg \times (TBW/70)^{0.72}$) for a surgical procedure aiming at BIS values between 40 and 60 was derived. An alternative strategy for propofol dosing is to target a specific propofol concentration, using TCI techniques. TCI anaesthesia is controlled by pharmacokinetic models that are based on lean patients, such as the Marsh model (32) and the Schnider model (33). By evaluation of the actual depth of anaesthesia at a specific target concentration by the anaesthesiologist, adjustment of the target concentration can be considered and entered into the TCI system. There are several reports on the performance of TCI in obese and morbidly obese patients. Cortinez et al. suggest that their model for obese patients leads to a performance that is similar to that of the Marsh model (9). Absalom et al. (34) warned that

for an excessive maintenance dose of propofol may be administered when LBW is used for TCI in morbidly obese patients using the Schnider model. Similarly, La Colla et al. (35) reported a clinically unacceptable performance bias with the use of TBW as input for the Marsh model and concluded that titration to target BIS values in morbidly obese patient remains necessary. While TCI can be considered an important approach to dose propofol for anaesthesia, it seems that TCI systems are not yet ready for this approach in morbidly obese patients. The results of this study can be used to fill this gap if implemented into the TCI system and tested in morbidly obese patients with TBW up to 170 kg, in conjunction with remifentanil analgesia. Until then, the dosing paradigm that has been derived from our final pharmacokinetic and pharmacodynamic model can be used to dose morbidly obese patients in clinical practice, with use of an adjusted TBW together with a specific infusion rate regimen, aiming for a BIS between 40 and 60.

Conclusion

A pharmacokinetic model for propofol in morbidly obese patients has been derived, with TBW as the major determinant of clearance, using an allometric function with an exponent of 0.72. No covariates for the other pharmacokinetic parameters were identified. The obtained BIS values in morbidly obese patients were described with a two-compartment biophase-distribution model, with a sigmoid E_{max} pharmacodynamic model without covariates.

References

1. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 2006 Apr 5;295(13):1549-55.
2. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009 Mar 28;373(9669):1083-96.
3. WorldHealthOrganisation. Obesity: Preventing and Managing the Global Epidemic. Geneva: World Health Organisation1997.
4. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. Clin Pharmacokinet. 2000 Sep;39(3):215-31.
5. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet. 2010;49(2):71-87.
6. Servin F, Farinotti R, Haberer JP, et al. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. Anesthesiology. 1993 Apr;78(4):657-65.
7. Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. Anesthesiology. 2000 Mar;92(3):727-38.
8. McLeay SC, Morrish GA, Kirkpatrick CM, et al. Encouraging the move towards predictive population models for the obese using propofol as a motivating example. Pharm Res. 2009 Jul;26(7):1626-34.
9. Cortinez LI, Anderson BJ, Penna A, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth. 2010 Oct;105(4):448-56.
10. Knibbe CA, Voortman HJ, Aarts LP, et al. Pharmacokinetics, induction of anaesthesia and safety characteristics of propofol 6% SAZN vs propofol 1% SAZN and Diprivan-10 after bolus injection. Br J Clin Pharmacol. 1999 Jun;47(6):653-60.
11. Knibbe CA, Zuideveld KP, DeJongh J, et al. Population pharmacokinetic and pharmacodynamic modeling of propofol for long-term sedation in critically ill patients: a comparison between propofol 6% and propofol 1%. Clin Pharmacol Ther. 2002 Dec;72(6):670-84.
12. van Kralingen S, Diepstraten J, van de Garde EM, et al. Comparative evaluation of propofol 350 and 200 mg for induction of anaesthesia in morbidly obese patients: a randomized double-blind pilot study. Eur J Anaesthesiol. 2010 Jun;27(6):572-4.
13. Egan TD, Huizinga B, Gupta SK, et al. Remifentanil pharmacokinetics in obese versus lean patients. Anesthesiology. 1998 Sep;89(3):562-73.
14. Knibbe CA, Koster VS, Deneer VH, et al. Determination of propofol in low-volume samples by high-performance liquid chromatography with fluorescence detection. J Chromatogr B Biomed Sci Appl. 1998 Mar 20;706(2):305-10.
15. Beal SL, Sheiner LB, Boeckmann A. NONMEM user's guide. San Francisco (CA): University of California; 1999.
16. Struys MM, Coppens MJ, De Neve N, et al. Influence of administration rate on propofol plasma-effect site equilibration. Anesthesiology. 2007 Sep;107(3):386-96.
17. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000 Sep;34(9):1066-9.
18. Janmahasatian S, Duffull SB, Ash S, et al. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
19. van Kralingen S, van de Garde EM, van Dongen EP, et al. Maintenance of anesthesia in morbidly obese patients using propofol with continuous BIS-monitoring: a comparison of propofol-remifentanil and propofol-epidural anesthesia. Acta Anaesthesiol Belg. 2011;62(2):73-82.
20. Han PY, Duffull SB, Kirkpatrick CM, et al. Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther. 2007 Nov;82(5):505-8.
21. Mathieu P, Lemieux I, Despres JP. Obesity, inflammation, and cardiovascular risk. Clin Pharmacol Ther. 2010 Apr;87(4):407-16.
22. Lloret Linares C, Decleves X, Oppert JM, et al. Pharmacology of morphine in obese patients: clinical implications. Clin Pharmacokinet. 2009;48(10):635-51.
23. Bjornsson MA, Norberg A, Kalman S, et al. A two-compartment effect site model describes the bispectral index after different rates of propofol infusion. J Pharmacokinet Pharmacodyn. 2010 Jun;37(3):243-55.
24. Sheiner LB, Stanski DR, Vozeh S, et al. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin Pharmacol Ther. 1979 Mar;25(3):358-71.
25. Mandema JW, Veng-Pedersen P, Danhof M. Estimation of amobarbital plasma-effect site equilibration kinetics. Relevance of polyexponential conductance functions. J Pharmacokinet Biopharm. 1991 Dec;19(6):617-34.
26. Visser SA, Smulders CJ, Reijers BP, et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling of concentration-dependent hysteresis and

biphasic electroencephalogram effects of alphaxalone in rats. J Pharmacol Exp Ther. 2002 Sep;302(3):1158-67.
27. Wang LP, McLoughlin P, Paech MJ, et al. Low and moderate remifentanil infusion rates do not alter target-controlled infusion propofol concentrations necessary to maintain anesthesia as assessed by bispectral index monitoring. Anesth Analg. 2007 Feb;104(2):325-31.
28. Ferreira DA, Nunes CS, Antunes LM, et al. The effect of a remifentanil bolus on the bispectral index of the EEG (BIS) in anaesthetized patients independently from intubation and surgical stimuli. Eur J Anaesthesiol. 2006 Apr;23(4):305-10.
29. Bouillon TW, Bruhn J, Radulescu L, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology. 2004 Jun;100(6):1353-72.
30. Liu N, Chazot T, Huybrechts I, et al. The influence of a muscle relaxant bolus on bispectral and datex-ohmeda entropy values during propofol-remifentanil induced loss of consciousness. Anesth Analg. 2005 Dec;101(6):1713-8.
31. Bonhomme V, Hans P. Muscle relaxation and depth of anaesthesia: where is the missing link? Br J Anaesth. 2007 Oct;99(4):456-60.
32. Marsh B, White M, Morton N, et al. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth. 1991 Jul;67(1):41-8.
33. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology. 1998 May;88(5):1170-82.
34. Absalom AR, Mani V, De Smet T, et al. Pharmacokinetic models for propofol--defining and illuminating the devil in the detail. Br J Anaesth. 2009 Jul;103(1):26-37.
35. La Colla L, Albertin A, La Colla G, et al. No adjustment vs. adjustment formula as input weight for propofol target-controlled infusion in morbidly obese patients. Eur J Anaesthesiol. 2009 May;26(5):362-9.

Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients receiving propofol-remifentanil or propofol-epidural anaesthesia

04

Jeroen Diepstraten, Simone van Kralingen, Vera H.M. Deneer, Bert van Ramshorst, Eric P.A. van Dongen, Catherijne A.J. Knibbe

Abstract

Reports on the influence of perioperative remifentanil on population pharmacokinetic and pharmacodynamics parameters of propofol are conflicting and for morbidly obese patients unexplored. In the current study we developed a population pharmacokinetic and pharmacodynamic model of propofol in twenty-six morbidly obese patients receiving propofol-remifentanil anaesthesia or propofol-epidural anaesthesia. Remifentanil was neither a covariate for the pharmacokinetic nor the pharmacodynamic parameters of propofol using the BIS as pharmacodynamics endpoint. In the final model, total body weight was a significant covariate for propofol clearance. These results suggest that there are no differences in the pharmacokinetic or pharmacodynamic parameters of propofol in morbidly obese patients receiving maintenance propofol-remifentanil or propofol-epidural anaesthesia when the BIS is used a pharmacodynamic endpoint.

Background

The dramatic increase in obesity rates across the world has augmented the obese population presenting for anaesthesia for various surgical procedures (1). Different strategies have been described for the complex anaesthesia of an obese patient. Most commonly, propofol in combination with remifentanil is used in morbidly obese patients. Alternatively, propofol anaesthesia can be combined with epidural analgesia. We reported before a pharmacokinetic-pharmacodynamic (PK-PD) model based dosing algorithm for propofol in combination with remifentanil in morbidly obese patients (2). Besides, we reported no difference in propofol maintenance dose between propofol-remifentanil anaesthesia and propofol-epidural anaesthesia in morbidly obese patients when aiming for stable Bispectral index and hemodynamic values (3). For non-obese patients, results studying the influence of remifentanil on propofol requirements are conflicting. No propofol infusion adjustments were reported when propofol was combined with remifentanil and dosing was based on target BIS values (4). In contrast, lower propofol concentrations were needed during laryngoscopy when propofol was combined with remifentanil in non-obese healthy volunteers (5). While changes in propofol dose may be caused by both PK and PD parameters, there are no studies on the influence of remifentanil on the separate PK and PD parameters of propofol in morbidly obese patients during surgery. Therefore, our aim was to develop a population PK-PD model of propofol in morbidly obese patients receiving maintenance of anaesthesia with propofol-remifentanil or with propofol-epidural anaesthesia. Bispectral index (BIS) values were used as PD endpoint.

Methods

Previously published data of a total of twenty-six morbidly obese patients scheduled to undergo bariatric surgery were used for this analysis (2, 3). Both the original study protocols were approved by the hospitals Ethics Committee and written informed consent was signed by each participating patient.

Before induction, an antecubital infusion line, an indwelling arterial blood pressure line and a 3-lead ECG were installed and a Bispectral index electrode was placed on the patient's forehead.

Twenty morbidly obese patients (group I) received either a propofol induction dose of 200 mg or 350 mg followed by an initial maintenance propofol infusion of 10 mg/kg times total body weight. Remifentanil was administrated 25 µg/h/kg based on ideal body weight (6). In six morbidly obese patients (group II), an epidural catheter was placed and anaesthesia was induced with a propofol bolus dose of 350 mg and maintained with a continuous infusion of propofol and epidural analgesia 8 ml/h of bupivacain 0.125% with 1 µg/ml sufentanil. In this group, propofol maintenance infusion was initiated at 5 mg/kg times total body weight. In both groups, propofol infusion rate was subsequently adjusted in order to keep BIS values between 40 and 60, the systolic arterial blood pressure between 80 and 160 mmHg and heart rate between 60 and 90 beats per minute (3). Whole-blood samples were collected on a regular basis for propofol analysis, mixed thoroughly and stored at 4°C until analysis by high-performance liquid chromatography with fluorescence detection at 276 nm and 310 nm (7).

Data analysis was performed by means of non-linear mixed-effects modeling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD) (8) with S-plus (version 6.2; Insightful software, Seattle, WA) to visualize the data. Population pharmacokinetic (PK) and pharmacodynamic (PD) data were sequentially analysed by using the individual PK empirical Bayes estimates as an input to the pharmacodynamic model, and with use of a previously reported PK-PD model for propofol in morbidly obese patients (2). For the covariate analysis, a $p< 0.005$ was applied to evaluate the covariates in the forward inclusion (OFV decrease >7.9), while the backward deletion procedure used a stricter criterion (OFV decrease >10.8; $p<0.001$).

Results

Data of twenty-six morbidly obese patients were analysed (Table I). A three-compartment pharmacokinetic (PK) model adequately described the time course of the propofol whole blood concentrations in morbidly obese patients receiving either propofol-remifentanil or propofol-epidural anaesthesia (Figure 1). Total body weight was a major determinant for clearance (CL), reducing the objective function value with 18 points ($p<0.005$). The relationship was expressed using an allometric function $CL_i = CL_{70\ kg} \bullet (TBW_i/70)^{0.87}$ where CL_i represents clearance in the ith individual, $CL_{70\ kg}$ is the population mean value for clearance in an individual of 70 kg, TBW_i is the total body weight of the ith individual, and 70 is the standard total body weight in kilograms. No differences in mean PK parameters of propofol between patients receiving either propofol-remifentanil or propofol-epidural anaesthesia were observed as shown in Figure 2. Separate

Table I *Baseline characteristics of twenty morbidly obese patients receiving propofol-remifentanil (group I) and six morbidly obese patient receiving propofol-epidural (group II) for maintenance of anaesthesia. Data are presented as mean with standard deviation (SD).*

	Group I Propofol-Remifentanil Mean (SD)	Group II Propofol-Epidural Mean (SD)
Number	20	6
Gender (M / F)	4/16	1/5
Age (years)	45 (12)	41 (9)
Total body weight (kg)	124 (20)	145 (28)
Ideal body weight (kg)	61 (7)	65 (6)
Body mass index (kg/m²)	43 (6)	49 (9)
Lean body weight (kg) (19)	60 (9)	66 (10)

M = male; F = female.

estimation of volume of distribution or clearance for each of the two groups did not result in improved performance of the model.
The measured BIS values over time in the 26 morbidly obese patients were adequately described with a two-compartment biophase distribution model with a sigmoid E_{max} pharmacodynamic (PD) model for both regimens (Figure 1). Separate estimation of the PD parameters for each of the two groups did not result in improved performance of the model. Tested covariates did not significantly improve the PD model of propofol in morbidly obese patients. Figure 3 illustrates that there is no significant difference in mean PD parameters EC_{50}, k_{eo} and E_{max} of the groups receiving propofol-remifentanil and propofol-epidural anaesthesia.

Discussion

In our study in morbidly obese patients undergoing bariatric surgery, no differences in pharmacokinetic (PK) and pharmacodynamic (PD) parameters of propofol when combined with remifentanil or epidural anaesthesia were observed using BIS values as PD endpoint.

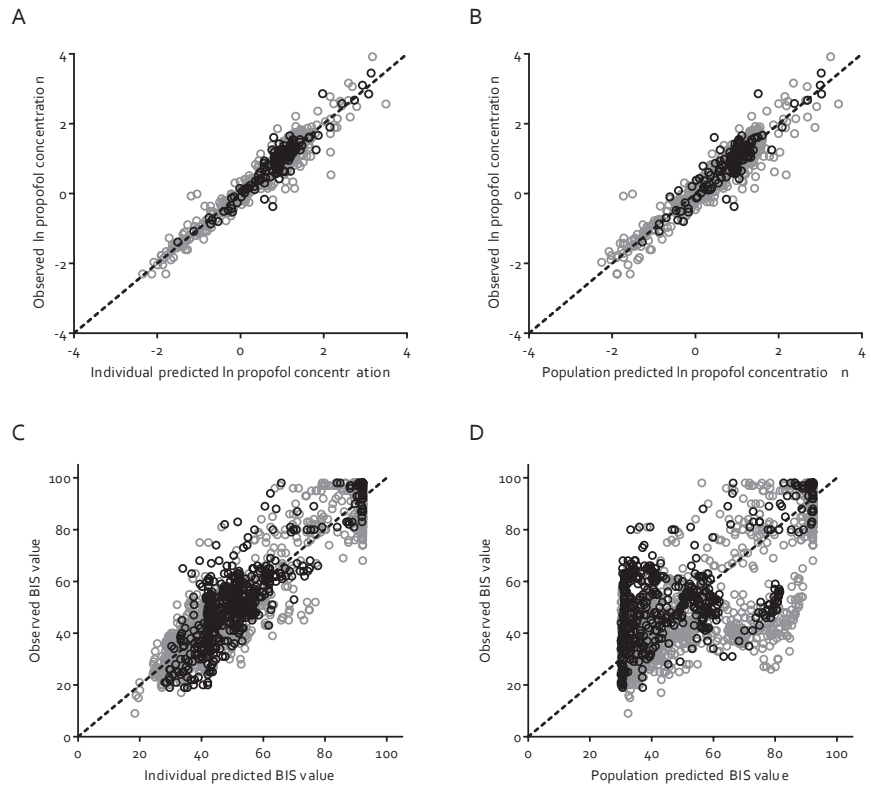


Figure 1 *Diagnostic plots for propofol pharmacokinetics (A and B) and pharmacodynamics (C and D) in morbidly patients showing individual (A and C) and population (B and D) model predictions versus observed values for final models. Morbidly obese patients receiving propofol-remifentanil anaesthesia are represented with grey open rounds and morbidly obese patients receiving propofol-epidural anaesthesia are represented with black open rounds. The dashed line represents the line of identity, x=y.*

Morbidly obese patients are at increased risk for complications during anaesthesia due to difficult intubation, positioning and diverse co-morbidities (9). Therefore, there is a need to understand the influence of excessive body weight on the PK and PD of drugs. The effect of epidural analgesia on propofol anaesthesia is rather unknown, although it cannot be excluded that epidural analgesia has a hypnotic effect (10, 11). Previously we reported no differences between propofol infusion rates and propofol concentrations when propofol dosing was based on BIS values and hemodynamic parameters in combination with remifentanil or epidural analgesia in morbidly obese patients (3). However, in non-obese patients there is debate about the influence of remifentanil on the PK of propofol and on BIS values as the effect of remifentanil is mostly evaluated in patients

with BIS values around 60 without surgical stimuli. In a study in non-obese patients, remifentanil was not found to influence the PK of propofol (12). However, the combination resulted in a reduction of BIS values during induction of anaesthesia (13, 14) and reduced propofol concentrations during extubation with the return of consciousness in a synergistic manner (15). Besides, adding remifentanil to low propofol infusion rates resulted in lower BIS values (16). In addition, lower BIS values for patients receiving higher remifentanil target concentrations were observed (17). In contrast, maintenance propofol infusion rates were not adjusted when propofol was combined with remifentanil (4) and varying the remifentanil effect-site concentration showed not to effect BIS values during target-controlled propofol infusion in non-obese patients (18). While the small sample size of patients receiving propofol-epidural anaesthesia is a limitation of the current study, our findings in morbidly obese patients are in accordance with the results in non-obese patients.

In conclusion, the present study in morbidly obese patients suggests that there are no differences in the population PK and PD parameters of propofol when combined with remifentanil or epidural anaesthesia during bariatric surgery. More data from morbidly obese patients receiving propofol-epidural anaesthesia are warranted to confirm the present results.

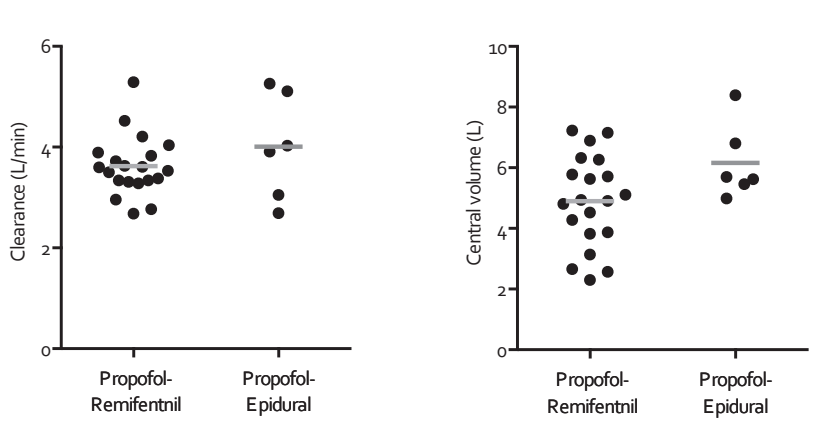


Figure 2 *Mean values (grey line) and empirical Bayes estimates for the pharmacokinetic parameters clearance (left panel) and central volume of distribution (right panel) of propofol in morbidly obese patients receiving propofol-remifentanil (n=20) or propofol-epidural anaesthesia (n=6).*

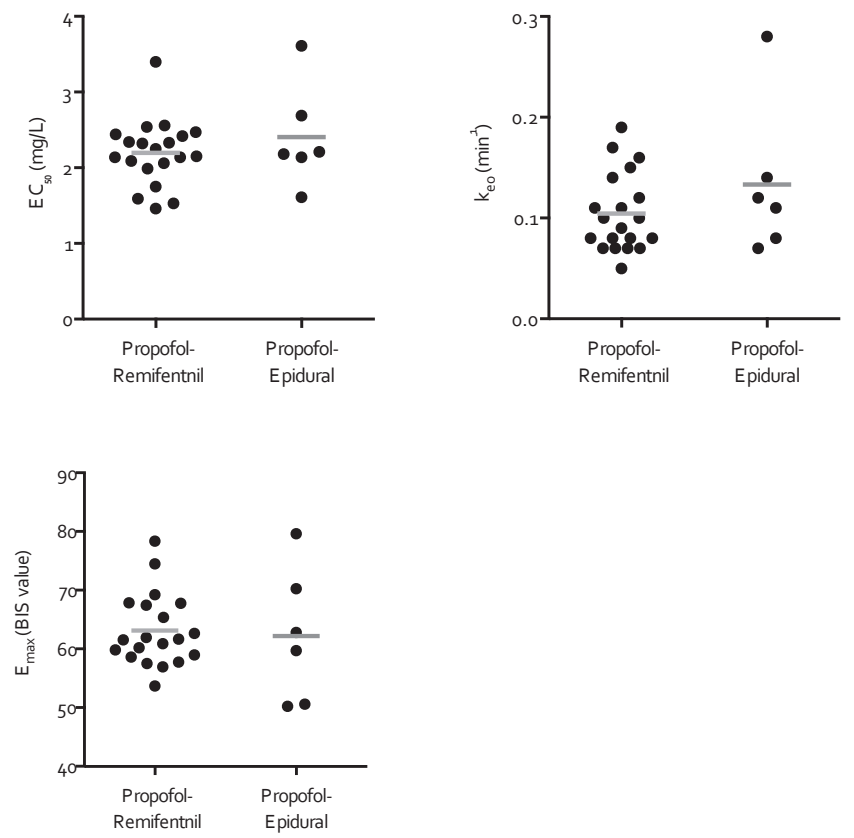


Figure 3 *Mean values (grey line) and empirical Bayes estimates for the pharmacodynamic parameters EC_{50}, k_{eo} and E_{max} of propofol in morbidly obese patients receiving propofol-remifentanil (n=20) or propofol-epidural anaesthesia (n=6).*

References

1.Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. Jama. 2012;307(5):491-7.

2.van Kralingen S, Diepstraten J, Peeters MY, Deneer VH, van Ramshorst B, Wiezer RJ, et al. Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. Clin Pharmacokinet. 2011;50(11):739-50.

3.van Kralingen S, van de Garde EM, van Dongen EP, Diepstraten J, Deneer VH, van Ramshorst B, et al. Maintenance of anesthesia in morbidly obese patients using propofol with continuous BIS-monitoring: a comparison of propofol-remifentanil and propofol-epidural anesthesia. Acta Anaesthesiol Belg. 2011;62(2):73-82.

4.Wang LP, McLoughlin P, Paech MJ, Kurowski I, Brandon EL. Low and moderate remifentanil infusion rates do not alter target-controlled infusion propofol concentrations necessary to maintain anesthesia as assessed by bispectral index monitoring. Anesth Analg. 2007;104(2):325-31.

5.Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology. 2004;100(6):1353-72.

6.Egan TD, Huizinga B, Gupta SK, Jaarsma RL, Sperry RJ, Yee JB, et al. Remifentanil pharmacokinetics in obese versus lean patients. Anesthesiology. 1998;89(3):562-73.

7.Knibbe CA, Koster VS, Deneer VH, Stuurman RM, Kuks PF, Lange R. Determination of propofol in low-volume samples by high-performance liquid chromatography with fluorescence detection. J Chromatogr B Biomed Sci Appl. 1998;706(2):305-10.

8.Beal SL, Sheiner LB, Boeckmann A. NONMEM user's guide. San Francisco: University of California; 1999.

9.Sinha AC. Some anesthetic aspects of morbid obesity. Curr Opin Anaesthesiol. 2009;22(3):442-6.

10.Tverskoy M, Shifrin V, Finger J, Fleyshman G, Kissin I. Effect of epidural bupivacaine block on midazolam hypnotic requirements. Reg Anesth. 1996;21(3):209-13.

11.Morley AP, Chung DC, Wong AS, Short TG. The sedative and electroencephalographic effects of regional anaesthesia. Anaesthesia. 2000;55(9):864-9.

12.Bouillon T, Bruhn J, Radu-Radulescu L, Bertaccini E, Park S, Shafer S. Non-steady state analysis of the pharmacokinetic interaction between propofol and remifentanil. Anesthesiology. 2002;97(6):1350-62.

13.Ferreira DA, Nunes CS, Antunes LM, Santos IA, Lobo F, Casal M, et al. The effect of a remifentanil bolus on the bispectral index of the EEG (BIS) in anaesthetized patients independently from intubation and surgical stimuli. Eur J Anaesthesiol. 2006;23(4):305-10.

14.Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E. Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth. 2001;86(4):523-7. Epub 2001/09/28.

15.Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J. Propofol reduces perioperative remifentanil requirements in a synergistic manner: response surface modeling of perioperative remifentanil-propofol interactions. Anesthesiology. 2003;99(2):347-59.

16.Strachan AN, Edwards ND. Randomized placebo-controlled trial to assess the effect of remifentanil and propofol on bispectral index and sedation. Br J Anaesth. 2000;84(4):489-90.

17.Koitabashi T, Johansen JW, Sebel PS. Remifentanil dose/electroencephalogram bispectral response during combined propofol/regional anesthesia. Anesth Analg. 2002;94(6):1530-3, table of contents.

18.Guignard B, Menigaux C, Dupont X, Fletcher D, Chauvin M. The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesth Analg. 2000;90(1):161-7.

19.Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000;34(9):1066-9.

Prospective clinical evaluation of a model-based dosing regimen for propofol anaesthesia in morbidly obese patients

05

Jeroen Diepstraten, Christine J. van Sasse van Ysselt, Simone van Kralingen, Ewoudt M.W. van de Garde, Bart A. van Wagensveld, Bert van Ramshorst, Catherijne A.J. Knibbe, Eric P.A. van Dongen

Ready to submit

Abstract

Background
In pharmacokinetic-pharmacodynamic (PK-PD) models for morbidly obese patients, total body weight (TBW) has been reported the best size descriptor for propofol clearance using an allometric function. Most recently, a nonlinear total body weight-based dosing algorithm for maintenance of anaesthesia with propofol was developed aiming for Bispectral index (BIS) values of 40 ± 10 in morbidly obese patients with varying body weights. The present study aims at evaluating this algorithm prospectively in a clinical setting.
Methods
After induction of anaesthesia, propofol maintenance dose was started at 7 mg/kg ABW/h (ABW = adjusted total body weight = 70kg * (TBW/70)$^{0.72}$) in combination with remifentanil. BIS values, haemodynamic parameters and the number of the propofol infusion adjustments were recorded for each patient. Observed BIS values were compared with BIS values predicted by the previously published PK-PD model for propofol in morbidly obese patients.
Results
Fifty-one morbidly obese patients were included in this prospective study with a mean total body weight of 134 kg (range 95 – 210 kg). During maintenance of anaesthesia, sixty-eight percent of the observed BIS values were within the target range of 40 ± 10. Except during the first 20 minutes after induction of anaesthesia, blood pressure and heart rate were within predefined ranges. Mean difference in propofol maintenance infusion rates was -0.43 mg/min (95%CI -0.49 – -0.36) compared to the proposed model-based infusion rates. Observed BIS values were predicted without bias and with accurate precision by the previously published population PK-PD model.
Conclusion
Stable and effective maintenance of anaesthesia was achieved using the PK-PD model-derived propofol dosing algorithm in morbidly obese patients with total body weights varying between 95 and 210 kg.

Introduction

The rise in prevalence of obesity leads to a growing number of obese patients that are treated by health care services for a variety of concomitant diseases (1-2). Because morbidly obese patients have an altered body composition, are prone to desaturation and have an altered cardiovascular state (3-4), safe and effective anaesthesia of morbidly obese individuals remains a challenge (5-6). To date, the number of studies that is available to define the optimal dose for anaesthesia for each individual (morbidly) obese patient is still limited.

Propofol is widely used for maintenance of anaesthesia in both non-obese and morbidly obese patients albeit at a variety of dosing regimens (7). In two recent population pharmacokinetic-pharmacodynamic (PK-PD) models for morbidly obese patients, it was reported that total body weight (TBW) is the best size descriptor for propofol clearance when parameterised with an allometric function (8-9). Besides, no influence of body weight on the pharmacodynamics of propofol using Bispectral index (BIS) values in morbidly obese patients was found (8). Based on this population PK-PD model, it was proposed to dose propofol maintenance infusion in morbidly obese patients on an adjusted total body weight (ABW = 70kg * $(TBW/70)^{0.72}$) in order to obtain Bispectral index (BIS) values of 40 ± 10 across the entire heterogeneous population of morbidly obese patients (8).

Before this model-based dosing algorithm can be widely implemented in clinical practice, it is of interest to evaluate in a prospective clinical study whether the new PK-PD model derived dosing algorithm results in safe and effective anaesthesia in morbidly obese patients. Therefore, the aim of the present study was to prospectively evaluate the PK-PD model-based propofol maintenance dosing algorithm (8) in morbidly obese patients undergoing laparoscopic bariatric surgery in terms of BIS values and haemodynamic parameters. In addition, observed propofol infusion rates aiming for a BIS target of 40 ± 10 were compared with the proposed model-based dosing scheme and observed BIS values were compared to BIS values predicted by the previously published PK-PD model of propofol in morbidly obese patients (8).

Methods

Patients

Morbidly obese patients undergoing laparoscopic bariatric surgery were included in this prospective study in two large teaching hospitals (26 patients in Nieuwegein and 25 patients in Amsterdam). Patients were enrolled in the study if their age was between 18 and 60 years, they had an American Society of Anesthesiologists (ASA) physical status classification of II or III and their BMI was over 40 kg/m^2 at the day of inclusion. Exclusion criteria included epilepsy, pregnancy, breastfeeding and known allergy to propofol, soy bean oil or egg lecithin. The hospital ethics committees of both hospitals approved the study protocol and waived the need for informed consent as the dosing algorithm based on the previously published pharmacokinetic-pharmacodynamic (PK-PD) model (8) was considered best standard of care in these hospitals.

Anaesthetic and study procedure

Anaesthesia was standardized according to the previous study in which the model-based dosing algorithm for propofol was developed (8) and was repeated as relevant for this study. Before induction of anaesthesia, an antecubital infusion line was installed, a BIS electrode was placed on the patient's forehead and a sphygmomanometer was placed on the patients' upper arm. Unpremedicated patients received a bolus injection of 350 mg of propofol given over 60 seconds for induction of anaesthesia followed by atracurium besilate or rocuronium 50 mg and fentanyl 250 mcg (10). Thereafter, the trachea was intubated and mechanical ventilation was initiated by the anaesthesiologist. Arterial oxygen saturation and end-tidal carbon dioxide were monitored throughout the procedure. The surgical position of all patients was the anti-Trendelenburg position. Anaesthesia was maintained with propofol according to the dosing algorithm that was previously developed based on a PK-PD model in morbidly obese patients (8). For this dosing algorithm an adjusted body weight was calculated for each patient (Equation 1) (8):

Adjusted body weight (ABW) = 70kg * $(TBW/70)^{0.72}$ (Eq. 1)

According to this dosing algorithm, from 3 minutes after induction of anaesthesia onwards, the initial infusion rate of propofol was set on 7 mg/kg ABW/h for 20 minutes, followed by 6.5 mg/kg ABW/h for 20 minutes, 6 mg/kg ABW/h for 20 minutes, and 5.5 mg/kg ABW/h until the end of surgery.

Appendix 1 shows the propofol infusion rates across different time frames of anaesthesia for different total body weights.
The propofol infusion rate as initiated based on Table II could be adjusted by the attending anaesthesiologist in order to obtain a BIS value of 40 ± 10, blood pressure within ± 30% of baseline values and heart rate between 60 – 90 beats/min. Adjustments in propofol infusion rates were made with 50 – 150 mg/h at the discretion of the attending anaesthesiologist, and with preferably no more than one infusion rate adjustment per five minutes. Propofol infusion rates were increased if BIS values and haemodynamic parameters were higher than the predefined values. When BIS values and haemodynamic parameters were lower than the predefined values, propofol infusion rate was decreased. When haemodynamic parameters were lower than the predefined values and BIS values were higher or equal to the predefined range, medication to improve the haemodynamic parameters was administered and the propofol infusion rate was adjusted to bring BIS values within the predefined range. When haemodynamic parameters were higher than the predefined range and BIS value were lower than or within the predefined range, signs of inadequate anaesthesia were checked. When adequate anaesthesia was confirmed, medication to correct haemodynamics was administered. If there were signs of inadequate anaesthesia, the propofol infusion rate was adjusted (8).
During the procedure, remifentanil was dosed 25 mcg/kg/h based on ideal body weight (IBW) (11). The remifentanil infusion rate was kept constant, if possible, in order to rule out influence of remifentanil on haemodynamic parameters and BIS values. If necessary, remifentanil infusion rate adjustments could be made at the discretion of the attending anaesthesiologist. Additional fentanyl bolus doses could be administered if needed throughout the surgical procedure as judged by the attending anaesthesiologist. About 30 minutes before the anticipated end of the surgical procedure, morphine 10 mg was administered.

Descriptive data analysis
The SPSS statistical package (version 19.0 for Windows; IBM) was used for these analyses. Continuous data are expressed as the mean ± SD or as median (interquartile range) where appropriate. Observed BIS values during propofol infusion, systolic arterial blood pressure and heart rate were averaged within 5 minute time intervals for each patient. Based on these data, box plots were constructed indicating median, interquartile rage and 95% confidence intervals. The actual propofol infusion rates were subtracted from predefined infusion rates at one minute time intervals for all patients. If at any time interval from less than 75% of the patients data were available, this is indicated in the figures. In all figures time-point 0 indicates the induction of anaesthesia.

Comparison of observed BIS values with model-based predicted BIS values
Non-linear mixed-effects modeling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD, USA) with S-Plus (version 6.2; Insightful Software, Seattle, WA, USA) was used to obtain model-based BIS predictions. These model-based BIS predictions were generated for each of the participating patient on the basis of their total body weight and actual administrated propofol doses during the entire procedure using the previously published PK-PD model for propofol in morbidly obese patients (8). In predicted versus observed plot, the observed BIS values were visually compared to the individual BIS value predictions by the model. For each patient and for each BIS observation, a prediction error (PE) was calculated from which median performance error (MDPE) and the median absolute performance error (MDAPE) were calculated (Equation 2, 3 and 4) (12):

Prediction error (PE) at the j^{th} BIS observed of subject i:
$PE_{ij} = BIS_{observed} - BIS_{predicted}$ (Eq. 2)

The median PE (MDPE): MDPE reflects the bias of BIS in the i^{th} subject:
$MDPE_i$ (BIS values) = median $[PE_{ij}, j = 1, \ldots, N_i]$ (Eq. 3)

The median absolute PE (MDAPE): MDAPE indicates the BIS precision in the i^{th} subject:
$MDAPE_i$ (BIS values) = median $[|PE_{ij}|, j = 1, \ldots, N_i]$ (Eq. 4)

Results

Patients and data
A total of 51 morbidly obese patients with a mean total body weight of 134 kg (range 95 – 210 kg) and mean BMI of 45 kg/m² (range 35 – 56 kg/m²) were enrolled in this study. All demographic characteristics of all patients are provided in Table I. Clinical data of the patients are presented until 75 minutes after propofol induction dose administration, as at that time point surgery had been completed in more than 25% of the patients. In five patients, propofol infusion for maintenance of anaesthesia was started 1 minute earlier than the proposed 3 minutes after the induction dose.

Table I *Baseline characteristics of 51 morbidly obese patients. Data are presented as mean with standard deviation (SD) and associated range.*

	Mean (SD)	Range
Sex (Male / Female)	18 / 33	-
Age (years)	45 (8.3)	22.0 – 63.0
TBW (kg)	134 (22.6)	95.0 – 210.0
BMI (kg/m²)	45 (5.6)	34.9 – 56.3
LBW (kg)	68 (13.7)	47.6 – 104.6
IBW (kg)	65 (11.4)	44.2 – 88.6
ABW (kg)	111 (13.7)	87.0 – 154.0
Duration of surgery (min)	74.1 (24.9)	40.0 – 158.0
Duration of anaesthesia (min)	89.3 (24.5)	51.0 – 176.0
Time between start of propofol infusion – start surgery (min)*	10.3 (4.0)	0.0 – 19.0
Time between stop of propofol infusion – extubation (min)	12.4 (5.8)	3.0 – 32.0
Time between end of surgery – extubation (min)**	14.6 (6.5)	7.0 – 33.0
Time between intubation – extubation (min)	97.0 (27.4)	30.0 – 189.0

** = data available of 70.6% of the patients*
*** = data available of 66.7% of the patients*
*TBW= total body weight, BMI= body mass index, LBW= lean body weight (19), IBW= ideal body weight (25), ABW= adjusted body weight (= 70kg * (TBW/70)$^{0.72}$).*

Anaesthesia

Figure 1 shows the median observed BIS values and interquartile ranges of the 51 morbidly obese patients during anaesthesia. It is shown that median and interquartile ranges were within the target BIS range of 40 ± 10 during anaesthesia from 5 until 75 minutes after induction of anaesthesia. In total, during this period 68% of the observed BIS values were within 40 ± 10.

Figure 2 shows mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) relative to baseline pressures measured at preoperative consultation over time. Overall, SBP and DBP dropped substantially during anaesthesia, particularly within the first 20 minutes after induction of anaesthesia. Afterwards, mean SBP and DBP stayed within the predefined target values of ± 30% from baseline values with average drops of 26% (95%CI 24-28) and 27% (95%CI 26-28) during period 5-75 minutes after induction of anaesthesia, respectively. Figure 2 shows that mean heart rate values were within the predefined range of 60 – 90 beats/min during the whole observation period, even though, similar to blood pressure, heart rates dropped during the first 20 minutes after induction of anaesthesia. End-tidal

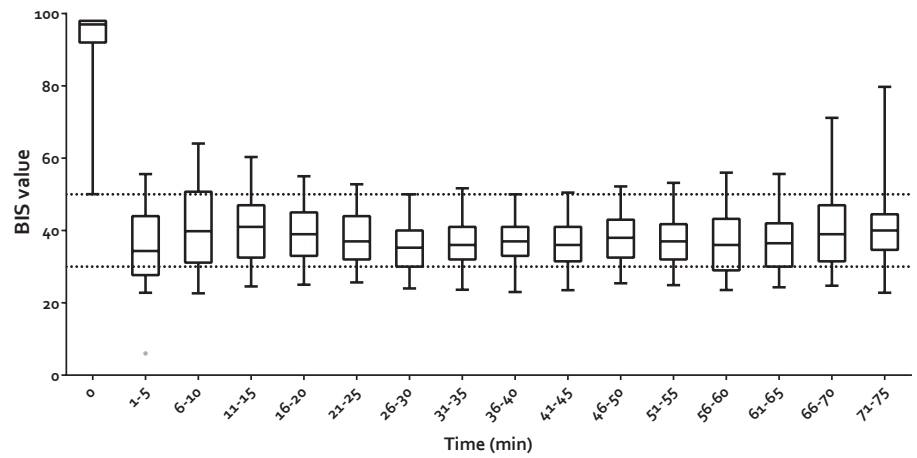


Figure 1 *Median Bispectral index (BIS) values with interquartile range (box) and 95% confidence intervals observed in time intervals of five minutes after induction of anaesthesia in 51 morbidly obese patients.*

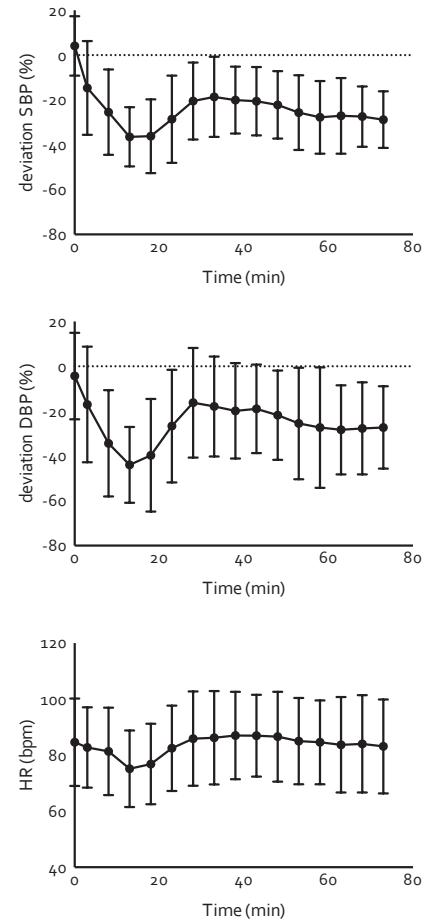


Figure 2 *Systolic blood pressure (SBP) (top panel) and diastolic blood pressure (DBP) (middle panel) at different time-points after induction of anaesthesia presented as percentage deviation from baseline values measured at preoperative consultation with standard deviations, and heart rate (HR) (bottom panel) at different time-points presented as mean with standard deviation.*

carbon dioxide measurements were not below 3.5 kPa or 26 mmHg across the observation period for all patients.
Figure 3 shows the difference between actual propofol infusion rates and proposed model-based infusion rates (Table II) from the start of the propofol maintenance infusion (at three minutes after induction of anaesthesia) until 75 minutes after the induction of anaesthesia. Overall mean difference was -0.43 mg/min (95%CI -0.49 – -0.36). It seems from this figure, that during the first ten minutes after the induction dose of 350 mg propofol, the interindividual variability in infusion rates was relatively large (Figure 3).

Table II *Proposed propofol maintenance infusion rates based on adjusted body weight (ABW) as derived from a previously published pharmacokinetic and pharmacodynamic model (8). This dosing algorithm consists of 7 mg/kg ABW*/h for 20 minutes, followed by 6.5 mg/kg ABW*/h for 20 minutes, 6 mg/kg ABW*/h for 20 minutes, and 5.5 mg/kg ABW*/h until the end of surgery.*

		7 mg/ kg ABW/ h	6,5 mg/ kg ABW/ h	6 mg/ kg ABW/ h	5,5 mg/ kg ABW/ h	5 mg/ kg ABW/ h
TBW (kg)	ABW* (kg)	Infusion rates (mL/h) using propofol 10 mg/mL				
100	90	63	59	54	50	45
105	94	66	61	56	52	47
110	97	68	63	58	53	48
115	100	70	65	60	55	50
120	103	72	67	62	57	52
125	106	74	69	64	58	53
130	109	77	71	66	60	55
135	112	79	73	67	62	56
140	115	81	75	69	63	58
145	118	83	77	71	65	59
150	121	85	79	73	67	61
155	124	87	81	74	68	62
160	127	89	83	76	70	63
165	130	91	84	78	71	65
170	133	93	86	80	73	66
175	135	95	88	81	74	68
180	138	97	90	83	76	69
185	141	99	92	85	78	70
190	144	101	93	86	79	72
195	146	102	95	88	81	73
200	149	104	97	89	82	75
205	152	106	99	91	83	76
210	154	108	100	93	85	77
215	157	110	102	94	86	79
220	160	112	104	96	88	80
225	162	114	105	97	89	81
230	165	115	107	99	91	82
235	167	117	109	100	92	84
240	170	119	110	102	93	85
245	173	121	112	104	95	86
250	175	123	114	105	96	88

** ABW = 70 * (Total body weight (=TBW)/70)$^{0.72}$*

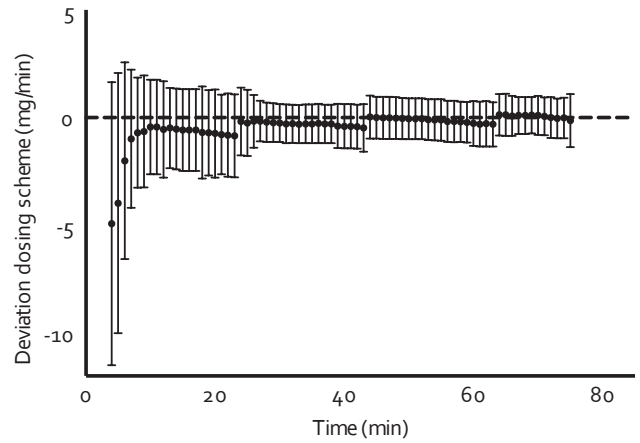


Figure 3 *Deviations in observed propofol infusion rates compared to the proposed propofol dosing algorithm as presented in Table II (mean ± SD) over time in 51 morbidly obese patients.*

Table III *Medication administered according to standardized anaesthesia protocol and additional medication presented as mean dose with standard deviation (SD).*

	Mean (SD)
Protocol medication	
Propofol bolus (mg)	362.2 (41.3)
Propofol maintenance (mg/kg/h*)	6.2 (0.54)
Remifentanil (mcg/kg/h**)	23.4 (4.8)
Fentanyl (mcg)	292.2 (77.1)
Atracurium (mg) (n=26)	54.8 (12.0)
Rocuronium (mg) (n=25)	52.2 (6.5)
Morphine (mg)	10.3 (2.8)
Additional medication (bolus doses)	
Ephedrine (mg) 0-20 min (#=27, n=22)	7.9 (2.5)
Ephedrine (mg) 21 min – end of surgery (#=18, n=11)	5.8 (1.9)
Phenylephrine 0-20 min (mg) (#=16, n=8)	0.12 (0.05)
Phenylephrine 21-end min (mg) (#=22, n=8)	0.11 (0.04)
Noradrenalin (mg) (n=5)	0.49 (0.2)

** based on model-based adjusted body weight (= 70kg * (TBW/70)$^{0.72}$)*
*** based on ideal body weight*
 # number of bolus administrations
n number of patients

Both protocol medication and additional medication that was administered during anaesthesia according to the standardised protocol are presented in Table III. Mean remifentanil dose was 23.4 mcg/kg/h (SD 4.8) based on ideal body weight (IBW) which was slightly lower than the predefined dose of 25 mcg/kg/h based on IBW (Table III). Sixty-five percent of the patients received co-medication to correct low blood pressure and/or heart rate at some time during the period of anaesthesia. In most cases, ephedrine was used to correct low blood pressures and 60% of all ephedrine doses were administered during the first 20 minutes after the start of the induction of anaesthesia.

Comparison of observed BIS values with model-based predicted BIS values
Figure 4 shows the individual predicted BIS values by the original pharmacokinetic and pharmacodynamic model (8) versus the observed BIS values of the morbidly obese patients. These plots indicate acceptable bias and adequate precision of the predictions of the BIS values. Overall performance variables were a median performance error (MDPE) -5.2 BIS points (SD 13.0) representing bias and a median absolute performance error (MDAPE) 10.5 BIS points (SD 9.3) representing precision.

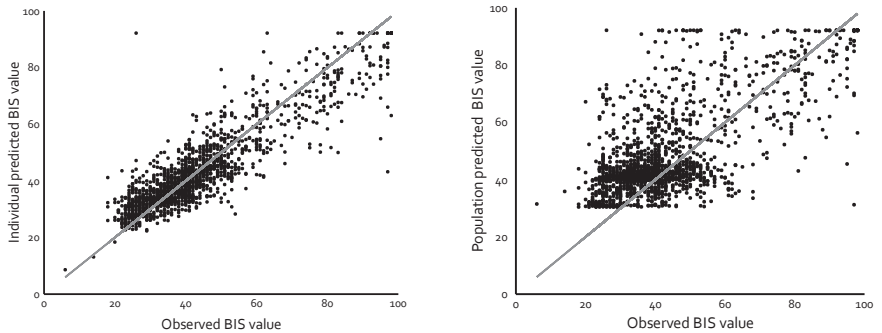


Figure 4 *Individual predicted BIS values by the original pharmacokinetic-pharmacodynamic model (8) versus the observed BIS values in the current study in fifty-one morbidly obese patients.*

Discussion

The present study prospectively evaluated a pharmacokinetic-pharmacodynamic (PK-PD) model-derived algorithm for maintenance of anaesthesia with propofol in morbidly obese patients thereby targeting on a BIS value of 40 together with stable haemodynamics. Using this propofol dosing algorithm in combination with remifentanil analgesia, effective anaesthesia was achieved with BIS values of 40 ± 10 and with haemodynamics that stayed within the predefined ranges across a wide range of total body weights from 95 to 210 kg. However, haemodynamics dropped substantially particularly within the first 20 minutes after induction of anaesthesia.
Prospective studies evaluating dosing guidelines derived from population PK-PD models on the used endpoints are scarce. The propofol dosing algorithm for morbidly obese patients evaluated in the present study was derived from a population PK-PD model in which total body weight was identified as key patient characteristic that can explain the interindividual variability of clearance of propofol in both non-obese and morbidly obese patients (8). Based on that model, when aiming for a stable BIS of 40 during maintenance of anaesthesia, an adjusted body weight (ABW); ABW = 70kg * $(TBW/70)^{0.72}$ as dosing scalar with doses reductions every 20 minutes was proposed (8). In the present evaluation of this PK-PD model-based dosing algorithm, we showed that using these propofol doses stable BIS values of 40 ± 10 were achieved in morbidly obese patients. Although the current bias and precision values for the observed BIS values were larger compared to in non-obese patients (13-14), the bias (MDPE) and precision (MDAPE) were acceptable with 10.5 (SD 9.3) and –5.2 BIS points (SD 13.0), respectively. There was also no difference in observed BIS values between the lower and higher total body weights (data not shown) indicating that the accuracy of the model is applicable for a wide range of total body weights. The present study demonstrates that PK-PD modeling in special patient groups such as morbidly obese patients can be of important value when developing evidence-based dosing algorithms for these patient groups.
In general, there may be concerns on the haemodynamic safety of propofol when used for anaesthesia in morbidly obese patients. Propofol is known to cause a decrease in systemic arterial blood pressure due to depressant effects on cardiac contractility and a reduction in venous and arteriolar systemic vascular resistance resulting in a decrease in pre- and afterload (15). While in our opinion, the risk for haemodynamic instability is reduced by dosing on adjusted body weight (Table II) instead of linear dosing on total body weight, we did observe a substantial decrease in blood

pressure over the first 20 minutes of the procedure in our study (Figure 2). Moreover, in a large number of patients additional medication to correct these haemodynamic effects were given (Table III). 20 minutes after the induction dose, the observed decrease of the haemodynamic values during propofol maintenance infusion remained within the predefined margins and there were no signs of hypoperfusion during anaesthesia. In addition, we emphasize that the decrease in observed haemodynamic values could be slightly overpredicted because of relatively high blood pressures that may be measured during preoperative consultation. As such we conclude that haemodynamic effects of propofol in morbidly obese patients are acceptable when the PK-PD model derived dosing algorithm as depicted in Table II is used for maintenance of anaesthesia.

After induction of anaesthesia, considerable variations in BIS values, blood pressures and heart rates were observed during the first 20 minutes. There is a number of possible explanations for this. First, a cause may lie in the fixed propofol induction dose of 350 mg for all morbidly obese patients. Recent study suggested to use lean body weight as dosing scalar to calculate propofol induction dose for morbidly obese patients instead of dose capping (16). This might have resulted in a lower induction dose for the less obese patients and a more stable start of anaesthesia. In an additional analysis of the present study, however, no correlation between decrease in BIS during the induction phase and lean body weight could be observed (data not shown). Second, propofol maintenance infusion was started 3 minutes after the propofol induction dose while surgery did not start in all cases. Mean time between start of surgery and start of propofol infusion was 10.3 minutes. Because start of surgery causes sympathetic activation, thereby increasing both blood pressure and heart rate (17), a delayed start of surgery and, thereby, a delayed stimulus of the sympathetic nerve system, may explain the extensive decline of blood pressure during the first minutes of propofol infusion. Therefore, before implementation, the present dosing algorithm has to be incorporated in conjugation with local practice in terms of timing of anaesthesia and start of surgery. Finally, cardiovascular consequences of obesity such as (silent) ischemic heart disease and cardiomyopathy may have aggravated the haemodynamic effects during induction of anaesthesia independent of propofol dose. Although in our study with the developed propofol dosing algorithm optimal conditions for intubation were achieved in all patients, there remains space for further improvement of the induction phase of the evaluated PK-PD model-based dosing regimen.

In our study, we decided to dose propofol based on both BIS values and hemodynamic parameters. Besides dosing based on BIS values, an alternative strategy for propofol dosing is to target to specific propofol blood concentrations using target controlled infusion techniques (TCI). La

Colla et al reported however a clinically unacceptable performance bias upon the use of total body weight as an input for the 'Marsh' model for TCI and concluded that titration on target BIS values in morbidly obese patient remains necessary (18). Although TCI can be considered an interesting approach to dose propofol for anaesthesia, it seems that the TCI systems are not yet ready for this approach in morbidly obese patients. The results of the present study show that the previously developed PK-PD model-based propofol maintenance dosing algorithm leads to stable BIS values and acceptable haemodynamics in morbidly obese patients and is ready for clinical implementation.

Conclusion

Stable and effective maintenance of anaesthesia was achieved using the PK-PD model-based propofol dosing algorithm in combination with remifentanil analgesia in morbidly obese patients varying in total body weight between 95 and 210 kg.

References

1.Kopelman PG. Obesity as a medical problem. Nature. 2000 Apr 6;404(6778):635-43.
2.Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 2006 Apr 5;295(13):1549-55.
3.Sinha AC. Some anesthetic aspects of morbid obesity. Curr Opin Anaesthesiol. 2009 Jun;22(3):442-6.
4.Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. Br J Anaesth. 2000 Jul;85(1):91-108.
5.Ingrande J, Lemmens HJ. Dose adjustment of anaesthetics in the morbidly obese. Br J Anaesth. 2010 Dec;105 Suppl 1:i16-23.
6.Morrish GA, Pai MP, Green B. The effects of obesity on drug pharmacokinetics in humans. Expert Opin Drug Metab Toxicol. 2011 Jun;7(6):697-706.
7.Absalom AR, Mani V, De Smet T, Struys MM. Pharmacokinetic models for propofol--defining and illuminating the devil in the detail. Br J Anaesth. 2009 Jul;103(1):26-37.
8.van Kralingen S, Diepstraten J, Peeters MY, Deneer VH, van Ramshorst B, Wiezer RJ, et al. Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. Clin Pharmacokinet. 2011 Nov 1;50(11):739-50.
9.Cortinez LI, Anderson BJ, Penna A, Olivares L, Munoz HR, Holford NH, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth. 2010 Oct;105(4):448-56.
10.van Kralingen S, Diepstraten J, van de Garde EM, van der Lely AJ, van Dongen EP, van Ramshorst B, et al. Comparative evaluation of propofol 350 and 200 mg for induction of anaesthesia in morbidly obese patients: a randomized double-blind pilot study. Eur J Anaesthesiol. 2010 Jun;27(6):572-4.
11.Egan TD, Huizinga B, Gupta SK, Jaarsma RL, Sperry RJ, Yee JB, et al. Remifentanil pharmacokinetics in obese versus lean patients. Anesthesiology. 1998 Sep;89(3):562-73.
12.Coppens MJ, Eleveld DJ, Proost JH, Marks LA, Van Bocxlaer JF, Vereecke H, et al. An Evaluation of Using Population Pharmacokinetic Models to Estimate Pharmacodynamic Parameters for Propofol and Bispectral Index in Children. Anesthesiology. 2011 May 6.
13.Absalom AR, Kenny GN. Closed-loop control of propofol anaesthesia using bispectral index: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery. Br J Anaesth. 2003 Jun;90(6):737-41.
14.Struys MM, De Smet T, Versichelen LF, Van De Velde S, Van den Broecke R, Mortier EP. Comparison of closed-loop controlled administration of propofol using Bispectral Index as the controlled variable versus "standard practice" controlled administration. Anesthesiology. 2001 Jul;95(1):6-17.
15.Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. Anaesthesia. 1985 Aug;40(8):735-40.
16.Ingrande J, Brodsky JB, Lemmens HJ. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. Anesth Analg. 2011 Jul;113(1):57-62.
17.Nguyen NT, Wolfe BM. The physiologic effects of pneumoperitoneum in the morbidly obese. Annals of surgery. [Review]. 2005 Feb;241(2):219-26.
18.La Colla L, Albertin A, La Colla G, Ceriani V, Lodi T, Porta A, et al. No adjustment vs. adjustment formula as input weight for propofol target-controlled infusion in morbidly obese patients. Eur J Anaesthesiol. 2009 May;26(5):362-9.
19.Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.

Propofol clearance in morbidly obese children and adolescents. Influence of age and body size

06

Jeroen Diepstraten, Vidya Chidambaran, Senthilkumar Sadhasivam, Hope Esslinger, Shareen Cox, Thomas Inge, Catherijne A.J. Knibbe, Alexander A. Vinks

Clin Pharmacokin. 2012(51): 543-51

Abstract

Background and objectives
Given the alarming increase in obesity among children undergoing surgery, the main aim of this study was to characterize propofol clearance in a cohort of morbidly obese children and adolescents in relation to their age and body weight characteristics.
Methods
A prospective pharmacokinetic study in morbidly obese children and adolescents undergoing elective surgery was conducted. Serial blood samples were collected and nonlinear mixed-effects modelling using NONMEM was performed to characterize propofol pharmacokinetics with subsequent evaluation of age and body size descriptors.
Results
Twenty obese and morbidly obese children and adolescents with a mean age of 16 years (range 9–18 years), a mean total body weight (TBW) of 125 kg (range 70–184 kg) and a mean body mass index of 46 kg/m^2 (range 31–63 kg/m^2) were available for pharmacokinetic modelling using a two-compartment pharmacokinetic model (n = 294 propofol concentration measurements). Compared with lean body weight and ideal body weight, TBW proved to be the most predictive covariate for clearance (CL (L/min) = 1.70 × (TBW/70)$^{0.8}$). Central volume of distribution, peripheral volume and intercompartmental clearance were 45.2 L, 128 L and 1.75 L/min, respectively, with no predictive covariates identifiable.
Conclusion
In the population pharmacokinetic model for propofol in morbidly obese children and adolescents, TBW proved to be the most significant determinant for clearance. As a result, it is anticipated that dosage of propofol for maintenance of anaesthesia in morbidly obese children and adolescents should be based on TBW using an allometric function.

Background

The prevalence of childhood obesity is dramatically increasing worldwide. In 2008, childhood obesity affected 17% of the children and adolescents in the US (1). Moreover, morbid obesity in children is also on the rise (2) and due to comorbidities related to obesity, these patients are more likely to utilize healthcare resources, including anesthesia for bariatric surgery (3). However, dosing guidelines for most commonly used drugs in this population are not available due to a lack of studies providing adequate pharmacokinetic and pharmacodynamic data. Serious problems may arise due to over- and underdosing, increasing adverse events and the risk of suboptimal efficacy, respectively (4). Therefore, systematic pharmacokinetic and pharmacodynamic studies in this special population of patients are urgently needed to improve the safety and efficacy of drugs used in these patients.

Propofol is widely used for induction and maintenance of anesthesia in children and adolescents. There has been extensive research on the pharmacokinetics of propofol in non-obese adults (5-6) and children (6-9). Propofol pharmacokinetics proved to be altered in children compared with adults, showing a higher propofol clearance per kg in children (6). Consequently, children require higher propofol doses per kg total body weight (TBW) than adults to obtain a similar propofol concentration (10). Concerning the influence of obesity on the pharmacokinetics of propofol in obese adults, different reports have been published. In adults, an increase in propofol clearance associated with TBW has been observed (11). Recently, two studies showed that this increase in propofol clearance can be described with an allometric function on the basis of TBW as body size descriptor and with an exponent of 0.75 and 0.72, respectively (12-13). In contrast, to date there are no data available describing the influence of overweight on the pharmacokinetics of propofol in (morbidly) obese children and adolescents. Therefore, the main aim of this study was to characterize the population propofol clearance in morbidly obese children and adolescents, ultimately to develop an optimal dosing algorithm. Therefore, we evaluated the pharmacokinetics of propofol in this special group of patients and analyzing the influence of age and body size descriptors such as TBW, body mass index (BMI), ideal body weight (IBW) and lean body weight (LBW) based on Janmahasatian et al. (14) and LBW based on Peters et al. (15) in order to account for variability in pharmacokinetic parameters.

Methods

Patients

Obese and morbidly obese children and adolescents scheduled to undergo bariatric surgery or other elective surgical procedures were enrolled in a prospective study from July 2009 through July 2010 (ClinicalTrials.gov identifier NCT00948597). From prior work in children we estimated that a cohort of 20 subjects for this study would allow adequate estimation of the primary outcomes variables propofol clearance and central volume of distribution (9, 16).

Patients were included if they were between 5 and 18 years of age, had a BMI of over 30 kg/m^2 at inclusion (equivalent to body weight > 95th percentile for age (17)), required propofol anesthesia for at least 60 minutes and had no known renal or liver disorders. Exclusion criteria included known neurological disorders, history of severe sleep apnea, anticipated difficult airway access, and known allergy for propofol, soy bean oil or egg lecithin. The study protocol was approved by the institutional review board and written informed assent and consent were obtained from all participants and/or their guardians as appropriate.

Anesthetic procedure

All patients received standard of care anesthesia with midazolam as premedication (either 20 mg orally or 2 mg intravenously). Before induction, an antecubital venous line and standard American Society of Anesthesiologists (ASA) monitors (ECG, non-invasive blood pressure and pulse oximeter) were placed. Anesthesia was induced with propofol as an infusion at a standardized rate of 1000 µg/kg/min on the basis of adjusted body weight (11).

Upon loss of consciousness, endotracheal intubation was performed after administration of either vecuronium or cisatracurium for muscular relaxation. Paralytic agents were titrated using a nerve stimulator to observe the train-of-four response at the orbicularis oculi by facial nerve stimulation (goal: one of four twitches). The induction dose of propofol was followed by propofol infusion at a rate of 250-350 µg/kg/min for 10 minutes and titrated in 25-50 µg/kg/min steps in order to keep the systolic arterial blood pressure and heart rate hemodynamics within 30% of baseline values. Fentanyl 100 µg was administered just after induction and 50 µg doses were administered in case of inadequate analgesia. When inadequate anesthesia or analgesia was not considered to be the reason for increase in blood pressure or heart rate, medications to correct the hemodynamics were administered. Typically

labetolol 5 mg was used to reverse increased heart rate and blood pressure, ephedrine 10 mg increments for decreased blood pressure and heart rate, and phenylephrine 100 µg increments for decreased blood pressure and increased heart rate. The propofol infusion was discontinued when skin sutures were being placed. Residual muscle relaxation was reversed with neostigmine 0.05-0.07 mg/kg and glycopyrrolate 0.1 mg/kg, and after clinical confirmation of reversal, the patient was extubated awake. Morphine was dosed incrementally towards the end of the surgery, titrated to respiratory rate of 14-16 breaths per minute.

Blood sampling and analytical methods

Venous blood samples (1 ml) were collected at the following timepoints: at baseline prior to the start of the propofol, approximately 15, 30, 45, 60, 120, 180 and 240 minutes after the start of the propofol infusion, just before and at 5 or 20 minutes after any dose adjustment, just before discontinuation of the propofol infusion, and at 5, 10, 15, 30, 45 and 120 minutes after discontinuation of the infusion. Whole-blood samples for propofol analysis were mixed thoroughly and stored at 4°C until analysis by high-performance liquid chromatography with fluorescence detection at 276 nm and 310 nm (within 1 month). With this method, the coefficients of variation for the intra-assay and inter-assay precision were less than 4.5% and 7.1%, respectively, over the concentration range from 0.05 to 10.0 mg/L, and the lower limit of quantification was 0.05 mg/L (18-19).

Data analysis and internal validation

The analysis was performed by means of non-linear mixed-effects modelling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD, US) (20) with S-plus (version 6.2; Insightful software, Seattle, WA, US) for data visualization. Discrimination between different models was made by comparison of the objective function value (OFV, i.e. –2 log likelihood). A significance level of $p<0.05$, corresponding to a decrease of 3.8 in OFV, was considered statistically significant. In addition, goodness-of-fit plots (observed versus individual-predicted concentration-time, observed versus population-predicted concentration-time, conditional weighted residuals versus time and conditional weighted residuals versus population-predicted concentration-time plots) were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the models. The internal validity of the population pharmacokinetics and models was assessed by the bootstrap re-sampling method using 250 replicates (20). Parameters obtained with the bootstrap replicates were compared with the estimates obtained from the original dataset.

Pharmacokinetic model

A two-compartment model and a three-compartment model were tested to fit the log-transformed propofol concentration data. The inter-individual value (post hoc value) of the parameters of the i^{th} individual was modelled equation 1:

$$\Theta_i = \Theta_{mean} * e^{\eta_i} \quad \text{(Eq. 1)}$$

where θ_{mean} is the population mean and η_i is a random variable with a mean of zero and variance of ω^2, assuming log-normal distribution in the population. The intra-individual variability, resulting from assay errors, model misspecifications and other unexplained sources, was best described with a proportional error model. This means for the j^{th} observed log-transformed propofol concentration of the ith individual, the relation (Y_{ij}) is described by equation 2:

$$Y_{ij} = \log C_{pred,ij} + \varepsilon_{ij} \quad \text{(Eq. 2)}$$

where C_{pred} is the predicted propofol concentration and ε_{ij} is a random variable with a mean of zero and variance of σ^2.

Covariate analysis

Covariates were plotted independently against the individual post hoc parameter estimates of all pharmacokinetic parameters and the conditioned weighted residuals to visualize potential relations. The Pearson's correlations coefficient (r) was calculated and a $p<0.05$ was considered significant. The following covariates were tested: TBW, BMI, IBW (21) and LBW on the basis of Janmahasatian et al. (14) and LBW on the basis of Peters et al. (15), sex and age. Covariates were tested using linear and allometric equations (equation 3):

$$P_i = P_p \cdot \left(\frac{Cov}{Cov_{standard}}\right)^z \quad \text{(Eq. 3)}$$

where P_i and P_p represent individual and population parameter estimates, respectively, Cov represents the covariate and $Cov_{standard}$ represents a standardized (i.e. 70 kg for TBW) or median value of the covariate for the population. The exponent z represents the exponential scaling factor, which

was fixed at 1 for a linear function or an estimated value for an allometric equation, while a 0.75 fixed value of the exponent was also tested (22). Potential covariates were separately entered into the model and statistically tested using the OFV and if applicable the 95% confidence interval values of the additional parameter. A $p<0.005$ was applied to evaluate the covariates in the forward inclusion (OFV decrease>7.9), while the backward deletion procedure used a stricter criterion (OFV decrease>10.8: $p<0.001$). When two or more covariates were found to significantly improve the model, the covariate causing the largest reduction in OFV was left in the model. Additional covariates had to reduce this OFV further to be retained in the model. The choice of the covariate model was further discussed in the Data analysis and internal validation section.

Comparison with non-obese children and adolescents

Individual clearance estimates obtained in this study were compared with propofol clearance values previously published in non-obese children by Schuttler and Ihmsen (6) and Kataria et al. (8), with TBW ranges of 12 – 61 kg and 15 – 61 kg, respectively. Schuttler and Ihmsen (6) described propofol clearance as equation 4:, while Kataria et al. (8) expressed propofol clearance (CL) as equation 5:

$$CL = 1.44 \text{ L/min} * (TBW/70)^{0.75} \quad \text{(Eq. 4)}$$

$$CL = 0.034 \text{ L/min} * TBW \quad \text{(Eq. 5)}$$

When using the TBW range observed in the present study, these two different clearance equations were evaluated for their extrapolation potential to predict clearance estimates in morbidly obese children and adolescents.

Results

Patients and data collection

A total of 23 morbidly obese pediatric patients were enrolled. One patient withdrew shortly before the procedure (no samples); and two patients were excluded because of missing data due to sampling errors. For the 20 patients included in the analysis 294 propofol concentration measurements were available. 17 patients were Caucasians and 3 patients were African-American. Morbidly obese patients had a mean TBW of 125 kg (range 70 – 184 kg) and a BMI of 46 kg /m^2 (range 31 – 65 kg/m^2). Demographic characteristics of the cohort are summarized in Table I.

Table I *Baseline characteristics of 20 obese and morbidly obese children and adolescents.*

Parameter	Mean (SD)	Range
Sex (F/M)	12/8	
TBW (kg)	125 (29)	70 – 184
BMI (kg/m^2)	46 (9)	31 – 63
LBW Janmahasatian et al. (14) (kg)	63 (14)	38 – 85
LBW Peters et al. (15) (kg)	75 (14)	47 - 98
Age (y)	16 (2)	9 – 18

BMI = body mass index; F = female; LBW = lean body weight; M = male; SD = standard deviation; TBW = total body weight.

Pharmacokinetics analysis

A two-compartment pharmacokinetic model most adequately described the time course of the propofol whole-blood concentrations in morbidly obese children and adolescents, parameterized in terms of volume of distribution of the central compartment (V1) and volume of distribution of the peripheral compartment (V2), intercompartmental clearance from the central compartment to the peripheral compartment (Q), and clearance from the central compartment (CL). The use of a three-compartment model did not result in an improved fit of the data and showed comparable estimates for propofol clearance to the two-compartment model.

Table II shows the result of the step wise covariate analysis in which age and body size descriptors were separately tested using both linear and allometric functions for their influence on the pharmacokinetic parameters. The table shows that, in general, the influence of covariates on CL resulted in a larger decrease in OFV than V1. The equation to estimate LBW for children by Peters et al. (15) showed a significantly ($p<0.005$) larger decrease in OFV than the equation by Janmahasatian et al. (14). TBW and BMI as covariate on propofol clearance reduced the OFV further (Table II). As BMI consists of two parameters (i.e. height and TBW) and there was no significant difference in OFV between the TBW models and the BMI model, a model based on TBW was preferred over the BMI model. Using TBW as covariate for clearance, both linear and allometric functions were tested and showed a comparable decrease in OFV value compared with the base model (Table II). Similar results were obtained for allometric functions using an estimated exponent (0.80) and a fixed exponent of 0.75 (Table II). As there were no differences between the linear and allometric functions, we preferred the model in

Table II *Stepwise covariate analysis for the pharmacokinetic model of propofol in 20 obese and morbidly obese children and adolescents.*

Parameter	Model	Relationship of covariate	No. of structural parameters	OFV
-	Base model	-	4	- 401
CL	Age	$CL_i = CL_{pop} \bullet (AGE_i/15)$	4	- 401
CL	LBW (14) linear	$CL_i = CL_{pop} \bullet (LBW_i/59)$	4	- 401
CL	LBW (15) linear	$CL_i = CL_{pop} \bullet (LBW_i/77)$	4	- 411
CL	BMI linear	$CL_i = CL_{pop} \bullet (BMI_i/23)$	4	- 416
CL	TBW linear	$CL_i = CL_{pop} \bullet (TBW_i/70)$	4	- 413
CL	TBW allometric	$CL_i = CL_{pop} \bullet (TBW_i/70)^{0.75}$	4	- 414
CL	TBW allometric	$CL_i = CL_{pop} \bullet (TBW_i/70)^{z}$	5	- 414
CL	TBW allometric	$CL_i = CL_{pop} \bullet (TBW_i/70)^{0.8}$	4	- 414
V1	Age linear	$V1_i = V_{1,pop} \bullet (AGE_i/15)$	4	- 403
V1	LBW (14) linear	$V1_i = V1_{pop} \bullet (LBW_i/59)$	4	- 401
V1	LBW (15) linear	$V1_i = V1_{pop} \bullet (LBW_i/77)$	4	- 403
V1	BMI linear	$V1_i = V1_{pop} \bullet (BMI_i/23)$	4	- 405
V1	TBW linear	$V1_i = V1_{pop} \bullet (TBW_i/70)$	4	- 405
CL and V1	TBW	$CL_i = CL_{pop} \bullet (TBW_i/70)^{0.8}$ $V1_i = V1_{pop} \bullet (TBW_i/70)$	4	- 419
Final TBW model		$CL_i = CL_{pop} \bullet (TBW_i/70)^{0.8}$		

BMI = body mass index; CL = clearance; CL_i = clearance in i^{th} individual; CL_{pop} = population mean value for clearance; LBW = lean body weight; TBW = total body weight; V1 = central volume of distribution; $V1_i$ = central volume of distribution in i^{th} individual; $V1_{pop}$ = population mean value for central volume of distribution; z = allometric scaling factor for clearance = 0.8 (coefficient of variation = 19%); OFV = objective function value.

which the allometric exponent was estimated, resulting in the final equation (equation 6:

$$CL_i = CL_{70\,kg} \bullet (TBW_i/70)^{0.8} \qquad \text{(Eq. 6)}$$

where CL_i represents clearance in the i^{th} individual, $CL_{70\,kg}$ is the population mean value for clearance in an individual of 70 kg, TBW_i is the total body weight of the i^{th} individual and 70 is the standard TBW in kilograms. Figure 1 shows the individual post hoc estimates for propofol clearance against TBW. Concerning covariates for V1, Table II shows there was only modest influence of age and body size descriptors on V1: more specifically, a trend toward an increase in V1 with TBW was observed (p>0.005). This observation was confirmed when the individual post hoc estimates for V1 were plotted against TBW (Figure 1), showing a non significant Pearson's correlation coefficient of 0.300 (p=0.199). There was no influence of the explored covariates and the other pharmacokinetic parameters (Q2 and V2) (data not shown).

The pharmacokinetic parameter estimates of the final model in which clearance is normalized to TBW using an allometric function are shown in Table III. Compared with the base model, the interindividual variability of clearance was reduced by 33% in the final model (from 26.3% to 17.5%; Table III). The diagnostic plots of the final model proved superior to the base model, especially for the population predictions versus observed concentrations (Figure 2). Figure 3 demonstrates that the final model adequately describes

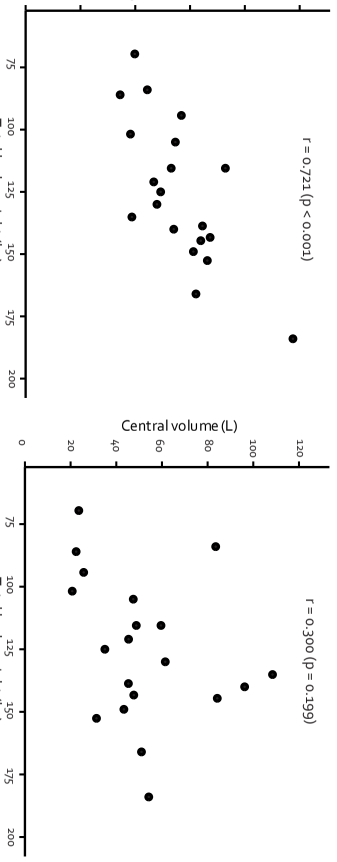


Figure 1 *Individual post hoc estimates for clearance (left) and central volume of distribution (right) of propofol versus total body weight in 20 obese and morbidly obese children and adolescents with Pearson's correlation coefficient (r).*

the individual propofol concentrations for the morbidly obese children and adolescents. The stability of the final TBW model was shown by the bootstrap analysis (Table III).

Comparison with non-obese children and adolescents

Figure 4 shows a comparison of the present results of propofol clearance (CL) values versus TBW in morbidly obese children and adolescents, and the extrapolated equations of Kataria et al. (8) (equation 5) and Schuttler and Ihmsen (6) (equation 4) which were both derived from non-obese children. This figure shows that extrapolating the equation of Kataria et al. (8) to morbidly obese children and adolescents would result in overestimation of propofol clearance values for this group. In contrast, the equation of Schuttler and Ihmsen (6) would only slightly underestimate propofol clearance in morbidly obese children and adolescents.

Table III *Population pharmacokinetic parameters for the base model and final total body weight (TBW) model for propofol in 20 morbidly obese children and adolescents.*

Parameter	Base model[a]	Final TBW model[a]	Bootstrap Final TBW model[a]
Number of patients	20	20	
CL (L/h)	161 (6.0)		
CL_{70kg} (L/h)[b]		103 (4.5)	102 (4.9)
V1 (L)	45.5 (19.2)	45.2 (19.5)	43.5 (21.4)
V2 (L)	126 (14.6)	128 (14.8)	134 (21.0)
Q (L/h)	107 (13.2)	105 (12.5)	109 (14.2)
OFV	-401	-414	-424
Interindividual variability (%)			
CL	26.3 (36.5)	17.5 (35.5)	17.3 (41.5)
V1	58.6 (38.0)	61.0 (38.3)	63.1 (47.7)
Proportional intra-individual error (%)	25.7 (19.2)	25.6 (19.1)	25.6 (19.6)

a The data are expressed as mean (%CV) unless specified otherwise.
b $CL_i = CL_{70kg} * (TBW/70)^{0.8}$
CL = clearance; CL70kg = clearance in an individual of 70 kg; CL_i = clearance in the ith individual; CV = coefficient of variation of the parameter values; OFV = objective function value; Q = compartmental clearance between V1 and V2; TBW = total body weight; V1 = central volume of distribution; V2 = peripheral volume of distribution 1.

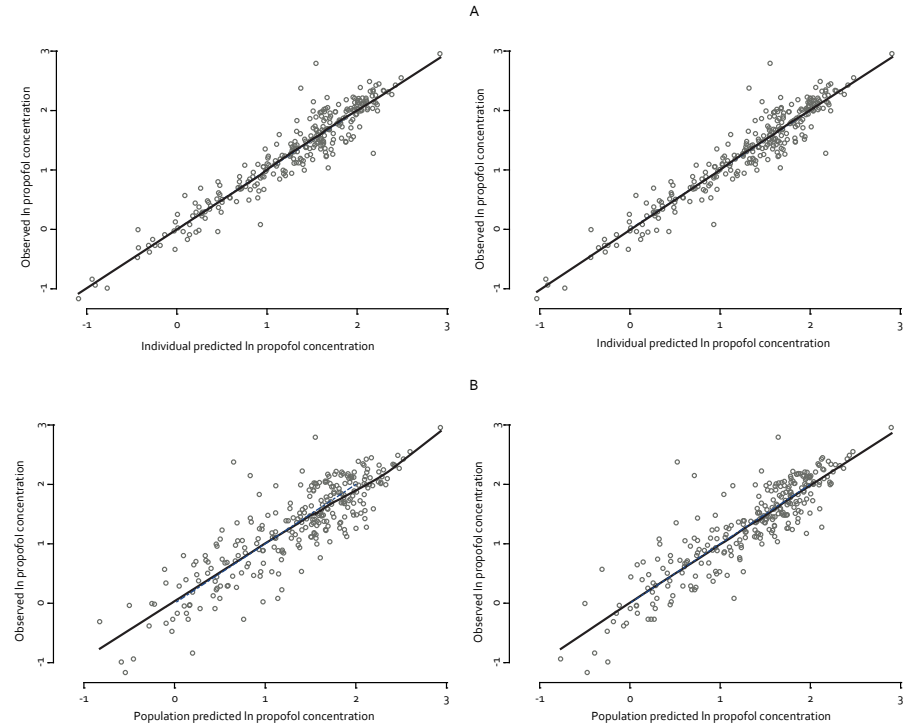


Figure 2 *Diagnostic plots for propofol pharmacokinetics in morbidly obese children and adolescents showing (A) individual log-normal propofol predictions versus observed logarithmic propofol concentrations and (B) population model log-normal propofol predictions versus observed log-normal propofol concentrations for the base and final total body weight (TBW) model. The solid line indicates the trend line, the dashed line represents the line of identity, x=y. ln = log-normal.*

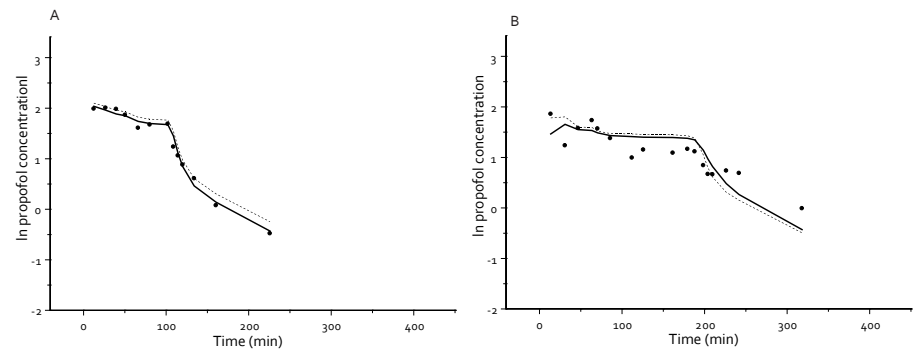


Figure 3 *Propofol concentration time relationships for the best (Age = 15 years old, TBW = 143 kg, BMI = 44 kg/m²) (A) and worst (Age = 15 years old, TBW = 145 kg, BMI = 54 kg/m²) (B) final TBW model predictions. The solid circles represent the measured propofol concentrations, the dotted lines represent the concentrations predicted by the population model and the solid black line represents the concentrations predicted using individual post hoc parameter estimates. ln = log-normal.*

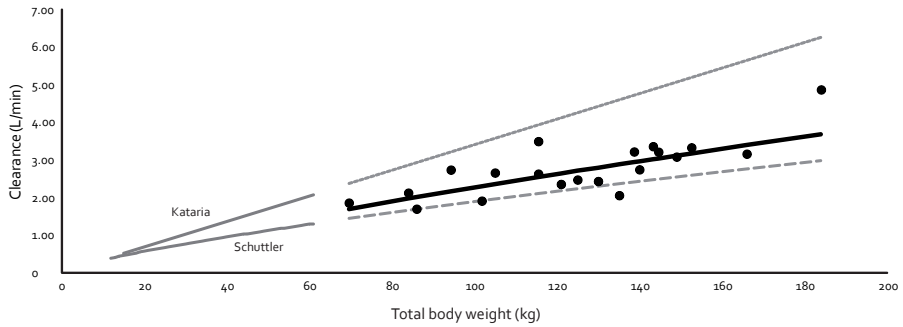


Figure 4 *Propofol clearance (CL) values versus TBW for morbidly obese children and adolescents of the present study (black line) and models of Kataria et al. (8) and Schuttler and Ihmsen (6) (grey lines). The black line indicates population clearance values for morbidly obese children and adolescents obtained in this study (CL = 1.70 L/min * (TBW/70)$^{0.8}$); black circles indicate individual post hoc clearance values from morbidly obese children and adolescents of the present study; grey lines indicate the linear model of Kataria et al. (8) and the allometric model of Schuttler and Ihmsen (6) in the TBW ranges of these studies; grey dotted lines indicate the estimations after extrapolation of the Kataria et al. (8) and Schuttler and Ihmsen (6) equations to the TBW range (70 – 184 kg) of the present study in morbidly obese children and adolescents.*

Discussion

In order to study the influence of obesity on the pharmacokinetics of propofol in morbidly obese children and adolescents, a population pharmacokinetic model was developed, in which clearance proved to scale best with TBW in an allometric function.

While there are no other reports on propofol pharmacokinetics in obese children, previous reports describing the best body size descriptor for propofol clearance in adults seem to be conclusive. Servin et al. were the first reporting an increase in propofol clearance with TBW in obese adults (11). More recently in two prospective studies, TBW was reported the best body size descriptor for propofol clearance in (morbidly) obese adults (12-13). TBW proved to be superior to LBW in morbidly obese adults (13) even though LBW had been proposed to capture the nonlinear increase in propofol clearance in adults (23). In the present study, lean body weight estimated by the equation of Peters et al. (15) developed for children, was a better body size descriptor than lean body weight estimated by the equation of Janmahasatian et al. (14) which had been developed for adults. While testing all available body size descriptors, and in accordance with findings in morbidly obese adults, we found that TBW was the best descriptor for propofol clearance in morbidly obese children and adolescents.

The observed increase in propofol clearance with TBW in morbidly obese children and adolescents was described with an allometric function using an estimated scaling factor of 0.8. An allometric function with a scaling factor of 0.75 is often used to describe the increase of drug clearance values with TBW in children, albeit not without debate (24-26). In contrast, for propofol clearance in non obese children, both a linear (exponent = 1.0) (8, 27) and an allometric function with an exponent of 0.75 (6) has been applied. Aprioiri use of a fixed exponent of 0.75 in obese patients would imply that obese individuals can be viewed as 'large individuals' (a different body size) instead of individuals 'having excess body fat' (a different body composition) (28). For morbidly obese adults an exponent of 0.72 (13) and 0.75 (12) has been described. It is however unknown whether these exponents can be used for different age ranges i.e. in children. In the present study in morbidly obese children and adolescents we estimated a scaling factor of 0.8 which was not significantly different from a linear function or fixed exponent of 0.75. It therefore seems that a larger study with a wider range in age and TBW is needed to conclude on the allometric exponent in morbidly obese children and adolescents.

The present study shows that for morbidly obese children and adolescents the equation for propofol clearance as proposed by Schuttler et al.(6) is superior to the equation of Kataria et al. (8). The latter which is widely used for target controlled infusion (TCI). Extrapolated clearance values using the Kataria et al. model (8) show an substantial overestimation of propofol clearance while the model of Schuttler et al. only results in a small underprediction (Figure 4). Besides, it has been shown in non obese children by Coppens et al. that the model of Kataria et al. was more biased and inaccurate compared to the other available pharmacokinetic models in children such as the model of Schuttler et al. (29). However, it should be emphasized that the current result only applies to propofol clearance and not to other pharmacokinetic parameters. Even though propofol TCI is often applied, the current available models are not suitable for morbidly obese children, adolescents or adults (13). The developed population model of propofol in morbidly obese children and adolescents provides a starting point to be considered for TCI in this population.

This study had a few limitations. We investigated a small cohort of 20 morbidly obese children and adolescents that included patients with a TBW range of 70 – 184 kg and an age range of 9 – 18 years. As mostly patients with an age of 16 years old were included in this study, more data is needed to describe the influence of excessive overweight for the total age range. In addition, for practical reasons we applied an early sampling strategy that did not allow us to adequately capture propofol's rapid initial distribution phase (three-compartment model) and to characterize a possible influence of excessive body weight on V1. Finally, in order to develop an integrated PK/PD

dosing algorithm for propofol in morbidly obese children and adolescents, a pharmacodynamic marker, such as BIS monitoring, is urgently needed. A prospective study taking into account these concerns is currently being planned to evaluate an allometric dosing regimen for propofol in obese and morbidly obese children and adolescents based on TBW and BIS monitoring.

Conclusion

A pharmacokinetic model for propofol in obese and morbidly obese children and adolescents has been derived with total body weight as the major determinant for clearance using an allometric function. As a result, it is anticipated that propofol for maintenance of anesthesia in morbidly obese children and adolescents should be dosed on the basis of total body weight in an allometric fashion.

References

1. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007-2008. Jama. 2010 Jan 20;303(3):242-9.
2. Skelton JA, Cook SR, Auinger P, et al. Prevalence and trends of severe obesity among US children and adolescents. Acad Pediatr. 2009 Sep-Oct;9(5):322-9.
3. Ingelfinger JR. Bariatric surgery in adolescents. N Engl J Med. 2011 Oct 13;365(15):1365-7.
4. Mulla H, Johnson TN. Dosing dilemmas in obese children. Arch Dis Child Educ Pract Ed. 2010 Aug;95(4):112-7.
5. Shafer A, Doze VA, Shafer SL, et al. Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology. 1988 Sep;69(3):348-56.
6. Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. Anesthesiology. 2000 Mar;92(3):727-38.
7. Jones RD, Chan K, Andrew LJ. Pharmacokinetics of propofol in children. Br J Anaesth. 1990 Nov;65(5):661-7.
8. Kataria BK, Ved SA, Nicodemus HF, et al. The pharmacokinetics of propofol in children using three different data analysis approaches. Anesthesiology. 1994 Jan;80(1):104-22.
9. Peeters MY, Prins SA, Knibbe CA, et al. Propofol pharmacokinetics and pharmacodynamics for depth of sedation in nonventilated infants after major craniofacial surgery. Anesthesiology. 2006 Mar;104(3):466-74.
10. Rigby-Jones AE, Sneyd JR. Propofol and children - what we know and what we do not know. Paediatr Anaesth. 2010 Nov 18.
11. Servin F, Farinotti R, Haberer JP, et al. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. Anesthesiology. 1993 Apr;78(4):657-65.
12. Cortinez LI, Anderson BJ, Penna A, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth. 2010 Oct;105(4):448-56.
13. van Kralingen S, Diepstraten J, Peeters MY, et al. Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. Clin Pharmacokinet. 2011 Nov 1;50(11):739-50.
14. Janmahasatian S, Duffull SB, Ash S, et al. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
15. Peters AM, Snelling HL, Glass DM, et al. Estimation of lean body mass in children. Br J Anaesth. 2011 May;106(5):719-23.
16. Peeters MY, Prins SA, Knibbe CA, et al. Pharmacokinetics and pharmacodynamics of midazolam and metabolites in nonventilated infants after craniofacial surgery. Anesthesiology. 2006 Dec;105(6):1135-46.
17. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007 Dec;120 Suppl 4:S164-92.
18. Knibbe CA, Koster VS, Deneer VH, et al. Determination of propofol in low-volume samples by high-performance liquid chromatography with fluorescence detection. J Chromatogr B Biomed Sci Appl. 1998 Mar 20;706(2):305-10.
19. Yeganeh MH, Ramzan I. Determination of propofol in rat whole blood and plasma by high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl. 1997 Apr 11;691(2):478-82.
20. Beal SL, Sheiner LB, Boeckmann A. NONMEM user's guide. San Francisco: University of California; 1999.
21. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000 Sep;34(9):1066-9.
22. Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.
23. McLeay SC, Morrish GA, Kirkpatrick CM, et al. Encouraging the move towards predictive population models for the obese using propofol as a motivating example. Pharm Res. 2009 Jul;26(7):1626-34.
24. Mahmood I. Application of fixed exponent 0.75 to the prediction of human drug clearance: an inaccurate and misleading concept. Drug Metabol Drug Interact. 2009;24(1):57-81.
25. Mahmood I. Evaluation of a morphine maturation model for the prediction of morphine clearance in children: how accurate is the predictive performance of the model? Br J Clin Pharmacol. 2011 Jan;71(1):88-94.
26. Krekels EH, DeJongh J, van Lingen RA, et al. Predictive performance of a recently developed population pharmacokinetic model for morphine and its metabolites in new datasets of (preterm) neonates, infants and children. Clin Pharmacokinet. 2011 Jan 1;50(1):51-63.
27. Marsh B, White M, Morton N, et al. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth. 1991 Jul;67(1):41-8.
28. Eleveld DJ, Proost JH, Absalom AR, et al. Obesity and allometric scaling of pharmacokinetics.

Clin Pharmacokinet. 2011 Nov 1;50(11):751-3.
29. Coppens MJ, Eleveld DJ, Proost JH, et al. An Evaluation of Using Population Pharmacokinetic Models to Estimate Pharmacodynamic Parameters for Propofol and Bispectral Index in Children. Anesthesiology. 2011 May 6.

An integrated population pharmacokinetic meta-analysis of propofol in morbidly obese and non-obese adults, adolescents and children

07

Jeroen Diepstraten, Vidya Chidambaran, Senthilkumar Sadhasivam, Heleen J. Blussé van Oud-Alblas, Thomas Inge, Bert van Ramshorst, Eric P.A. van Dongen, Alexander A. Vinks, Catherijne A.J. Knibbe

Submitted for publication

Abstract

This study describes a population pharmacokinetic meta-analysis of propofol to characterize the influence of body size measures and age in morbidly obese and non-obese adults, adolescents and children. Sixty morbidly obese and non-obese adult patients (55 – 167 kg, 21 – 79 years) and 34 morbidly obese and non-obese adolescents and children (37 – 184 kg, 9 – 20 years) were included. The results show that clearance increased with total body weight in an allometric function while age was found to influence clearance in a bilinear fashion with two distinct slopes, reflecting an initial increase and subsequent decrease as a result of aging. Using these two functions, the influence of both (over)weight and age on propofol clearance was well characterized, which may provide a basis for dosing across this diverse group of patients.

Background

While total body weight of children and adolescents increases due to growth-related processes across childhood, obesity may also substantially contribute to increases in body weight (1). As a result, morbidly obese children and adolescents may be as heavy as adults, even though growth-related processes have not yet been completed. The question then arises whether total body weight, which is commonly used to adjust dosing in children and adolescents, is the appropriate measure to adjust doses of drugs in obese children and adolescents. Similarly for adults, there is a lively discussion about the best size descriptor for changes in pharmacokinetics due to obesity (2, 3). As little is known on how key pharmacokinetic parameters such as clearance change in morbidly obese children, adolescents and adults compared to their non-obese controls, studies are needed analyzing a wide range of ages and related total body weights.

Propofol is widely used for induction and maintenance of anesthesia in both non-obese and (morbidly) obese adults, adolescents and children. Recently, the pharmacokinetics of propofol have been compared in premature neonates and adults (4), in morbidly obese and obese adults (5, 6) and in (morbidly) obese children and adolescents (7). In all these studies, total body weight proved the most predictive covariate for clearance, either by using a standard allometric function (5-7) or a total body weight dependent exponent allometric function (4). However, a meta-analysis on the basis of all datasets in morbidly obese adults, adolescents and children together with their non-obese controls in which the influence of obesity and ageing is disentangled has not been performed.

Therefore, the aim of this study was to perform a population pharmacokinetic meta-analysis of propofol combining data from morbidly obese and non-obese adults, adolescents and children. In order to study how obesity and age influence pharmacokinetic parameter estimates in this diverse patient group, specific emphasis was placed on the evaluation of the influence of total body weight (TBW), body mass index (BMI), ideal body weight (IBW) (8), lean body weight (LBW) (9, 10) and/or age on the different pharmacokinetic parameters.

Methods

Patients

Data of five previously published studies were used for this analysis (6, 7, 11-13). Patient characteristics of the five different studies are provided in Table I. Details of the studies are briefly summarized when relevant to the current analysis.

Morbidly obese adults (6)

Twenty morbidly obese adults scheduled for bariatric surgery with a mean total body weight of 124 kg (range 98 – 167 kg) received either a propofol induction dose of 200 mg or 350 mg. Maintenance propofol infusion rate was initiated at 10 mg/kg times total body weight and adjusted in order to keep Bispectral index (BIS) values between 40 and 60 (6).

Non-obese adults (11, 12)

Forty non-obese adults with a mean total body weight of 74 kg (range 55 – 98 kg) were included. Twenty-four female patients received a bolus injection of 2.5 mg/kg of propofol for induction of anesthesia while anesthesia was maintained with isoflurane (11). Of these twenty-four patients, twenty patients were included from this study as a height measure of four patients was not available. Another twenty non-obese intensive care patients received continuous propofol infusions for 2-5 days with propofol doses based on the Ramsay six-point scale (12).

Morbidly obese children and adolescents (7)

In twenty morbidly obese adolescents and children scheduled for bariatric surgery with mean total body weight 125 kg (range 70 – 184 kg) and mean age of 16 years old (range 9 – 18 years) propofol was dosed using dosing weight calculated according to the method of Servin et al. (7, 14).

Non-obese children and adolescents (13)

In fourteen non-obese adolescents and children with mean total body weight of 54 kg (range 37 – 82 kg) and a mean age of 14 years old (range 9 – 20 years), anesthesia was induced with a bolus dose of propofol (4 mg/kg) and maintained with propofol by continuous infusion (2 – 10 mg/kg/h) for scoliosis surgery (13).

Table I *Baseline characteristics of all morbidly obese and non-obese adults, adolescents and children included in the current analysis. Data are presented as mean with standard deviation (SD).*

	All Patients	Adults		Adolescents and children	
		Morbidly obese (6)	Non-obese (11, 12)	Obese (7)	Non-obese (13)
Number	94	20	40	20	14
Gender (M / F)	30/64	4/16	16/24	8/12	2/12
Age (years)	38 (20)	45 (12)	55 (12)	16 (2)	14 (3)
TBW (kg)	94 (35)	124 (20)	74 (11)	125 (29)	54 (13)
BMI (kg/m²)	33 (12)	43 (6)	26 (4)	46 (9)	21 (6)
IBW (kg)	61 (9)	61 (7)	64 (8)	59 (12)	55 (9)
LBW (kg)	54 (14)	60 (9)	50 (10)	63 (14)	37 (8)

BMI = body mass index; IBW = ideal body weight (8); F = female; LBW = lean body weight (9); M = male; SD = standard deviation; TBW = total body weight.

Data analysis and internal validation

The analysis was performed by means of non-linear mixed-effects modeling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD) (15) with S-plus (version 6.2; Insightful software, Seattle, WA) to visualize the data. Discrimination between different models was made by comparison of the objective function value (-2 log likelihood (OVF)). A value of $p < 0.05$, representing a decrease of 3.8 in the OVF, was considered statistically significant. In addition, goodness-of-fit plots (observed versus individually predicted, observed versus population predicted, conditional weighted residuals versus time and conditional weighted residuals versus population predictions) were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual plots were used to evaluate the model. η-shrinkage as defined by Karlsson et al. (16), was calculated for all model parameters for which interindividual variability was estimated. The internal validity of the population pharmacokinetic models was assessed by a per study stratified bootstrap re-sampling method using 250 replicates (15).

Pharmacokinetic model

Log transformed propofol concentration data were described by a three-compartment model (NONMEM VI, ADVAN11, TRANS4) parameterized in terms of volume of distribution of the central (V1), first (V2), and second peripheral compartment (V3), intercompartmental clearance from the central to the first (Q2) and from the central to the second (Q3) peripheral compartment, and clearance from the central compartment (CL).
The interindividual value (post hoc value) of the parameters of the i^{th} subject was modeled by:

$$\Theta_i = \Theta_{mean} * e^{\eta_i} \qquad \text{(Eq. 1)}$$

where θ_{mean} is the population mean and η_i is a random variable with mean zero and variance ω^2, assuming lognormal distribution in the population.
The intra-individual variability, resulting from assay errors, model misspecifications, and other unexplained sources, was best described with a proportional error model. This means for the j^{th} observed log transformed propofol concentration of the i^{th} individual, the relation (Y_{ij}):

$$Y_{ij} = \log C_{pred,ij} + \varepsilon_{ij} \qquad \text{(Eq. 2)}$$

where c_{pred} is the predicted propofol concentration and ε_{ij} is the random variable with mean zero and variance σ^2.

Covariate analysis

Covariates were plotted independently against the individual post hoc parameter estimates of all pharmacokinetic parameters and the conditioned weighted residuals to visualize potential relations. The following covariates were tested: total body weight (TBW), body mass index (BMI), ideal body weight (IBW) (8) and lean body weight (LBW) (9, 10), gender and age. Covariates were tested using linear and power equations:

$$P_i = P_p \cdot \left(\frac{Cov}{Cov_{standard}}\right)^z \qquad \text{(Eq. 3)}$$

in which P_i and P_p represent individual and population parameter estimates, respectively, Cov represents the covariate and $Cov_{standard}$ represents a standardized (i.e. 70 kg for TBW) or median value of the covariate for the population. z represents the scaling factor, which was fixed to 1 for a linear function or an estimated value for a power equation.
The influence of the covariate age on clearance was also tested using a bilinear function with two distinct slopes, i.e. a linear increase in clearance

for age values below the median age and a linear decrease in clearance for age values higher than the median age (17) (Equation 4).

$$CL_i = CL_{pop} * F_{age} \quad \text{(Eq. 4)}$$

F_{age} (age ≤ median age) = (1 + b * (age – median age))
F_{age} (age > median age) = (1 + c * (age – median age))

Potential covariates were separately entered into the model and statistically tested by use of the objective function value (OFV) and if applicable the 95% confidence interval of the additional parameter. A $p < 0.005$ was applied to evaluate the covariates in the forward inclusion (OFV decrease > 7.9), while the backward deletion procedure used a stricter criterion (OFV decrease > 10.8; $p < 0.001$). When more than one significant covariate for the simple model was found, the covariate-adjusted model with the largest decrease in objection function was chosen as a basis to sequentially explore the influence of additional covariates using the same criteria. Finally, after forward inclusion, a backward exclusion procedure was applied to justify the covariate. The choice of the covariate model was further evaluated as discussed under Data analysis and internal validation.

Results

Subjects

Ninety-four adults, adolescents and children with a mean total body weight (TBW) of 94 kg (range 37 – 184 kg) were included from which 1652 concentration measurements were available. Demographic characteristics of the morbidly obese patients and non-obese patients are summarized in Table I.

Pharmacokinetics

A three-compartment pharmacokinetic model adequately described the time course of the propofol whole blood concentrations in all morbidly obese and non-obese adults, adolescents and children. Exploratory plots of the tested covariates total body weight, body mass index, ideal body weight, lean body weight and age against individual post hoc parameter estimates of the simple model without covariates (Model A) showed a potential relation between clearance and total body weight, with lower values for children and adolescents across the entire body weight range (Figure 1, model A). In

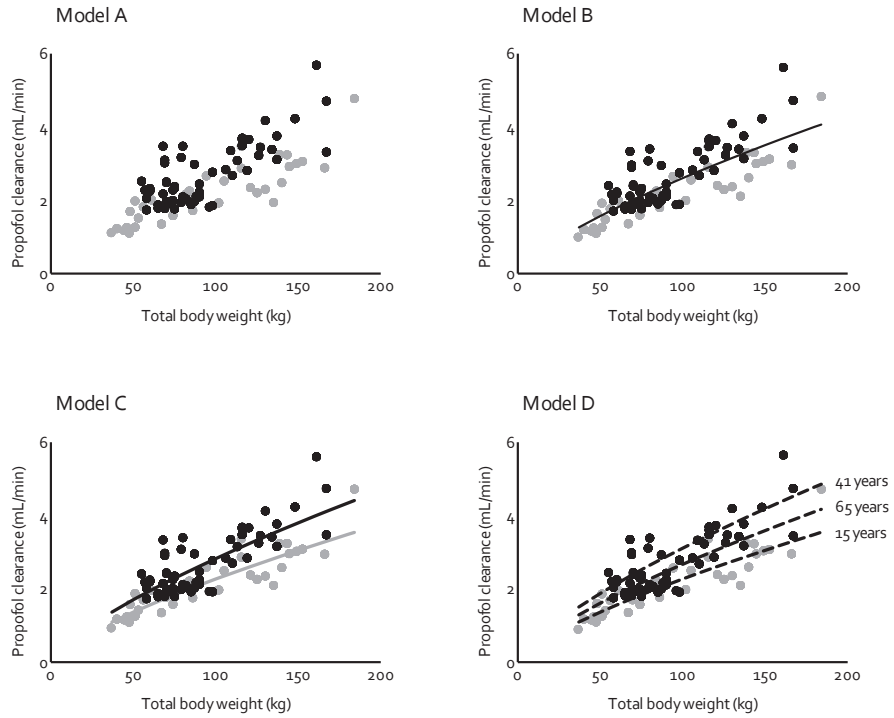


Figure 1 *Individual post hoc propofol clearance estimates (symbol) versus total body weight for the simple model (model A) and three covariate pharmacokinetic models (B, C and D) for morbidly obese adults (black circles), adolescents and children (grey circles) and their non-obese controls (n=94). In model B, the black line indicates the population clearance values for both the adult and adolescent population, in model C the black line indicates the population clearance values for adults and the grey line the population clearance values for adolescents and in model D the black dotted lines indicate the population clearance values for 15, 41 and 65 years.*

addition, potential relationships were observed between central volume of distribution (V1) and total body weight or lean body weight, and between intercompartmental clearance from the central to the second peripheral compartment (Q3) and total body weight (figures not shown). There were no visual trends between the explored covariates and other pharmacokinetic parameters in the simple model without covariates (model A).
Subsequently, as depicted in Table II all body size measures and age were separately incorporated on clearance, central volume of distribution and Q3 in the model and tested for significance (see section Methods, covariate analysis). The analysis showed that total body weight was the most predictive covariate for propofol clearance when implemented using an allometric function (model B, decrease in objective function value (OFV) of 84.4 points,

p<0.001, Table II). Figure 1 model B (and model A), shows that adolescents with the same total body weight as adults had lower clearance values (grey versus black symbols, respectively). Therefore, in model C a separate value for propofol clearance in adolescents versus adults was estimated. This resulted in another reduction in OFV with 23.5 points (p<0.001) with individual clearance values for an adolescent of 70 kg and an adult of 70 kg of 1.75 mL/min and 2.18 mL/min, respectively (Table II, Model C). The non-linear increase of propofol clearance with total body weight proved the same for both groups and was best described using an allometric function with an estimated exponent of 0.73 (CV% 6.9) (Figure 1, Model C).
However, when the simple model without covariates was evaluated for the effect of age (Figure 2, left panel), it was found that clearance increased until the median age of 41 years after which it decreased. As a result, instead of estimation of two different population values for adolescents versus adults as in model C, in model D age was implemented using a bilinear function which significantly reduced the OFV (ΔOFV compared to model C = -8.2 points, p<0.005). On the basis of the covariates of model D, the interindividual variability of propofol clearance was reduced by 50%. Figure 2 right panel, shows that after implementation of age in a bilinear function, interindividual variability was randomly distributed with age. Figure 1, model D, shows the post hoc propofol clearance estimates for model D versus total body weight with population predictions for clearance for three different ages (15, 41 and 65 years), illustrating the bilinear relation with age in model D. The final equation for propofol clearance was (Equation 5):

$$CL_i = CL_{pop} \bullet (TBW_i/70)^{0.77} * F_{age}^{\ *} \qquad \text{(Eq. 5)}$$

* Age ≤ 41 y: $F_{age} = (1 + 0.0103 * (Age - 41))$
Age > 41 y: $F_{age} = (1 - 0.00539 * (Age - 41))$

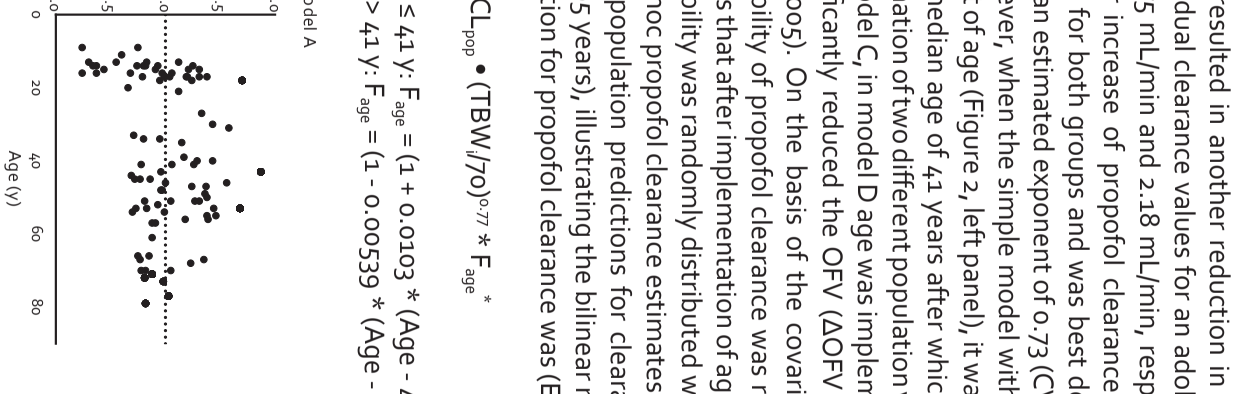


Figure 2 *Interindividual variability of propofol clearance versus age for the simple model without covariates (Model A) and the final covariate model including age and total body weight on propofol clearance (Model E).*

Table II *Results of covariate analysis for the three-compartment pharmacokinetic model of propofol in the combined dataset of morbidly obese and non-obese adults, adolescents and children.*

Parameter	Model	Model description	Relationship of covariate	No. of structural Parameters	ΔOFV
-	**A**	**Simple model**	**-**	**11**	
CL		Age bilinear	$CL_i = CL_{pop} \bullet F_{age}^{\ *}$	13	- 16.7
CL		LBW (9) linear	$CL_i = CL_{pop} \bullet (LBW_i/60)$	11	- 45.8
CL		TBW linear	$CL_i = CL_{pop} \bullet (TBW_i/70)$	11	- 68.5
CL	**B**	**TBW allometric**	$\mathbf{CL_i = CL_{pop} \bullet (TBW_i/70)^z}$	**12**	**- 84.4**
CL	**C**	**TBW allometric, $CL_{adolescents}$ and CL_{adults}**	$\mathbf{CL_i = CL_{pop,\ adolescents} \bullet (TBW_i/70)^z}$ $\mathbf{CL_i = CL_{pop,\ adults} \bullet (TBW_i/70)^z}$	**13**	**-107.9**
CL	**D**	**TBW allometric and age bilinear**	$\mathbf{CL_i = CL_{pop} \bullet (TBW_i/70)^z \bullet F_{age}^{\ *}}$	**14**	**- 116.1**
V1		TBW linear	$V1_i = V1_{pop} \bullet (TBW_i/70)$	11	- 0.2
V1		LBW (9) linear	$V1_i = V1_{pop} \bullet (LBW_i/60)$	11	- 5.8
Q3		TBW linear	$Q3_i = Q3_{pop} \bullet (TBW_i/70)$	11	- 18.1
Q3		TBW allometric	$Q3_i = Q3_{pop} \bullet (TBW_i/70)^d$	12	- 18.1
Final model CL and Q3	**E**	**TBW allometric and age bilinear on CL and TBW linear on Q3**	$\mathbf{CL_i = CL_{pop} \bullet (TBW_i/70)^z \bullet F_{age}^{\ *}}$ $\mathbf{Q3_i = Q3_{pop} \bullet (TBW_i/70)}$	**14**	**- 143.0**

** Age ≤ 41 y: $F_{age} = (1 + b * (Age - 41))$ and Age > 41 y: $F_{age} = (1 + c * (Age - 41))$*
CL = clearance; CL_i = clearance in i^{th} individual; CL_{pop} = population mean value for clearance; F_{age} = age factor for clearance; LBW = lean body weight; ΔOFV = delta objective function value compared to simple model; Q3 = compartmental clearance between V1 and V3; TBW = total body weight; V1 = central volume of distribution; z = allometric scaling factor in $CL_i = CL_{70\ kg} * (TBW/70)^z$

where CL_i represents clearance in the ith individual, CL_{pop} is the population mean value for clearance in an individual of 70 kg and of 41 years, TBW_i is the total body weight of the ith individual and 70 is the standard body weight in kilograms.

Concerning covariates for V1, Table II shows there was only a modest influence of the body size descriptors on V1 with a trend towards an increase in V1 with lean body weight ($p>0.005$). There was substantial shrinkage (43%) on V1, which renders not only plots using post hoc parameter estimates less reliable but also indicates that the individual data in the datasets are not rich in information about this parameter (18). Therefore, no covariate on V1 was incorporated in the final model. In contrast, total body weight as covariate for intercompartmental clearance from the central to the second peripheral compartment (Q3) significantly improved the model ($\Delta OFV = -18.1$, $p<0.005$) (Table II) and was therefore considered the final model (model E, Table II). There was no influence of the explored covariates on the other pharmacokinetic parameters (Q2 and V2).

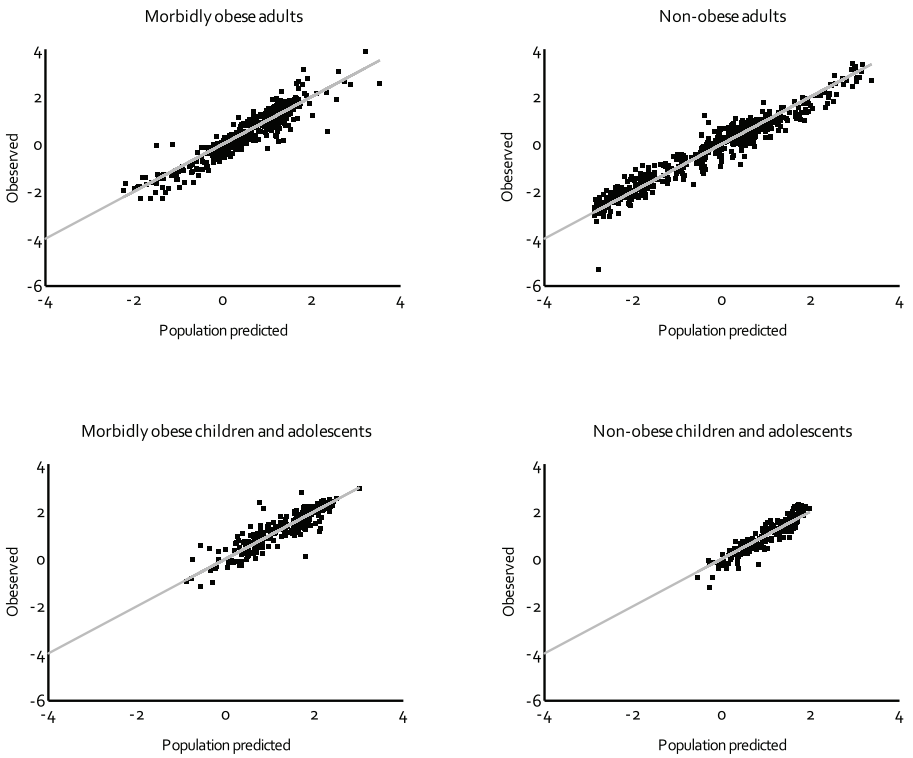


Figure 3 *Observed versus population predicted ln propofol concentrations of the final model (Model E). Panels represent data of morbidly obese adults, non-obese adults, morbidly obese children and adolescents and non-obese children and adolescents. The solid grey line represents the line of identity, x=y.*

Table III lists all parameter estimates including their coefficients of variation (CV values) and objective function values of the simple model (Model A) and the final model (model E). The observed versus population predicted plots stratified by the different cohorts in Figure 3 confirm that the final model not only describes the study population as a whole, but also the individual study populations without bias. The stability of the final model was shown by the bootstrap analysis (Table III).

Figure 4 shows population propofol clearance values versus age for different total body weights using the final model E. This figure shows both the allometric increase of propofol clearance with total body weight as the distance between the weight classes decreases with increasing total body weight, and the bilinear relationship of propofol clearance with age.

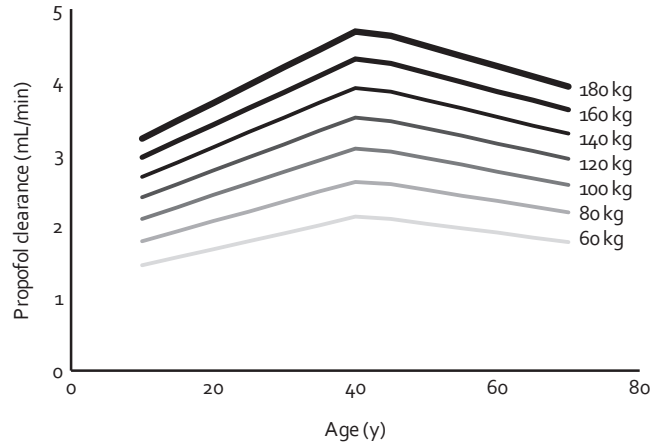


Figure 4 *Model based predictions of population clearance estimates of propofol versus age for patients with different total body weights.*

Table III *Population pharmacokinetic parameter estimates for the simple and the final pharmacokinetic model for propofol in non-obese and (morbidly) obese children, adolescents and adults including the bootstrap values of the final model.*

Parameter	Simple model Mean (CV%)	Final model Mean (CV%)	Bootstrap final model Mean (CV%)
Model #	A	E	-
Number of patients	94	94	250
CL (L/min)	2.37 (3.8)	-	-
$CL_{70\,kg,\,41\,yr}$ (L/min)*	-	2.34 (4.3)	2.31 (4.6)
z	-	0.77 (6.9)	0.77 (7.4)
*b***	-	0.0103 (13.5)	0.0094 (18.5)
*c***	-	-0.00539 (-33.8)	-0.00485 (-39.7)
V1 (L)	3.33 (11.5)	3.17 (11.3)	3.16 (10.0)
V2 (L)	6.55 (14.5)	5.89 (15.0)	5.78 (15.3)
V3 (L)	118 (9.1)	116 (7.5)	117 (6.7)
Q2 (L/min)	1.74 (9.7)	1.60 (11.7)	1.57 (12.2)
Q3 (L/min)	2.00(7.6)	-	-
$Q3_{70\,kg}$ (L/min)***	-	1.50 (6.2)	1.46 (5.0)
Interindividual variability (%)			
CL	35.1 (15.5)	17.5 (13.9)	17.7 (12.6)
V1	46.6 (44.4)	50.6 (41.3)	51.1 (38.8)
V3	40.4 (42.0)	36.2 (34.9)	35.4 (27.8)
Q3	48.1 (42.3)	40.4 (37.5)	35.1 (34.4)
Proportional intra-individual error (%)	24.3 (10.4)	24.3 (10.3)	24.1 (11.1)
OFV	-2331	-2474	-2500

** $CL_i = CL_{70\,kg} * (TBW/70)^z * F_{age}$*
*** Age ≤ 41 y: $F_{age} = (1 + b * (age - 41))$ and Age > 41 y: $F_{age} = (1 + c * (age - 41))$*
**** $Q3_i = Q3_{70\,kg} * (TBW/70)$*
b = age factor for clearance age ≤ 41 y; c = age factor for clearance age > 41 y; CL = clearance; $CL_{70\,kg}$ = population mean value for clearance in an individual of 70 kg; $CL_{70\,kg,\,41\,y}$ = population mean value for clearance in an individual of 70 kg and 41 years; CV = coefficient of variation of the parameter values; F_{age} = age factor for clearance; OFV = objective function value; Q2 = compartmental clearance between V1 and V2; Q3 = compartmental clearance between V1 and V3; Q3 70 kg = population mean value for compartmental clearance between V1 and V3 in an individual of 70 kg; V1 = central volume of distribution; V2 = peripheral volume 1; V3 = peripheral volume 2; z = allometric scaling factor in $CL_i = CL_{70\,kg} * (TBW/70)^z$

Discussion

In order to describe the influence of obesity and age on the pharmacokinetics of propofol, a population pharmacokinetic meta-analysis was performed using data from morbidly obese adults, adolescents and children, and their non-obese controls. In the current study, a wide range in total body weight (37 – 184 kg) and age (9 – 79 years) was studied, with data from (morbidly) obese and non-obese individuals in each age range. The results of the systematic analysis shows that a combination of total body weight and age proved to best capture changes in propofol clearance as a result of obesity and ageing. While it is yet unknown how these results should be put in physiological perspective, the current model seems to provide the best description of the data from these largely divergent patient populations.

In recent reports in (morbidly) obese adults it was shown that the increase in propofol clearance was related to total body weight and could be best described using an allometric function (5, 6). In addition, an allometric relationship between total body weight and propofol clearance was found in a dataset of morbidly obese adolescents (7). Allometric scaling factors of 0.72 (6) and 0.80 (7) were estimated for morbidly obese adults and children and adolescents, respectively. As these factors are close to the factor of 0.75 predicted by allometry theory (19), this implies that obese individuals can be viewed as 'large individuals' (a different body size) instead of individuals 'having excess body fat' (a different body composition) (2). While these results were confirmed in the current meta-pharmacokinetic analysis, we also showed that morbidly obese adolescents cannot be viewed as 'adults' as their propofol clearance proved lower than that of morbidly obese adults with the same total body weight (Figure 1, model A). This difference in propofol clearance could be described with two separate functions for propofol clearance; i.e. one equation for children and adolescents and one equation for adults (model C). Alternatively and significantly better, age was incorporated as covariate on propofol clearance using a bilinear function (model D and E). Therefore in the final model, the influence of age and obesity on propofol clearance was described using both total body weight and age as covariates for propofol clearance. This final equation (equation 5) is independent of the definitions for age (e.g. adolescents and adults) and obesity (e.g. obese and morbidly obese) categories and might prove useful for clinical practice.

In the current study, there was no significant relationship between body size measures and volumes of distribution. Previously, age and total body weight have been identified as covariates for volumes of distribution of propofol in non-obese and obese patients (5, 14, 20). As a result of the finding that lean body weight correlated with central volume of distribution, Ingrande et al. suggested to use lean body weight for the induction of anesthesia with propofol (21). The lack of significant influence of lean body weight on volume of distribution in our analysis may be explained by the fact that the studies included in the current analysis mainly contained observations following propofol maintenance infusions. As such these datasets did not contain sufficient observations just after the induction bolus dose of propofol to adequately describe early (re-)distribution and the influence of covariates on volumes of distribution. It therefore seems that additional research is needed to characterize covariates predictive of volume of distribution that will allow estimation of propofol loading doses in morbidly obese adults and children.

It remains to be speculated how the influence of total body weight on propofol clearance that was found in our study can be explained. Studies have shown that obese patients suffer from low-grade inflammation (22), which is probably the underlying cause of the high prevalence of non-alcoholic steatohepatitis (23). It is known that non-alcoholic steatohepatitis increases fat deposition in the liver causing sinusoidal narrowing and altered functional morphology of the liver (24). In contrast, because of increased blood volume and cardiac output, hepatic blood flow is possibly increased in obese subjects (25). As a result, increased propofol clearance may be anticipated as propofol is a high extraction ratio drug (26) mainly metabolized by various UDP-glucuronosyltransferase (UGT) enzymes (27). Data on other high extraction drugs and drugs metabolized by UGT suggest that both UGT activity (28-30) and liver blood flow (31, 32) are increased in obese adults. Furthermore, UGT activity is increased in obese adolescents compared to non-obese adolescents (33). Even though this cannot be proven, it can be hypothesized that hepatic blood flow is even more increased due to prolonged duration of obesity in adults compared to adolescents with the same total body weight. This is supported by the fact that age could be incorporated as covariate on propofol clearance. As propofol clearance is limited by the blood flow through the liver, the effect of both total body weight and age on propofol may be explained by changes in liver blood flow.

Conclusion

In this pharmacokinetic meta-analysis, we developed a model for scaling propofol clearance over wide ranges of total body weight and age using data from morbidly obese adults, adolescents and children and their

non-obese controls. The results show that total body weight was the most predictive covariate for propofol clearance across patients when implemented as an allometric function. In addition, age was incorporated using a bilinear function with two distinct slopes, reflecting an initial increase and subsequent decrease in clearance as a result of age. Using these two functions, the influence of both (over)weight and age on propofol clearance was well characterized, which may provide a basis for dosing across this diverse group of patients.

References

1. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. Jama. 2010;303(3):242-9.
2. Eleveld DJ, Proost JH, Absalom AR, Struys MM. Obesity and allometric scaling of pharmacokinetics. Clin Pharmacokinet. 2011;50(11):751-3.
3. Han PY, Duffull SB, Kirkpatrick CM, Green B. Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther. 2007;82(5):505-8.
4. Wang C, Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Krekels EH, Tibboel D, et al. A Bodyweight-Dependent Allometric Exponent for Scaling Clearance Across the Human Life-Span. Pharm Res. 2012.
5. Cortinez LI, Anderson BJ, Penna A, Olivares L, Munoz HR, Holford NH, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth. 2010;105(4):448-56. Epub 2010/08/17.
6. van Kralingen S, Diepstraten J, Peeters MY, Deneer VH, van Ramshorst B, Wiezer RJ, et al. Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. Clin Pharmacokinet. 2011;50(11):739-50.
7. Diepstraten J, Chidambaran V, Sadhasivam S, Esslinger HR, Cox SL, Inge TH, et al. Propofol clearance in morbidly obese children and adolescents: influence of age and body size. Clin Pharmacokinet. 2012;51(8):543-51.
8. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000;34(9):1066-9.
9. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
10. Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. Br J Anaesth. 2011;106(5):719-23.
11. Knibbe CA, Voortman HJ, Aarts LP, Kuks PF, Lange R, Langemeijer HJ, et al. Pharmacokinetics, induction of anaesthesia and safety characteristics of propofol 6% SAZN vs propofol 1% SAZN and Diprivan-10 after bolus injection. Br J Clin Pharmacol. 1999;47(6):653-60.
12. Knibbe CA, Zuideveld KP, DeJongh J, Kuks PF, Aarts LP, Danhof M. Population pharmacokinetic and pharmacodynamic modeling of propofol for long-term sedation in critically ill patients: a comparison between propofol 6% and propofol 1%. Clin Pharmacol Ther. 2002;72(6):670-84.
13. Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010;49(4):269-75.
14. Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. Anesthesiology. 1993;78(4):657-65.
15. Beal SL, Sheiner LB, Boeckmann A. NONMEM user's guide. San Francisco: University of California; 1999.
16. Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007;82(1):17-20.
17. Jonsson EN, Karlsson MO. Automated covariate model building within NONMEM. Pharm Res. 1998;15(9):1463-8.
18. Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. 2009;11(3):558-69.
19. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32.
20. Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. Anesthesiology. 2000;92(3):727-38.
21. Ingrande J, Brodsky JB, Lemmens HJ. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. Anesth Analg. 2011;113(1):57-62.
22. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005;115(5):1111-9.
23. Guzzaloni G, Grugni G, Minocci A, Moro D, Morabito F. Liver steatosis in juvenile obesity: correlations with lipid profile, hepatic biochemical parameters and glycemic and insulinemic responses to an oral glucose tolerance test. Int J Obes Relat Metab Disord. 2000;24(6):772-6.
24. Farrell GC, Teoh NC, McCuskey RS. Hepatic microcirculation in fatty liver disease. Anat Rec (Hoboken). 2008;291(6):684-92.
25. Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. J Clin Anesth. 2005;17(2):134-45.
26. Al-Jahdari WS, Yamamoto K, Hiraoka H, Nakamura K, Goto F, Horiuchi R. Prediction of total propofol clearance based on enzyme activities in microsomes from human kidney

and liver. Eur J Clin Pharmacol. 2006;62(7):527-33.
27. Kiang TK, Ensom MH, Chang TK. UDP-glucuronosyltransferases and clinical drug-drug interactions. Pharmacol Ther. 2005;106(1):97-132.
28. Abernethy DR, Divoll M, Greenblatt DJ, Ameer B. Obesity, sex, and acetaminophen disposition. Clin Pharmacol Ther. 1982;31(6):783-90.
29. Van Wart S, Phillips L, Ludwig EA, Russo R, Gajjar DA, Bello A, et al. Population pharmacokinetics and pharmacodynamics of garenoxacin in patients with community-acquired respiratory tract infections. Antimicrob Agents Chemother. 2004;48(12):4766-77.
30. Abernethy DR, Greenblatt DJ, Divoll M, Shader RI. Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med. 1983;101(6):873-80.
31. Sparreboom A, Wolff AC, Mathijssen RH, Chatelut E, Rowinsky EK, Verweij J, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol. 2007;25(30):4707-13.
32. Schwartz AE, Matteo RS, Ornstein E, Young WL, Myers KJ. Pharmacokinetics of sufentanil in obese patients. Anesth Analg. 1991;73(6):790-3.
33. Barshop NJ, Capparelli EV, Sirlin CB, Schwimmer JB, Lavine JE. Acetaminophen pharmacokinetics in children with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr. 2011;52(2):198-202.

Section 03

The influence of morbidly obesity on the pharmacodynamics of nadroparin in adults

Treatment of pulmonary embolism in an extremely obese patient

08

Jeroen Diepstraten, Simone van Kralingen, Repke J. Snijder, Christian M. Hackeng, Bert van Ramshorst, Catherijne A.J. Knibbe

Obesity Surgery; 2009(19): 1186-9

Abstract

The low-molecular-weight heparins are effective as initial therapy for pulmonary embolism (PE) in a weight-based dosing regimen up to known total body weights of 160 kg.
The present case reports an extremely obese man of 252 kg (body mass index (BMI) 74 kg/m^2) with PE who was treated with tinzaparin, dosed on a total body weight of 160 kg.
Morbid obesity defined as a BMI higher than 40 kg/m2 is becoming more common in general practice, but there are no evidence-based drug dosing strategies for these patients.
This case demonstrates the successful use of a maximum dose of 28,000 anti-Xa international units of tinzaparin for an extremely obese patient with proven PE, instead of the accepted doses of 175 IU/kg, as bridge therapy to a coumarin.

Case report

A 47-year-old male patient weighing 252 kg, who was scheduled for bariatric surgery later that year, was admitted to our hospital because of chest pain radiating to his left arm and acute dyspnea. The pain was not exercise-related and treatment with nitroglycerin did not relieve the symptoms. The patient's weight increased over the last few years; the actual body mass index (BMI) was 74 kg/m^2 at presentation. His medical history included gout, systemic hypertension, primary hyperventilation syndrome, appendectomy and cholecystectomy. The patient acknowledged being a smoker (25 cigarettes/day). There was no history of deep vein thrombosis or pulmonary embolism (PE).

Upon arrival in the emergency room, his blood pressure was 160/75 mm Hg with a pulse rate of 75 bpm, a temperature of 37.2 °C and an arterial oxygen saturation of 94% with support of 1 L/min of oxygen. When the patient was breathing room air the saturation dropped to 84 %. The laboratory results showed increased D-dimer levels of 2,749 µg/L (0-250 µg/L), a pro-B-type natriuretic peptide value of 75 pg/mL (< 88 pg/mL), a glucose level of 6.1 mmol/L and a serum creatinine level of 72 µmol/L. After medical examination, there were no clinical signs of deep venous thrombosis, like leg pain or other signs of thrombophlebitis in the lower limbs or presence of varices expect edema in both ankles due to morbid obesity.

Pulmonary embolism was suspected and a lung ventilation and perfusion scan was performed because the patient was unable to pass the CT-scan. The perfusion scan performed with 192 MBq (instead of 100 MBq) macroaggregates of albumin labelled with Technetium-131 (TechneScan® LyoMAA) and the ventilation scan performed with Krypton-81m gas confirmed the diagnosis of PE, with more than two lung segments showing no perfusion and normal ventilation.

According to the local protocol, the patient was treated with tinzaparin. Due to overall stability of the patient and in accordance to the guidelines of the American College of Chest Physicians, no further interventions were considered (1). Tinzaparin was started 3 h after admission with a dose of 175 IU anti-Xa/kg subcutaneously, according to the labelled dose of tinzaparin, which resulted for this total body weight of 252 kg in a total dose of 42,000 IU (2.7 ml). In consultation with the Department of Clinical Pharmacy, it was then decided to continue with a once daily dose of 28,000 IU anti-Xa a day (175 IU/kg dose capped at 160 kg instead of 252 kg), because 175 IU/kg based on a total body weight of 160 kg had previously been reported to be safe and effective and because it was assumed that a total body weight above 160 kg would not influence the clearance nor the volume of distribution of tinzaparin any further (2-4). In addition to this dosing advice, anti-Xa activity measurement was proposed to monitor the effect of this dose, thereby preventing concentrations lower than 0.5 IU/mL 4-5 h after the s.c. dose (5) and targeting at a concentration of 1-2 IU/mL 4-5 h after the s.c. dose at day 3 of treatment (6). Plasma levels of anti-Xa activity were measured with a STA-Rack Evolution (Diagnostica Stago, Asnières, France) using an anti-Xa clotting assay (StaClot®Heparin, Diagnostica Stago, Asnières, France). The anti-Xa assay standard calibration curve of tinzaparin ranged from 0 to 1.5 IU/mL. The within assay and among assay precision (coefficient of variation) were 4.7% and 4.9%, respectively. Also on day 1, 6 mg of acenocoumarol was administrated orally and adjusted based on the measured prothrombin time (PT/INR) (Table I).

During and following treatment with tinzaparin and acenocoumarol, the patient was relieved from his pain after 2 days and supplemental oxygen could be stopped after 4 days because he recovered from his dyspnea symptoms. Anti-Xa levels remained within the predetermined target values (Table I). No bleeding, bruising events or other complications occurred. He was discharged after 5 days when an adequate PT/INR > 2.0 was established (Table I). Both acenocoumarol and tinzaparin (for 3 more days) were continued after discharge. Three days after his discharge, the patient was readmitted because of constipation. During this readmission anti-Xa levels were measured after his last dose of tinzaparin (Table I). Five months after this event, the patient was stable without clinical signs of venous tromboembolism, and no additional coagulation testing was used to determine the presence of any ongoing thrombotic activity. Gastric bypass surgery was performed after which the patient recovered and was discharged.

Discussion

Obesity is an increasing health risk worldwide, with the US, UK and Australia recording a prevalence in adults of around 20 % (7). Approximately 4.8 % of the overall population are considered to be morbidly obese with a BMI higher than 40 kg/m2 (8-9). While in the overall population in the US pulmonary embolism (PE) resulted in approximately 200,000 deaths in 20 years (10), prospective data indicate that obesity is associated with an increased risk for a PE in women (11). In the treatment and prevention of PE, low-molecular-weight heparins (LMWH) have proven to be effective (12-13) and tinzaparin once daily is labelled for the treatment of PE. According to

Table I *Tinzaparin and acenocoumarol doses and anti-Xa and PT/INR levels in the 252 kg patient.*

Day	Time (h)	Tinzaparin (IU)	Tinzaparin (IU/kg)	anti-Xa (IU/mL)	Acenocoumarol (mg)	PT/INR
1	2:00					
1	5:00	42,000	166.3			
1	20:00			0.54 (= A)		
1	22:00	28,000	110.9		6	
2	8:00			0.72 (= B)		1.1
2	16:00	28,000	110.9			
2	22:00				4	
3	8:00	28,000	110.9			
3	13:40			1.34 (= C)		
3	22:00	28,000	110.9		2	
4	8:00					1.8
4	22:00	28,000	110.9		3	
5	8:00					2.1
5	22:00	28,000	110.9		3	
6	8:00					
6	17:00	28,000	110.9		3	
7	8:00					
7	17:00	28,000	110.9		2	
8	8:00					3.1
8	20:00	28,000	110.9		2	
9	8:00					2.7
9	14:00			0.28 (= D)		
9	20:00				2	
10	8:00					2.3

the label, tinzaparin dose corresponds to 175 IU/kg and should be based on the actual total body weight of the patient (14).

However, no dosing guidelines are available for the treatment of PE in extremely obese patients. Previously, reports of tinzaparin provided information that a safe and effective use of 175 IU/kg total body weight could only be guaranteed for total body weights up to 160 kg (2). A similar linear weight-based dosing regimen using once daily dalteparin has been proposed before, but total body weights were restricted to a maximum of 190 kg and the indication was treatment of venous tromboembolism instead of PE (14-15). Also for enoxaparin linear weight-based schemes have been reported up to a total body weight of 165 kg for the treatment of acute venous thromboembolism (16), which is similar to the proposed weight-based regimen for nadroparin in the prophylaxis of tromboembolism in obese patients up to a total body weight of 152 kg (17). The patient described in this report weighs over 250 kg, which results in a very high dose when total body weight is used for calculation of the dose, thereby potentially leading to bleeding risks. Therefore a fixed dose, capped at a 160 kg was considered, similar to a previously proposed dosing regimen for enoxaparin, e.g. a standard dose of 40 mg for a BMI up to 50 kg/m^2 and 60 mg enoxaparin for a BMI higher than 50 kg/m^2 (18). For the same reasons of safety issues, more recently, a dosage based on lean body weight (LBW) has been proposed (19), which results in lower dosages compared to calculations based on total body weight in extremely obese patients such as in our case. LBW is based on sex, weight and height and does not linearly increase with total body weight and is therefore expected to correlate better with the clearance of LMWHs (20). However, this study was performed in only 11 patients with a maximum total body weight of 120 kg, and therefore, the wide introduction of LBW as a basis for dosing in extremely obese patients may be too early. Beside safety issues, the final decision to administer a dose capped at a total body weight of 160 kg was also based on reports in obese patients that total body weight is not a significant predictor for tinzaparin clearance (3). Additionally, based on the pharmacokinetic properties of LMWH, the volume of distribution of tinzaparin was not expected to have a linear relationship with total body weight in extremely obese patients (e.g. BMI > 50 kg/m^2 or total body weight > 150 kg) as tinzaparin does not expected to distribute in adipose tissue. As a result of all these considerations, it was concluded that the use of a linear weight-based dosing regimen in extremely obese patients may potentially lead to overdosing and higher risks of bleeding (6), and therefore in our case a dose cap at 160 kg was chosen together with anti-Xa measurements.

A possibility to evaluate the efficacy of a proposed dosing regimen is to monitor anti-Xa levels. Although the relationship between anti-Xa levels and efficacy or safety of LMWH treatment is not entirely clear (6, 21), levels

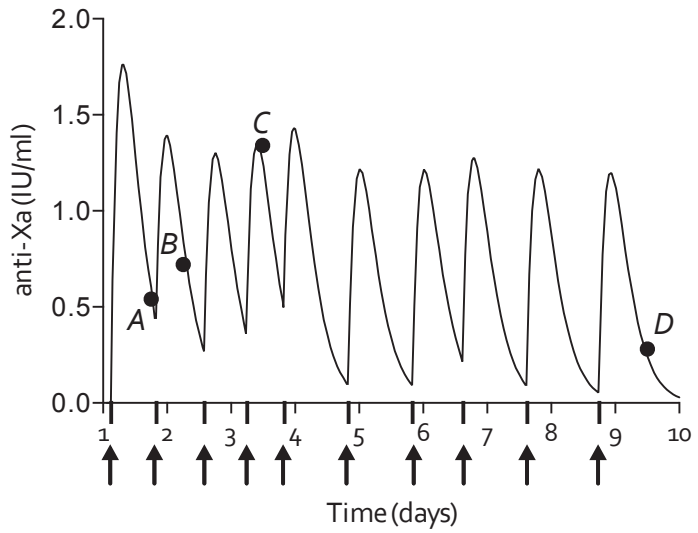


Figure 1 *Observed anti-Xa levels (circle) in the 252 kg patient with line of best fit according to a one-compartment model (line) and dosing records of tinzaparin (arrow). Measured anti-Xa levels are plotted in the figure (A, B, C and D), for details see table 1. Day 1 is the day the patient arrived at our hospital.*

of 1.0- 2.0 IU/mL have been suggested for treatment of PE with once daily tinzaparin, when measured 4-5 hours after the subcutaneous injection on day 3 (22). Additionally, for enoxaparin, it has been demonstrated that anti-Xa concentrations lower than 0.5 IU/mL, 4-6 h after administration of the second dose, resulted in an increased risk of mortality at 30 days (5). Results from a study in obese volunteers with a maximum total body weight of 165 kg (BMI of 61 kg/m^2) show that the maximum concentration of anti-Xa was 0.81 IU/mL (0.76 – 0.86 IU/mL) 4 h after subcutaneous administration of a single dose of 175 IU/kg tinzaparin (2), which seems to be in accordance with the previously mentioned target concentrations. Also in our patient, we monitored anti-Xa concentrations in order to evaluate whether our assumptions on tinzaparin behaviour in extremely obese patients were correct. We found that all anti-Xa concentrations were within the predetermined target values (see Table I).

For the purpose of the current report, we retrospectively fitted the anti-Xa measurements of the patient from Table I using a one-compartment pharmacokinetic model (iterative two-stage Bayesian fitting using MWPharm 3.50, Mediware, The Netherlands) with pharmacokinetic parameters of tinzaparin in non-obese patients (23). It was found that the line very adequately described the observed anti-Xa levels in our patient, which seems to confirm our assumption that tinzaparin does not distribute any further over adipose tissue in extremely obese patients (Figure 1; pharmacokinetic parameters of anti-Xa in this patient were found to be 1.14 L/h for clearance, 5.28 L for volume of distribution with an assumed bioavailability of 59%). From Figure 1 it can also be concluded that, based on measurements at day 1, pharmacokinetic modelling can be applied to estimate whether the target concentration, which is defined for day 3, will be reached, as the line of best fit very adequately describes the observed anti-Xa concentrations. However, it should be realized that there is a highly degree of uncertainly because the fitted data is based on 4 measurements of anti-Xa of only one extremely obese patient, and therefore, more research is needed to confirm these findings.

In summary, this case describes the successful treatment of PE in a 252 kg patient (BMI 74 kg/m2) with tinzaparin in a fixed dose of 28,000 IU per day, corresponding to 175 IU/kg for a total body weight of 160 kg. Larger studies are needed to confirm whether this fixed dose of tinzaparin is effective and safe in extremely obese patients.

References

1.Eikelboom JW, Karthikeyan G, Fagel N, et al. American association of orthopedic surgeons and american college of chest physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: what are the implications for clinicians and patients? Chest. 2009 Feb;135(2):513-20.

2.Hainer JW, Barrett JS, Assaid CA, et al. Dosing in heavy-weight/obese patients with the LMWH, tinzaparin: a pharmacodynamic study. Thromb Haemost. 2002 May;87(5):817-23.

3.Barrett JS, Gibiansky E, Hull RD, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. Int J Clin Pharmacol Ther. 2001 Oct;39(10):431-46.

4.Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med. 1992 Apr 9;326(15):975-82.

5.Montalescot G, Collet JP, Tanguy ML, et al. Anti-Xa activity relates to survival and efficacy in unselected acute coronary syndrome patients treated with enoxaparin. Circulation. 2004 Jul 27;110(4):392-8.

6.Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3 Suppl):188S-203S.

7.Kopelman PG. Obesity as a medical problem. Nature. 2000 Apr 6;404(6778):635-43.

8.WorldHealthOrganisation. Obesity: Preventing and Managing the Global Epidemic. Geneva: World Health Organisation1997.

9.Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 2006 Apr 5;295(13):1549-55.

10.Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Arch Intern Med. 2003 Jul 28;163(14):1711-7.

11.Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. Jama. 1997 Feb 26;277(8):642-5.

12.Wells PS, Anderson DR, Rodger MA, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Arch Intern Med. 2005 Apr 11;165(7):733-8.

13.Hull RD. Treatment of pulmonary embolism: The use of low-molecular-weight heparin in the inpatient and outpatient settings. Thromb Haemost. 2008 Mar;99(3):502-10.

14.Neely JL, Carlson SS, Lenhart SE. Tinzaparin sodium: a low-molecular-weight heparin. Am J Health Syst Pharm. 2002 Aug 1;59(15):1426-36.

15.Wilson SJ, Wilbur K, Burton E, et al. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular- weight heparin for the treatment of venous thromboembolism. Haemostasis. 2001 Jan-Feb;31(1):42-8.

16.Davidson BL, Buller HR, Decousus H, et al. Effect of obesity on outcomes after fondaparinux, enoxaparin, or heparin treatment for acute venous thromboembolism in the Matisse trials. J Thromb Haemost. 2007 Jun;5(6):1191-4.

17.Heizmann M, Baerlocher GM, Steinmann F, et al. Anti-Xa activity in obese patients after double standard dose of nadroparin for prophylaxis. Thromb Res. 2002 May 15;106(4-5):179-81.

18.Borkgren-Okonek MJ, Hartm DR, Pantanom DJ, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis. 2008 Feb 6;In press.

19.Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004 Aug;58(2):119-33.

20.Barras MA, Duffull SB, Atherton JJ, et al. Individualized compared with conventional dosing of enoxaparin. Clin Pharmacol Ther. 2008 Jun;83(6):882-8.

21.Paige JT, Gouda BP, Gaitor-Stampley V, et al. No correlation between anti-factor Xa levels, low-molecular-weight heparin, and bleeding after gastric bypass. Surg Obes Relat Dis. 2007 Jul-Aug;3(4):469-75.

22.Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3 Suppl):401S-28S.

23.Pedersen PC, Ostergaard PB, Hedner U, et al. Pharmacokinetics of a low molecular weight heparin, logiparin, after intravenous and subcutaneous administration to healthy volunteers. Thromb Res. 1991 Mar;61(5-6):477-87.

Thromboprophylaxis in obese surgical patients in the Netherlands, current practice and a review of the available guidelines

09

Jorine Boer, Jeroen Diepstraten, Marije Russcher, Catherijne A. J. Knibbe, Bert van Ramshorst

Submitted for publication

Abstract

Background
Obesity is associated with an increased risk of venous thromboembolism. Low-molecular-weight heparins (LMWH) significantly reduce this risk. So far there is no consensus on the optimal dose and duration of LMWH in obese patients. The aim of this study is to assess the current practice of thromboprophylaxis in obese patients in the Netherlands and to describe current guidelines for thromboprophylaxis in obese patients.
Methods
Data on type, duration and dose of thromboprophylaxis for obese patients from all the departments of general surgery (n=90) in the Netherlands were obtained by online questionnaires and telephone interviews. A literature search was conducted to identify available guidelines.
Results
With a response of 93% (n=84) of institutes, 63% reported the use of an in-hospital protocol of thromboprophylaxis for surgical patients. In 77% LMWH dose was adjusted, based on pre-determined total body weight (72%) or body mass index (BMI) (18%). Most hospitals (62%) doubled the standard dose above a pre-determined cut-off limit of body weight. These cut-off limits varied widely ranging from 70-150 kg total body weight or a BMI from 30-50 kg/m^2. In 13% of hospitals obese patients were given thromboprophylaxis for an extended period after discharge, with a maximum of six weeks. None of the identified guidelines in the literature search included advice about dose adjustments or adjustments in duration of thromboprophylaxis for this special group of patients.
Conclusion
There is a wide variety in the current practice of thromboprophylaxis in obese surgical patients in the Netherlands. As current guidelines lack practical dosing advices, further research to identify the optimal dose and duration is mandatory.

Introduction

The prevalence of obesity (body mass index (BMI) > 30kg/m^2) has doubled worldwide in the last two decades, now affecting a global estimate of over 1.7 billion individuals (1, 2). Obesity is associated with multiple co-morbidities, such as type 2 diabetes mellitus and hypertension (2), and a two to three times increased relative risk of venous thromboembolism (VTE) compared to non-obese patients (3).
The administration of low-molecular-weight heparins (LMWH) in surgical patients significantly reduces the incidence of VTE postoperatively (4-6). LMWH derives its antithrombotic activity mainly by binding to anti-thrombin and thereby trapping factor Xa out of the coagulation. LMWH has several benefits over unfractionated heparin, such as a single daily dosing, a more predictable dose-response relationship and a higher effectiveness in the prevention of VTE following bariatric surgery (7, 8).
The increase in the prevalence of obesity introduces new issues in patient care such as the optimal dose and duration of administration of LMWH for this group of patients. Only few studies are available on the optimal dosage of LMWH in patients with (morbid) obesity (9-11), as this patient group is often excluded from clinical trials.
We conducted a survey to analyse the current practice in thromboprophylaxis in obese surgical patients in the Netherlands and conducted a literature search to identify specific guidelines on dosing and duration of thromboprophylaxis in obese patients.

Methods

Questionnaire
The survey was designed using freely available Google™ Docs tools (Google Inc, CA, USA) and was uploaded as a Google™ Docs form. A link to the questionnaire with an introductory cover letter was sent by email to one representative of each department of general surgery (n=90) in the Netherlands. The survey consisted of 10 multiple choice questions and two open questions on thromboprophylaxis in obese patients (Table I). Type of coagulation, duration and dose of thromboprophylaxis in obese patients were assessed, as well as the used definition of obesity and the availability of hospital-based guidelines concerning thromboprophylaxis in obese patients. Data were completed by repeated mailing and telephone interviews with non-responders.

Table I *Questions of survey on prophylactic doses of low-Aolecular weight heparin in obese surgical patients.*

1.Which low-molecular-weight heparin (LMWH) is used in healthy normal-weight and obese patients for thromboprophylaxis?
2.What LMWH dose is used in healthy normal-weight patients for thrombosis prophylaxis?
3.How many days will thromboprophylactic therapy with LMWH be continued after general surgical procedures to prevent venous thromboembolic complications in normal-weight patients with a healthy kidney function (patients without oral anticoagulation)?
4.Will the prophylactic dose of LMWH be adjusted for obese patients?
5.Is there a protocol for prophylactic dose adjustment of LMWH in obesity in your hospital?
6.If so, to what patient groups does this protocol apply?
7.What is the cut-off body weight for LMWH adjustment?
8.Based on what body weight will LMWH doses be adjusted?
9.How will LMWH doses be adjusted in obesity?
10.How many days will LMWH be continued after general surgical procedures to prevent venous thromboembolic complications in obese patients (patients without oral anticoagulation and normal kidney function)?
11.Are anti-Xa levels checked in obese patients receiving venous thromboembolic prophylaxis?
12.Does the surgical department in your hospital perform bariatric procedures?

Statistical methods
Data analysis was done using SPSS 17.0 (IBM Corporation, NY, USA) for Windows. We compared differences in prescription practice in teaching hospitals (university and non-university) to non-teaching hospitals, and bariatric clinics to non-bariatric clinics using the chi-squared test. The probability level accepted for statistical significance was set at $p < 0.05$ for all comparisons.

Guidelines
A literature search for (inter)national guidelines on thromboprophylaxis in obese patients was performed in Pubmed and SUM Search. The following search terms were used ("Thrombosis"[Mesh] OR "Venous Thrombosis"[Mesh] OR "thrombosis" OR "thromboprophylaxis" OR "thromboembolism") AND ("Heparin, Low-Molecular-Weight"[Mesh] OR "low-molecular weight heparin" OR "LMWH") AND ("Guideline" OR "Guidelines as Topic"[Mesh] OR "Guideline" [Publication Type]).

Results

Questionnaire

Of the 90 contacted surgical departments, questionnaires were completed by 84 hospitals (93% response). The most commonly used LMWH for VTE prophylaxis was nadroparin (n=62, 74%), followed by dalteparin (n=16, 19%) and enoxaparin (n=6, 7%). Of the hospitals that used nadroparin, 74% (n=55) used nadroparin 2,850 IU once daily as standard dose for non-obese patients. Dalteparin was most commonly dosed as 2,500 IU per day (n=13, 81%), although three hospitals (19%) reported a dosage of 5,000 IU for non-obese patients. Enoxaparin was either dosed as 20 mg per day (n=3, 50%) or 40 mg per day (n=3, 50%) for non-obese patients. The majority of the surgical departments continued thromboprophylaxis in non-obese patients until discharge (n=69, 82%). In 12% of hospitals (n=10) thromboprophylaxis was extended in these patients after discharge until the non-obese patient was ambulating well. The duration of thromboprophylaxis was reported to be depending on the surgical procedure in 5% of the hospitals.

Of all institutes, 63% (n=53) reported the use of an in-hospital thromboprophylaxis protocol for obese patients. In 65 hospitals (77%), the prophylactic LMWH doses were adjusted for obese patients. Adjustments were mostly based on total body weight (n=47, 72%) and less commonly on pre-determined BMI (n=12, 18%), individual characteristics (n = 1) or in consultation with the anaesthesiologist (n = 1). Four hospitals (6%) did not report the basis on which the LMWH dose was adjusted. In two hospitals (3%), LMWH dose was only adjusted in (morbidly) obese patients undergoing bariatric surgery.

Cut-off limits for dosing adjustment varied widely, with a median BMI of 33 kg/m2 (range 30 - 50 kg/m^2), and a median total body weight of 80 kg (range 70 - 150 kg). Two hospitals used variable cut-off limits, based on individual characteristics. Most centres adjusted LMWH doses by doubling the dose used in non-obese patients (n=53, 62%). In other hospitals (n=7, 8%), the dose of LMWH was increased with a factor 1.3 - 1.5, resulting for nadroparin in 3,800 IU (n=6) and for dalteparin in 7,500 IU (n=1). Five hospitals (6%) individualized the LMWH by dosing on IU per kilograms. Eleven hospitals (13%) extended the LMWH prophylaxis in patients with obesity, to a duration varying from 1 to 6 weeks postoperative. In 7% (n=6) of the hospitals, anti-Xa levels were measured in individual cases. However, none of these hospitals reported whether and how the dose of LMWH should be adjusted based on these anti-Xa levels.

Comparing teaching hospitals (n=52) with non-teaching hospitals (n=32), we found no significant differences for type of LMWH, adjustment of dose or duration, presence of an in-hospital protocol for obese patients or testing of anti-Xa levels (Table II). Dose adjustment of LMWH did not significantly vary between bariatric (n=27, 32%) and non-bariatric centres (n=57, 68%). Bariatric clinics did more often extend the duration of thromboprophylaxis (33% versus 4%, p<0.005), however in some of these clinics thromboprophylaxis was only extended in patients undergoing bariatric surgery (n=3). Neither the choice of LWMH, nor the existence of a protocol for adjusting LMWH in obese patients, nor the number of hospitals testing anti-Xa levels did significantly differ between bariatric and non-bariatric centres (Table III).

Table II *Survey results of teaching hospitals versus non-teaching hospitals.*

	Total (n=84) n (%)	Non-teaching (n = 32) n (%)	Teaching (n = 52) n (%)	p-value
LMWH used:				0.058
dalteparin	16 (19)	6 (19)	10 (19)	
enoxaparin	6 (7)	5 (16)	1 (2)	
nadroparin	62 (74)	21 (66)	41 (79)	
Adjusting LMWH dose for obese	65 (77)	38 (73)	27 (84)	0.229
Adjusting LMWH duration for obese	11 (13)	2 (6)	9 (17)	0.145
Existence of hospital protocol for obese	53 (63)	22 (73)	31 (67)	0.582
Anti-Xa tested in obese	6 (7)	1 (3)	5 (10)	0.258

Guidelines

The most recent guideline on thromboprophylaxis is the guideline of the American College of Chest Physicians (ACCP), which has been revised in February 2012. This 9th edition advises to follow manufacturers' recommendation for pharmacological thromboprophylaxis (12-14). The ACCP guideline recognized obesity as a risk factor for VTE in both medical and bariatric surgical patients. It states that even though coagulation monitoring is generally not necessary, monitoring in special patient groups, including obese patients is advised (14). The guidelines of the National Institute for Health and Clinical Excellence (NICE) (15) and the Dutch Institute for Healthcare Improvement (16) also recognize obesity as a risk factor, but do not include advices about adjustments in dose or duration of thromboprophylaxis in obese patients. The guideline of the Scottish

Table III *Survey results of bariatric clinics versus non-bariatric clinics.*

	Total (n=84) n (%)	Bariatric (n = 27) n (%)	Non-bariatric (n = 57) n (%)	p-value
LMWH used:				0.073
dalteparin	16 (19)	8 (30)	8 (14)	
enoxaparin	6 (7)	0 (0)	6 (11)	
nadroparin	62 (74)	19 (70)	43 (75)	
Adjusting LMWH dose for obese	65 (77)	21 (78)	44 (77)	0.952
Adjusting LMWH duration for obese	11 (13)	9 (33)	2 (4)	< 0.05
Existence of hospital protocol for obese	53 (63)	18 (72)	35 (69)	0.764
Anti-Xa tested in obese	6 (7)	2 (8)	4 (7)	0.946

Intercollegiate Guidelines Network (SIGN) does include obesity as a risk factor, but consequently states that patients undergoing bariatric surgery should receive thromboprophylaxis as recommended for those undergoing general surgery. Weight-based dose adjustments are not advised for LMWH according to the SIGN guideline, although it is advised to monitor LMWH activity in patients at extremes of weight (17). The German guideline describes obesity as a moderate risk factor and it recognizes that sometimes weight-based dose adjustments are made, without any specification or appraisal. No specific recommendations regarding dose or duration adjustments are made (18). The guideline of the French Society of Anaesthesiology and Reanimation only advises dose adjustments of prophylactic LMWH in overweight obstetric patients and does not make specific recommendations for surgical patients (19).

Discussion

In this survey we showed that in the majority of hospitals (77%), the LMWH dose is increased for obese patients but various regimens are used in clinical practice both in terms of dosing and duration of antithrombotic treatment. Besides, available guidelines lack practical dosing advices for this special group of patients.

Obesity, defined as a BMI > 30 kg/m^2 or greater, is a known risk factor for venous thromboembolism (VTE) (20) with a more than two times increased relative risk for deep venous thrombosis (DVT) (3) and pulmonary embolism (PE) for hospitalized patients compared to non-obese (21). A linear association between body weight and risk of VTE has been shown with an estimated six-fold increase in the risk of PE in women with a BMI > 35 kg/m^2 (22). With the rising incidence of obesity, health services worldwide are confronted with an ever increasing number of patients undergoing bariatric surgery. Most clinical trials and retrospective analyses on the incidence of VTE in (morbidly) obese patients involve the group of patients undergoing bariatric surgery. The perioperative incidence of VTE, either symptomatic or asymptomatic, after laparoscopic bariatric surgery appears to be relatively low (below 1%), regardless of the antithrombotic prophylaxis regimen (23). This is probably due to short operation times and short immobilization. The incidence of VTE after laparoscopic bariatric surgery for patients receiving thromboprophylactic therapy increases to almost 3% up to 6 months following surgery (24). Within the bariatric population, several contributing risk factors identified for VTE were: previous VTE, age > 55 years, smoking and male sex (24). The risk of postoperative VTE in obese patients undergoing orthopaedic, major gynaecological of oncologic abdominal surgery may be higher, underlining the need for optimal and individualized prophylactic therapy in this special group of patients.

Different dosing strategies for LMWH in obese patients have been proposed but most reports are inconclusive on how to individualize the LMWH dosing regimen (9-11). Retrospective subgroup analyses from large VTE prophylaxis trials using a similar standard dose of LMWH in obese and non-obese hospitalized patients show no significant difference in postoperative VTE in both groups (25, 26). Prospective studies on different dosing regimens for VTE prophylaxis in morbidly obese subjects, mostly involving patients undergoing bariatric surgery, show equivocal results. Kalfarentos et al. comparing two doses of nadroparin (5,700 IU vs. 9,500 IU) in a randomized study among morbidly obese patients undergoing Roux-en-Y gastric bypass surgery, reported no VTE events in both groups. However, the higher dose resulted in two major haemorrhages while no major bleeding event occurred in patients receiving the lower dose (27). A higher dose of 40 mg enoxaparin showed to reduce non-fatal VTE compared to 30 mg for obese patients (0.6% vs. 5.4%) without increased incidence of bleeding complications (28). Singh et al. found no VTE events in 170 morbidly obese patients (BMI 40-59 kg/m^2) using a BMI-stratified enoxaparin dosing schedule, with doses ranging for 30 to 60 mg (29). These results support the evidence to increase the LMWH dose for obese patients, although the optimal dose is still unknown.

As there are currently no evidence-based dosing guidelines available for prophylactic LMWH therapy in obese patients, monitoring of anti-Xa levels

four hours after the first dose is often recommended (30). No therapeutic range has been defined for obese patients, but it seems rational to aim for the prophylactic range in non-obese patients of 0.2-0.5 IU/mL at four hours after administration of LMWH (11). Most studies have focused on the effect of increased LMWH doses on anti-Xa levels. Rowan et al. achieved a higher percentage of therapeutic anti-Xa levels (9% vs. 41.7%) for 40 mg enoxaparin compared to 30 mg enoxaparin (31). Although therapeutic levels were not reached in over 50% of patients, no VTE events were reported. In another study less subtherapeutic levels (0% vs. 40%) were achieved with a higher dose of 60 mg enoxaparin compared to 40 mg enoxaparin, without increasing the number of bleeding complications (32). Both studies involved patient groups with a mean BMI of 48 kg/m^2 (31, 32). Although results of some of the aforementioned studies may seem inconclusive, it appears that a standard dose of LMWH as used in the non-obese population is insufficient in the (morbidly) obese population and dose adjustments are warranted. A recent review by Nutescu et al. recommended a 30% higher dose for morbidly obese patients, as well as monitoring anti-Xa levels in individuals weighting over 190 kilograms (11).

In a previous study among bariatric patients we showed that after a double dose of nadroparin compared to non-obese patients, still 50% of the morbidly obese patients showed peak anti-Xa levels below the recommended range. These peak anti-Xa levels correlated with lean body weight and therefore lean body weight was proposed as dosing scalar for thromboprophylaxis with LMWH nadroparin (33). In addition, peak anti-Xa levels in morbidly obese patients were not found to correlate with total body weight or BMI (34). As LMWH distribute mainly to the intravascular compartment, instead of tissues and body fat, these findings might be explained by the non-linear increase of plasma volume with the increase in total body weight (35).

The currently available guidelines do not specifically advise dose adjustment of LMWH in morbidly obese patients, and most recommend to use product labels (12-19). This advice is often ignored, as proven by Barras et al., showing that 96% of questioned hospitals had a LMWH strategy that contravened with product labels (9). In clinical practice in Dutch hospitals, 62% of the hospital doubled the LMWH dose for thromboprophylactic therapy in obese patients. However, the cut-off point for body weight above which the LMWH dose was increased differed between hospitals.

Beside the optimal dose, there is debate about the duration of prophylaxis after surgery. Our study shows that extended duration of prophylaxis is not yet common practice in the Netherlands. Only 13% of respondents indicate to adjust duration of prophylaxis in obese patients. Significantly more surgical departments performing bariatric surgery (33%, $p<0.05$) extended the duration of thromboprophylaxis after discharge. The benefits of extended duration of prophylaxis have been studied in bariatric populations and showed a reduced incidence of thromboembolic complications in patients receiving prophylaxis up to ten days post-discharge (10, 36, 37). To date, guidelines do not include this evidence.

As bariatric procedures are exponentially increasing worldwide this patient group could be a target population for the study of perioperative thromboprophylaxis regimen in the subset of obese patients. As the incidence of post-operative VTE appears to be rather low in the bariatric population, future studies should focus on risk groups within this population, i.e. patients within the highest ranges of BMI or comorbidities. Prospective studies should identify the optimal dosing schedules for the obese patients and clarify the benefit of extended prophylaxis. The increasing numbers of obese surgical patients and the current wide variety in the practice of thromboprophylaxis demonstrate the necessity of uniform guidelines for LMWH prophylaxis in obese patients.

References

1. Deitel M. Overweight and obesity worldwide now estimated to involve 1.7 billion people. Obes Surg. 2003;13(3):329-30.
2. Kopelman PG. Obesity as a medical problem. Nature. 2000;404(6778):635-43.
3. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005;118(9):978-80.
4. Alikhan R, Cohen AT. Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). Cochrane Database Syst Rev. 2009(3):CD003747.
5. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg. 2001;88(7):913-30.
6. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev. 2009(1):CD004318.
7. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):338S-400S.
8. Birkmeyer NJ, Finks JF, Carlin AM, Chengelis DL, Krause KR, Hawasli AA, et al. Comparative Effectiveness of Unfractionated and Low-Molecular-Weight Heparin for Prevention of Venous Thromboembolism Following Bariatric Surgery. Arch Surg. 2012;147(11):994-8.
9. Barras MA, Kirkpatrick CM, Green B. Current dosing of low-molecular-weight heparins does not reflect licensed product labels: an international survey. Br J Clin Pharmacol. 2010;69(5):520-8.
10. Borkgren-Okonek MJ, Hart RW, Pantano JE, Rantis PC, Jr., Guske PJ, Kane JM, Jr., et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis. 2008;4(5):625-31.
11. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-83.
12. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e24S-43S.
13. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in Nonorthopedic Surgical Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S-77S.
14. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e326S-50S.
15. Hill J, Treasure T. Reducing the risk of venous thromboembolism in patients admitted to hospital: summary of NICE guidance. BMJ. 2010;340:c95.
16. CBO. Diagnostiek, preventie en behandeling van veneuze trombo-embolie en secundaire preventie arteriële trombose (Dutch). Utrecht: CBO; 2009.
17. SIGN. Prevention and management of venous thromboembolism. A national clinical guideline. Edinburgh, Scotland: 2011.
18. AWMF. Leitlinie Prophylaxe der venösen Thromboembolie (VTE). Marburg, Germany: 2010.
19. SFAR. Prévention de la maladie thromboembolique veineuse périopératoire et obstétricale. Recommandations pour la pratique clinique. Nancy, France: 2005.
20. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):381S-453S.
21. Stein PD, Matta F, Goldman J. Obesityand pulmonary embolism: The mounting evidence of risk and the mortality paradox. Thromb Res. 2011. Epud 2011/11/15
22. Kabrhel C, Varraso R, Goldhaber SZ, Rimm EB, Camargo CA. Prospective study of BMI and the risk of pulmonary embolism in women. Obesity (Silver Spring). 2009;17(11):2040-6.
23. Becattini C, Agnelli G, Manina G, Noya G, Rondelli F. Venous thromboembolism after laparoscopic bariatric surgery for morbid obesity: clinical burden and prevention. Surg Obes Relat Dis. 2012;8(1):108-15.
24. Steele KE, Schweitzer MA, Prokopowicz G, Shore AD, Eaton LC, Lidor AO, et al. The long-term risk of venous thromboembolism following bariatric surgery. Obes Surg. 2011;21(9):1371-6.
25. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. Blood Coagul Fibrinolysis. 2003;14(4):341-6.
26. Kucher N, Leizorovicz A, Vaitkus PT, Cohen AT, Turpie AG, Olsson CG, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med. 2005;165(3):341-5.
27. Kalfarentzos F, Stavropoulou F, Yarmenitis S, Kehagias I, Karamesini M, Dimitrakopoulos A, et al. Prophylaxis of venous thromboembolism using two different doses of low-molecular-weight heparin (nadroparin) in bariatric surgery: a prospective randomized trial. Obes Surg. 2001;11(6):670-6.
28. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obes Surg. 2002;12(1):19-24.
29. Singh K, Podolsky ER, Um S, Saba S, Saeed I, Aggarwal L, et al. Evaluating the safety and efficacy of BMI-based preoperative administration of low-molecular-weight heparin in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. Obes Surg. 2012;22(1):47-51.
30. Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost. 2004;2(4):547-50.
31. Rowan BO, Kuhl DA, Lee MD, Tichansky DS, Madan AK. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. Obes Surg. 2008;18(2):162-6.
32. Simone EP, Madan AK, Tichansky DS, Kuhl DA, Lee MD. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. Surg Endosc. 2008. Epud 2008 Jul 2
33. Diepstraten J, Hackeng CM, Van Kralingen S, Zapletal J, Van Dongen EP, Wiezer MJ, et al. Anti-Xa levels 4 hours after subcutaneous administration of 5700 IU nadroparin strongly correlate with lean body weight in morbidly obese patients. Obes Surg. 2012;Epub 1 feb.
34. Rondina MT, Wheeler M, Rodgers GM, Draper L, Pendleton RC. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res. 2010;125(3):220-3.
35. Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006;16(6):773-6.
36. Hamad GG, Choban PS. Enoxaparin for thromboprophylaxis in morbidly obese patients undergoing bariatric surgery: findings of the prophylaxis against VTE outcomes in bariatric surgery patients receiving enoxaparin (PROBE) study. Obes Surg. 2005;15(10):1368-74.
37. Raftopoulos I, Martindale C, Cronin A, Steinberg J. The effect of extended post-discharge chemical thromboprophylaxis on venous thromboembolism rates after bariatric surgery: a prospective comparison trial. Surg Endosc. 2008;22(11):2384-91.

Anti-Xa levels 4 h after subcutaneous administration of 5,700 IU nadroparin strongly correlate with lean body weight in morbidly obese patients

10

Jeroen Diepstraten, Christian M. Hackeng, Simone van Kralingen, Jiri Zapletal, Eric P.A. van Dongen, René J. Wiezer, Bert van Ramshorst, Catherijne A.J. Knibbe

Obesity Surgery 2012, published online

Abstract

Background

Morbidly obese patients (BMI > 40 kg/m^2) are at increased risk for venous thromboembolism, especially after surgery. Despite limited evidence, morbidly obese patients are often administered a double dose of nadroparin for thromboprophylaxis compared to non-obese patients. The aim of this study was to evaluate the influence of different body size descriptors on anti-Xa levels after a double dose of nadroparin (5,700 IU) in morbidly obese patients.

Methods

In 27 morbidly obese patients with a mean total body weight (TBW) of 148 kg (range 107 – 260 kg), anti-Xa levels were determined peri-operatively until 24 h after administration of a subcutaneous dose of 5,700 IU of nadroparin.

Results

Anti-Xa level 4 h after administration (A_{4h}, mean 0.22 ± 0.07 IU/ml) negatively correlated strongly with lean body weight (LBW) (r = -0.66 (p<0.001)), moderately with TBW (r = -0.56 (p=0.003)) and did not correlate with BMI (r = -0.26 (p=0.187)). The area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}, mean 2.80 ± 0.97 h*IU/ml) correlated with LBW (r = -0.63 (p=0.007)), but did not correlate with TBW (r = -0.44 (p=0.075)) or BMI (r = -0.10 (p=0.709)).

Conclusion

Following a subcutaneous dose of nadroparin 5,700 IU, A_{4h} and AUA_{0-24h} were found to negatively correlate strongly with LBW. From these results, individualized dosing of nadroparin based on LBW should be considered in morbidly obese patients.

Introduction

Currently more than 30% of the US population is obese (Body Mass Index (BMI)>30 kg/m²) and 2.8% of adult men and 6.9% of adult women are morbidly obese (BMI>40 kg/m²) (1). Consequently, there is a marked increase of this special group of patients presenting for various types of surgery, including bariatric surgery. In obese patients, the relative risk for venous thromboembolism (VTE) is more than doubled compared to non-obese patients, and even five times higher in obese patients with an age of 40 years or younger (2).

Low-molecular-weight heparins (LMWH) have shown to substantially reduce the risk for VTE by inactivating clotting factor Xa (3-4). Compared to unfractionated heparin, LMWH have a more favourable benefit-risk ratio and a more predictable dose-response relationship (5). In the ACCP guidelines, LMWH are recommended for prophylactic use in morbidly obese patients albeit without any specific recommendation for the dose in this special population (5-6). These guidelines recommend to monitor the effect of LMWH in morbidly obese patients using anti-Xa levels (6). Since LMWH are a mixture of polysaccharides that includes biologically inactive species, it is not possible to measure LMWH levels directly (4). The commonly reported prophylactic range of anti-Xa levels for non-obese patients is 0.2 – 0.5 IU/ml 4 h after administration (7).

In the lack of specific dosing guidelines for dose adjustment of LMWH in morbidly obese patients, different body size descriptors have been proposed, such as total body weight (TBW) (8) and BMI (9-10). However, in clinical practice the prophylactic dose of LMWH is often doubled in morbidly obese patients resulting in 5,700 IU nadroparin (11). The aim of this study was to evaluate the influence of different body size descriptors on anti-Xa levels following a dose of 5,700 IU of nadroparin in morbidly obese patients. In this study, anti-Xa levels 4 h after administration (A_{4h}) and the area under the anti-Xa level-time curve from 0 to 24 h ($AUA_{0\text{-}24h}$) were considered and studied for a correlation with LBW (12), TBW and BMI.

Materials and methods

Patients

Twenty-seven morbidly obese patients scheduled to undergo laparoscopic gastric banding or gastric bypass surgery were enrolled in two prospective studies (ClinicalTrials.gov identifier cohort 1: NCT01097148 and cohort 2: NCT01309152). Patients were included if they were between 18 and 60 years old, had an American Society of Anesthesiologists (ASA) physical status classification of II or III, a normal renal and liver function as assessed by routine laboratory testing, and a BMI of over 40 kg/m² at the day of screening. Exclusion criteria included a BMI lower than 35 kg/m² at the day of surgery, LMWH administration within 48 h preceding surgery, pregnancy, breast feeding, epilepsy and known allergy for propofol, soy bean oil or egg lecithin. Both study protocols were approved by the hospitals ethics committee and written informed consent was signed by each participating patient.

Procedure

In both cohorts, before induction, an antecubital infusion line, an indwelling arterial blood pressure line and a three-lead ECG were installed. No pre-anaesthetic medication was given, and all patients were fasting for 6 h before surgery to minimize the risk of aspiration during induction. Following a propofol bolus injection of 350 mg, intravenous fentanyl and cefazolin were given in fixed doses of 250 µg and 2 g, respectively, followed by 5,700 IU (0.6 ml) nadroparin subcutaneously administered in the thigh. Anaesthesia was maintained with continuous infusions of propofol and remifentanil after induction of anaesthesia according to routine clinical practice.

Blood sampling and analytical methods

Blood samples for determination of anti-Xa-levels were collected before induction of anaesthesia (t=0), at 10, 30, 60, 90, 120, 180, 240, 300 and 420 minutes after nadroparin dosing and the next morning within 24 h after administration in cohort 1, and before induction of anaesthesia, 120 and 240 minutes after nadroparin dosing and the next morning within 24 h after administration in cohort 2. Blood samples were collected in 3.2% buffered sodium citrate containing tubes and were immediately stored on ice until centrifugation. All samples were centrifuged at 4 °C within one hour after collection to obtain plasma samples, and stored at –80 °C until analysis within 1 month after collection. Plasma levels of anti-Xa activity were measured with a STA-Rack Evolution (Diagnostica Stago, Asnières, France) using an anti-Xa clotting assay (StaClot®Heparin, Diagnostica Stago, Asnières, France). The rate of chromophobe appearance at 405 nm was measured. Calibration occurred with eight concentrations of nadroparin (STA® Multi Calibrator) in normal pooled plasma. The calibration curve was found to be linear between 0.00 and 1.60 IU/ml. The within assay and among assay precision (coefficient of variation) were 4.7 % and 4.9 %, respectively. Regression analysis was used to determine the calibration curve values from

which the experimental values were obtained.

Data analysis

Statistical software (PASW Statistics 19.0 for Windows; IBM, Chicago, IL, US) was used for statistical analysis. Continuous data were expressed as mean ± SD. To study the association between anti-Xa level 4 h after administration (A_{4h}) and the area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) and different body size descriptors (TBW, BMI and LBW (12)) the Pearson's correlations coefficient (r) was calculated. A $p<0.05$ was considered significant. The area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) was calculated using the linear trapezoidal method (13) with estimating the levels at t = 24 h using the last two or three samples. Lean body weight, which is considered to closely approximate fat free mass (12), was calculated using formulas of Janmahasatian et al, for men: (9,270 * TBW (kg)) / (6,680 + 216 * BMI) and for women: (9,270 * TBW (kg)) / (8,780 + 244 * BMI) (12).

Results

Patients and Data

Twenty-seven morbidly obese patients with a mean TBW of 149 kg (range 107 - 260 kg) were enrolled and a total of 240 blood samples were available. Nineteen patients were included from cohort 1, and eight patients from cohort 2. All demographic characteristics of the morbidly obese patients from cohort 1, cohort 2 and total study population are provided in Table I.

Anti-Xa levels 4 h after administration (A_{4h}) were available in all 27 patients of cohort 1 and 2. While in cohort 2 there were insufficient data to calculate the area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}), AUA_{0-24h} could be analyzed in 17 patients of cohort 1.

Anti-Xa levels

Mean anti-Xa levels 4 h after administration (A_{4h}) after the administration of 5,700 IU nadroparin in those morbidly obese patients and the area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) are shown in Table II. Thirteen morbidly obese patients (48%) showed anti-Xa-levels below the prophylactic range of 0.20 - 0.50 IU/ml .

Figure 1 shows that A4h strongly correlated with LBW (r = -0.66, $p<0.001$), moderately correlated with TBW (r = -0.56, p=0.003) and did not correlate with BMI (r = 0.26, p=0.187). Figure 2 demonstrates that AUA_{0-24h} strongly negatively correlated with LBW (r = -0.78, p=0.007) and did not correlate with TBW (r = -0.44, p=0.075) or BMI (r = -0.10, p=0.709).

Figure 3 shows the results of both A_{4h} and AUA_{0-24h} from this study together with previously reported values in the literature of non-obese (14-19) and (morbidly) obese patients (11, 19) versus nadroparin dose. The figure demonstrates that in non-obese patients there is a linear dose-response curve for both A_{4h} and AUA_{0-24h}. The results of this study after administration of 5,700 IU nadroparin in morbidly obese patients show an A_{4h} and AUA_{0-24h} that are lower than would be expected from these dose-response relationships. Similar results are shown for anti-Xa levels in obese patients that were previously reported (Figure 3).

Table I *Patient characteristics of twenty-seven morbidly obese patients receiving 5,700 IU nadroparin subcutaneously.*

Parameter	Total study population (mean (SD))	Cohort 1 (mean (SD))	Cohort 2 (mean (SD))
Patients (n)	27	19	8
Age (y)	44 (9)	45 (10)	40 (6)
Sex (M / F)	10 / 17	9 / 10	1 / 7
TBW (kg)	149 (32)	153 (35)	140 (23)
IBW (kg)	67 (10)	68 (11)	64 (7)
LBW (kg)	71 (14)	74 (15)	66 (9)
BMI (kg/m²)	49 (10)	50 (10)	47 (6)

BMI = body mass index; F = female; IBW = ideal body weight (28); LBW = lean body weight(12); M = male; SD = standard deviation; TBW = total body weight

Table II *Mean anti-Xa levels 4 h after administration (A_{4h}) and mean area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) after 5,700 IU of nadroparin (prophylactic range of anti-Xa levels 4 h after administration is 0.2 – 0.5 IU/ml for non-obese patients (7)).*

	Mean (SD)	Number
A_{4h} (IU/mL)	0.22 ± 0.07	27
A_{4h} percentage below prophylactic range (%)	48%	
AUA_{0-24h} (h * IU/mL)	2.80 ± 0.97	17

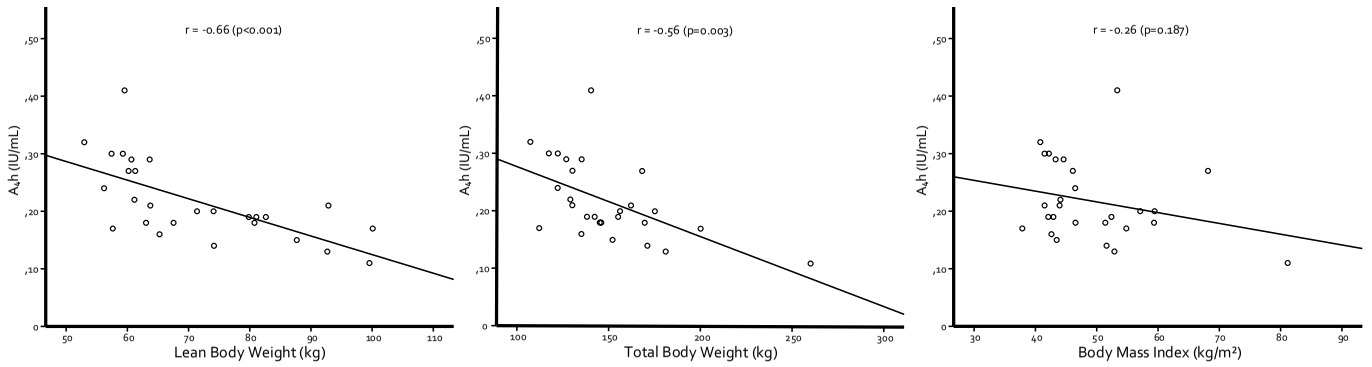


Figure 1 *Anti-Xa levels 4 h after administration (A_{4h}) versus lean body weight (12), total body weight and body mass index in 27 morbidly obese patients after administration of 5,700 IU of nadroparin subcutaneously, including Pearson's correlation coefficient (r).*

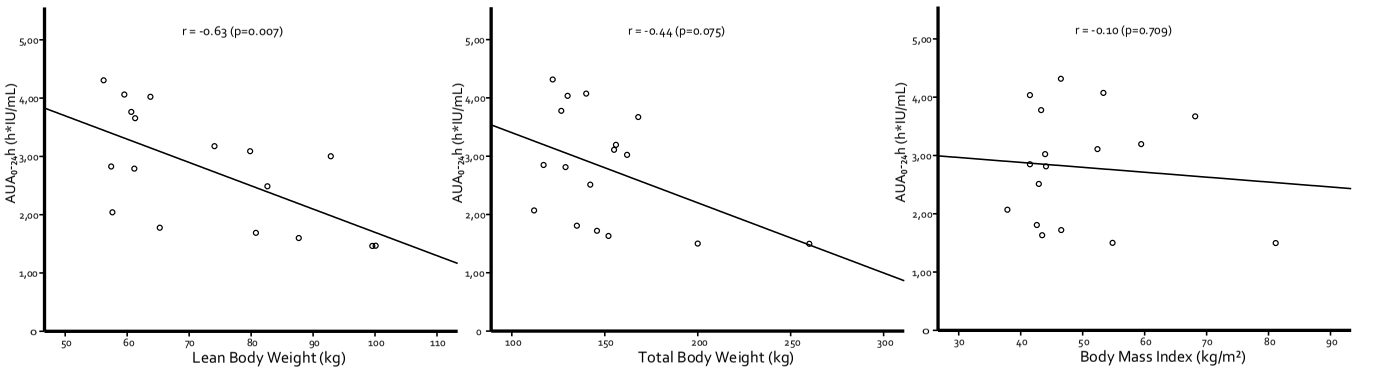


Figure 2 *The area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) versus lean body weight (12), total body weight and body mass index in 17 morbidly obese patients after administration of 5,700 IU of nadroparin subcutaneously including Pearson's correlation coefficient (r).*

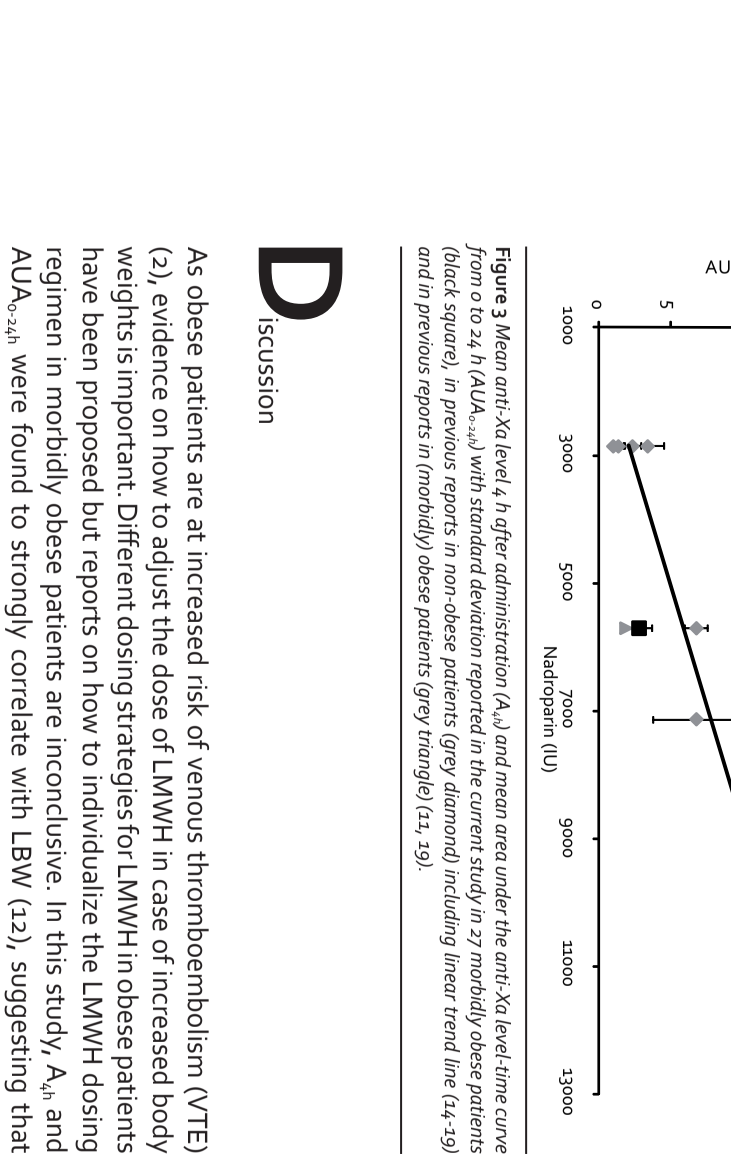


Figure 3 *Mean anti-Xa level 4 h after administration (A_{4h}) and mean area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) with standard deviation reported in the current study in 27 morbidly obese patients (black square), in previous reports in non-obese patients (grey diamond) including linear trend line (14-19) and in previous reports in (morbidly) obese patients (grey triangle) (11, 19).*

Discussion

As obese patients are at increased risk of venous thromboembolism (VTE) (2), evidence on how to adjust the dose of LMWH in case of increased body weights is important. Different dosing strategies for LMWH in obese patients have been proposed but reports on how to individualize the LMWH dosing regimen in morbidly obese patients are inconclusive. In this study, A_{4h} and AUA_{0-24h} were found to strongly correlate with LBW (12), suggesting that

this body size descriptor deserves further study in morbidly obese patients.
As stated before, measurement of anti-Xa levels is recommended in morbidly obese patients (6, 20) in absence of established dosing protocols for LMWH for these patients. Although no range has been established in morbidly obese patients and morbidly obese patients are at increased risk for VTE (2), it seems rational to aim for at least anti-Xa levels of 0.2 - 0.5 IU/mL, which is the reported prophylactic range for non-obese patients (7). Half of the morbidly obese patients in this study (48 %) showed anti-Xa levels below this window, suggesting increased doses might be necessary. In addition, since the relationship between anti-Xa levels and the occurrence of bleedings (21) or VTE (22) is unknown, studies on this relationship in morbidly obese patients receiving prophylaxis with LMWH are urgently needed to define the optimal window of anti-Xa levels in morbidly obese patients.
It has been reported before by Heizmann et al. that a linear increase in nadroparin dose does not result in a linear increase in maximum anti-Xa levels after 4 h and AUA levels in obese patients and that dosing should not be based on TBW (19). The reported anti-Xa levels were, however, not correlated to other body size descriptors and, therefore, no conclusions could be drawn on how to optimize nadroparin doses in obese patients. Similarly, for enoxaparin, peak anti-Xa levels in morbidly obese patients were not found to correlate with TBW or BMI (8). A dosing regimen based on LBW instead of TBW would seem to make more sense since it has a non-linear increase with height and TBW. It has therefore been proposed before for the therapeutic dose of enoxaparin for patients weighing more than 100 kg (23). LBW, representing fat free mass in individuals, can be measured with bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA). To estimate LBW, the formula by Janmahasatian et al. (12) is the most commonly used method as it was found to provide good predictive performance of the Fat Free Mass measured with bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA) (12). In this study, we investigated the correlation between LBW (12) and anti-Xa levels and $AUA_{0\text{-}24h}$. As shown in Figure 3, there is a substantial influence of excessive body weight on anti-Xa levels after subcutaneous administration of nadroparin in morbidly obese patients as the results of morbidly obese patients are well below the line for non-obese patients. These results seem in accordance with the correlation described in this study between LBW (12) and A_{4h}. As LMWH are mainly distributed over vascular tissue and blood, an explanation for this relation for A_{4h} may be the non-linear increase of plasma volume with body weight (24). Since there are no reports available indicating a reduced biological availability of LMWH in obese patients (25-26), it may be anticipated that the lower $AUA_{0\text{-}24h}$ in morbidly obese patients compared to non-obese patients is caused by an increased glomerular filtration in morbidly obese patients (27) which increases nadroparin clearance. These hypotheses need clarification in future studies.
In conclusion, both anti-Xa levels 4 h after administration and the area under the anti-Xa level-time curve from 0 to 24 h after subcutaneous administration of nadroparin in morbidly obese patients were negatively correlated strongly with LBW (12). From these results, individualized dosing on the basis of LBW should be considered in morbidly obese patients.

References

1. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 2006 Apr 5;295(13):1549-55.
2. Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005 Sep;118(9):978-80.
3. Turpie AG, Chin BS, Lip GY. Venous thromboembolism: pathophysiology, clinical features, and prevention. BMJ. 2002 Oct 19;325(7369):887-90.
4. Duplaga BA, Rivers CW, Nutescu E. Dosing and monitoring of low-molecular-weight heparins in special populations. Pharmacotherapy. 2001 Feb;21(2):218-34.
5. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):381S-453S.
6. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004 Sep;126(3 Suppl):188S-203S.
7. Nutescu EA, Spinler SA, Wittkowsky A, et al. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009 Jun;43(6):1064-83.
8. Rondina MT, Wheeler M, Rodgers GM, et al. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res. 2010 Mar;125(3):220-3.
9. Borkgren-Okonek MJ, Hart RW, Pantano JE, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis. 2008 Sep-Oct;4(5):625-31.
10. Singh K, Podolsky ER, Um S, et al. Evaluating the Safety and Efficacy of BMI-Based Preoperative Administration of Low-Molecular-Weight Heparin in Morbidly Obese Patients Undergoing Roux-en-Y Gastric Bypass Surgery. Obes Surg. 2011 Apr 9;Epub ahead of print.
11. Kalfarentzos F, Stavropoulou F, Yarmenitis S, et al. Prophylaxis of venous thromboembolism using two different doses of low-molecular-weight heparin (nadroparin) in bariatric surgery: a prospective randomized trial. Obes Surg. 2001 Dec;11(6):670-6.
12. Janmahasatian S, Duffull SB, Ash S, et al. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
13. Rowland M, Tozer T. Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications:. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2010.
14. Agnelli G, Iorio A, Renga C, et al. Prolonged antithrombin activity of low-molecular-weight heparins. Clinical implications for the treatment of thromboembolic diseases. Circulation. 1995 Nov 15;92(10):2819-24.
15. Boneu B, Navarro C, Cambus JP, et al. Pharmacodynamics and tolerance of two nadroparin formulations (10,250 and 20,500 anti Xa IU x ml(-1)) delivered for 10 days at therapeutic dose. Thromb Haemost. 1998 Feb;79(2):338-41.
16. Collignon F, Frydman A, Caplain H, et al. Comparison of the pharmacokinetic profiles of three low molecular mass heparins--dalteparin, enoxaparin and nadroparin--administered subcutaneously in healthy volunteers (doses for prevention of thromboembolism). Thromb Haemost. 1995 Apr;73(4):630-40.
17. Freedman MD, Leese P, Prasad R, et al. An evaluation of the biological response to Fraxiparine, (a low molecular weight heparin) in the healthy individual. J Clin Pharmacol. 1990 Aug;30(8):720-7.
18. Harenberg J, Wurzner B, Zimmermann R, et al. Bioavailability and antagonization of the low molecular weight heparin CY 216 in man. Thromb Res. 1986 Nov 15;44(4):549-54.
19. Heizmann M, Baerlocher GM, Steinmann F, et al. Anti-Xa activity in obese patients after double standard dose of nadroparin for prophylaxis. Thromb Res. 2002 May 15;106(4-5):179-81.
20. Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost. 2004 Apr;2(4):547-50.
21. Paige JT, Gouda BP, Gaitor-Stampley V, et al. No correlation between anti-factor Xa levels, low-molecular-weight heparin, and bleeding after gastric bypass. Surg Obes Relat Dis. 2007 Jul-Aug;3(4):469-75.
22. Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. J Thromb Haemost. 2004 Apr;2(4):551-4.
23. Barras MA, Duffull SB, Atherton JJ, et al. Individualized compared with conventional dosing of enoxaparin. Clin Pharmacol Ther. 2008 Jun;83(6):882-8.
24. Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006 Jun;16(6):773-6.
25. Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis. 1996;26 Suppl 2:24-38.
26. Sanderink GJ, Le Liboux A, Jariwala N, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther. 2002 Sep;72(3):308-18.
27. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. Hypertension. 1995 Oct;26(4):610-5.
28. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000 Sep;34(9):1066-9.

Population pharmacodynamic model for low-molecular-weight heparin nadroparin in morbidly obese and non-obese patients using anti-Xa levels as endpoint

11

Jeroen Diepstraten, Esther J.H. Janssen, Christian M. Hackeng,
Eric P.A. van Dongen, René J. Wiezer, Bert van Ramshorst, Catherijne A.J. Knibbe

Submitted for publication

Abstract

Background
In absence of specific dosing guidelines, the optimal dose of low-molecular-weight heparins for thrombosis prophylaxis in morbidly obese patients (BMI > 40 kg/m^2) remains unknown. In order to guide dosing in this patient group, a pharmacodynamics model is developed for nadroparin in morbidly obese and non-obese patients using anti-Xa levels as an endpoint, thereby characterizing the influence of excessive body weight on different pharmacodynamic model parameters.
Methods
Twenty-eight morbidly obese and seven non-obese patients receiving 5,700 IU and 2,850 IU s.c. nadroparin for surgery, respectively, were included with a mean total body weight (TBW) of 135 kg (range 72–252 kg). Up to 11 anti-Xa levels were collected from start until 24 hours after nadroparin administration. Population pharmacodynamic modelling with covariate analysis was performed using NONMEM.
Results
In a two-compartment pharmacodynamic model with baseline endogenous anti-Xa levels, the effect of nadroparin was found to be delayed and could be best described using a transit compartment. TBW was the most predictive covariate for clearance (CL = 23.0 mL/min * (TBW/70)), while lean body weight (LBW) proved the most predictive covariate for central volume of distribution (V1 = 7.0 L * (LBW/60)).
Conclusion
A pharmacodynamic model was developed characterizing anti-Xa levels after s.c. administration of nadroparin in patients weighing between 72 to 252 kg with TBW and LBW as the major determinant for clearance and volume of distribution, respectively. Based on simulations using the final covariate pharmacodynamic model it appeared that a dose of 5,700 IU nadroparin will lead to target anti-Xa levels in morbidly obese patients with a LBW below 90 kg.

Introduction

Western countries, the incidence of obesity (body mass index (BMI) > 30 kg/m^2) is increasing resulting in a percentage of 30% of the population of the United States (1). In addition, the incidence of morbidly obese patients (BMI > 40 kg/m^2) is on the rise as well (2, 3). Obesity is associated with a two times increased relative risk of venous thromboembolism (VTE) compared to non-obese patients (4). More specifically, the prevalence of pulmonary embolism in hospitalized patients is higher in obese patients than in non-obese patients (5).

Low-molecular-weight heparins (LMWHs) are widely used for the prevention of VTE both in non-obese patients and (morbidly) obese patients, even though for the latter population dosing advices largely vary (6). In addition, different weight scales have been proposed to adjust the dose of LMWH in obese patients, such as total body weight (TBW) (7) and BMI (8, 9). In clinical practice, the prophylactic dose of LMWH for morbidly obese patients is often capped at a certain dose, resulting for instance for nadroparin in a fixed dose of 5,700 IU (= 0.6 mL) for the heterogeneous group of morbidly obese patients in which body weights are still increasing (10).

Population modelling is a well-established approach for the characterization of the pharmacokinetics and pharmacodynamics of a drug and can serve as the scientific basis for the development of rational and individualized dosing schemes (11). Population pharmacodynamic studies of LMWHs describing the influence of body weight are scarce and do often not include morbidly obese patients. For enoxaparin in non-obese patients, both lean body weight (LBW) and TBW have been identified as the best size descriptor for clearance and volume of distribution (12-16). In a population pharmacodynamic analysis of enoxaparin in non-obese and obese patients (TBW range 66 - 160 kg), LBW proved to be the best size descriptor for clearance, while for central volume of distribution TBW was identified (17). As body weights of patients are still increasing, data should be gathered across a wide body weight range including morbidly obese patients to properly study the influence of different weight-based covariates on the pharmacodynamics of LMWHs.

Therefore, in this study a population pharmacodynamic model of nadroparin used for thrombotic prophylaxis is developed in morbidly obese and non-obese patients, using anti Xa-levels as a pharmacodynamic endpoint, in order to characterize the influence of excessive body weight on different pharmacodynamic model parameters. In a systematic covariate analysis, potential factors (TBW, BMI, ideal body weight (IBW) and LBW (18)) influencing the pharmacodynamic parameters of nadroparin are tested for their influence, ultimately to provide a guide for dosing nadroparin in morbidly obese patients.

Methods

Patients

A total of thirty-five patients were included in two prospective clinical studies: twenty-eight morbidly obese patients (BMI > 40 kg/m^2) which were scheduled to undergo laparoscopic gastric banding or gastric bypass surgery and seven non-obese patients which underwent laparoscopic Toupet fundoplication surgery (Study 1: 20 morbidly obese patients, ClinicalTrials.gov/ NCT01097148 (19) and Study 2: 8 morbidly obese patients and 7 non-obese patients, ClinicalTrials/gov/ NCT01309152). Clinical data of 27 of the 28 morbidly obese patients have been published before in a descriptive paper (19). Patients were included if they were between 18 and 60 years old, had an American Society of Anesthesiologists (ASA) physical status classification of II or III in case of morbidly obese patients and I or II for non-obese patients and had a normal renal and liver function as assessed by routine laboratory testing. Exclusion criteria included LMWH administration within 48 hours preceding surgery, pregnancy, breast feeding, epilepsy and known allergy for propofol, soybean oil or egg lecithin. Both study protocols were approved by the hospitals Ethics Committee and written informed consent was signed by each participating patient.

Procedure

In both studies, before induction of anesthesia an antecubital infusion line, an indwelling arterial blood pressure line and a three-lead ECG were installed. No pre-anesthetic medication was given and all patients were fasting for 6 hours before surgery to minimize the risk of aspiration during induction. Following a propofol bolus injection, intravenous fentanyl and cefazolin were given in fixed doses of 250 µg and 2 g, respectively. Then 5,700 IU (0.6 ml) nadroparin for morbidly obese patients and 2,850 IU (0.3 ml) nadroparin for non-obese patients was administered subcutaneously in the thigh, the exact time being recorded. Anesthesia was maintained with continuous infusions of propofol and remifentanil according to routine clinical practice.

Blood sampling and analysis

Blood samples for determination of anti-Xa levels were collected before induction of anesthesia (t=0), at 10, 30, 60, 90, 120, 180, 240, 300 and 420 minutes after nadroparin dosing and the next morning within 24 hours

after administration in the 20 morbidly obese patients of Study 1 and 7 non-obese patients of Study 2, and before induction of anesthesia, 120 and 240 minutes after nadroparin dosing and the next morning within 24 hours after administration in 8 morbidly obese patients of Study 2. Blood samples were collected in 3.2% buffered sodium citrate containing tubes and were immediately stored on ice until centrifugation. All samples were centrifuged at 4 °C within one hour after collection to obtain plasma samples, and stored at –80 °C until analysis within one month after collection. Plasma levels of anti-Xa activity were measured with a STA-Rack Evolution (Diagnostica Stago, Asnières, France) using an anti-Xa clotting assay (STA Rotachrom®Heparin 4, Diagnostica Stago, Asnières, France). The rate of chromophobe appearance at 405 nm was measured. Calibration occurred with eight concentrations of nadroparin (Lot number used for patients) in normal pooled plasma. The calibration curve was found to be linear between 0.00-1.60 IU/ml. The within assay and among assay precision (coefficient of variation) were 4.2% and 4.7%, respectively. Regression analysis was used to determine the calibration curve values from which the experimental values were obtained.

Data analysis and internal validation

The analysis was performed by means of non-linear mixed effects modelling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD, USA) (20) with S-plus (version 6.2; Insightful software, Seattle, WA, USA) for data visualization. Discrimination between different models was made by comparison of the objective function value (OFV, i.e.–2 log likelihood). A significance level of $p<0.05$, corresponding to a decrease of 3.8 in OFV, was considered statistically significant. In addition, goodness-of-fit plots (observed versus individually-predicted anti-Xa level-time, observed versus population-predicted anti-Xa level-time, conditional weighted residuals versus time and conditional weighted residuals versus population-predicted anti-Xa level-time plots) were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the models.

The internal validity of the models was assessed by the bootstrap re-sampling method using 250 replicates (20). Parameters obtained with the bootstrap replicates were compared with the estimates obtained from the original data set. Besides, normalized prediction distribution errors (NPDE) method was used to validate the model (21). This method was implemented using the NPDE add-on software package that was run in R. In this study, each observation was simulated 1000 times. The results of NPDE method are visualized in different graphs: (i) a histogram showing the distribution of the NPDEs, which are expected to follow normal distribution; (ii) a scatterplot NPDE vs. time; and (iii) a scatterplot NPDE vs. predicted anti-Xa levels.

Pharmacodynamic model of nadroparin

A one-compartment and a two-compartment model were tested to fit observed anti-Xa levels. To describe the observed delay in effect of subcutaneously administrated nadroparin, different absorption models were evaluated including a lag time model (20) and a model with one or more additional transit compartments (22). Transit compartments were described using a first-order rate constant describing the transfer from the dose compartment into the transit compartment and subsequently into the central compartment (22).

The individual value (empirical Bayes estimate) of the parameters of the i^{th} individual was modeled by (equation 1):

$$\Theta_i = \Theta_{mean} * e^{\eta_i} \qquad \text{(Eq. 1)}$$

where θ_{mean} is the population mean, and η_i is a random variable with a mean of zero and variance of ω^2, assuming log-normal distribution in the population.

The intraindividual variability, resulting from assay errors, model misspecifications and other unexplained sources, was best described with an additive error model while a proportional error model and a combination of an additive and a proportional error model were tested as well. This means for the j^{th} observed anti-Xa level of the i^{th} individual, the relation (Y_{ij}) is described by equation 2.

$$Y_{ij} = C_{pred,ij} + \varepsilon_{ij} + BLS \qquad \text{(Eq. 2)}$$

where c_{pred} is the predicted anti-Xa level, and ε_{ij} is a random variable with a mean of zero and variance of σ^2. Incorporation of baseline endogenous anti-Xa levels (BLS) into the model was explored as reported before (23, 24). This means for the j^{th} observed anti-Xa level of the i^{th} individual, the relation (Y_{ij}) is described by equation 2, where BLS represents the baseline endogenous anti-Xa level.

Covariate analysis

Covariates were plotted independently against the individual empirical Bayes estimates of the pharmacodynamic parameters to visualize potential relations. The following continuous covariates were tested: total body weight (TBW), body mass index (BMI), ideal body weight (IBW) (25), lean

body weight (LBW) (18) and age. For calculating LBW, equations 3 and 4 were used (18):

$$LBW_{male}(kg) = \frac{9270 * TBW}{6680 + 216 * BMI} \quad \text{(Eq. 3)}$$

$$LBW_{female}(kg) = \frac{9270 * TBW}{8780 + 244 * BMI} \quad \text{(Eq. 4)}$$

Continuous covariates were tested using linear and power equations:

$$P_i = P_p \cdot (\frac{Cov}{Cov_{standard}})^z \quad \text{(Eq. 5)}$$

in which P_i and P_p represent individual and population parameter estimates, respectively, Cov represents the covariate and $Cov_{standard}$ represents a standardized (i.e. 70 kg for TBW) or median value of the covariate for the population. The exponent z represents the exponential scaling factor, which was fixed at 1 for a linear function or an estimated value for a power equation, while also a 0.75 fixed value of the exponent was tested when TBW was the covariate (26). Categorical covariates (e.g. the subgroups morbidly obese patients and non-obese patients, and sex) were tested by estimation of an additional parameter on a structural parameter for one of the categories. Potential covariates were separately entered into the model and statistically tested using the objective function and if applicable the 95% confidence interval values of the additional parameter. A $p<0.005$ was applied to evaluate the covariates in the forward inclusion (OFV decrease >7.9), while the backward deletion procedure used a stricter criterion (OFV decrease >10.8, $p<0.001$). When two or more covariates were found to significantly improve the model, the covariate causing the largest reduction in objective function was left in the model. Additional covariates had to reduce this OFV further to be retained in the model. The choice of the covariate model was further evaluated as under the section Data analysis and internal validation.

Simulations

Based on the final pharmacodynamic model, simulations in morbidly obese patients were performed to aim for a target anti-Xa level of 0.2 IU/ml 4 hours after administration (27).

Results

Patients and data

A total of 35 patients were enrolled in two studies resulting in a total of 28 morbidly obese patients and 7 non-obese patients, from which 319 anti-Xa levels were available. Clinical data of 27 of the 28 morbidly obese patients were published before in a descriptive manner (19). Morbidly obese patients had a mean total body weight (TBW) of 148 kg (range 107 – 252 kg) and a mean BMI of 49 kg /m² (38 – 79 kg/m²) while non-obese patients had a TBW of 86 kg (72 – 105 kg) and a mean BMI of 28 kg/m² (24 – 31 kg/m²). Demographic characteristics are summarized in Table I.

Table I *Patient characteristics of the total study population of thirty-five patients consisting of twenty-eight morbidly obese patients and seven non-obese patients from two studies.*

	Total study population Mean (Range)	Morbidly obese (Study 1) Mean (SD)	Morbidly obese (Study 2) Mean (SD)	Non-obese (Study 2) Mean (SD)
Number (n)	35	20	8	7
Gender (M / F)	14/21	9/11	1/7	4/3
Age (years)	45 (22 – 59)	44 (11)	40 (6)	53 (6)
Total body weight (kg)	135 (72 – 252)	151 (33)	140 (23)	86 (12)
Ideal body weight (kg)	66 (50 – 86)	67 (11)	64 (7)	68 (9)
Lean body weight (kg) (18)	68 (44 – 100)	73 (15)	66 (9)	58 (11)
Body mass index (kg/m²)	45 (24 – 79)	50 (10)	47 (6)	28 (3)

SD = standard deviation

Pharmacodynamic analysis

A two-compartment pharmacodynamic model (NONMEM VI) parameterized in ADVAN5 adequately described the time course of the anti-Xa levels after subcutaneous dosing of nadroparin, parameterized in terms of the volume of distribution of the central compartment (V1), volume of distribution of the peripheral compartment (V2), inter-compartmental clearance from the central compartment to the peripheral compartment (Q) and clearance from the central compartment (CL) (Figure 1). A two-compartment model was superior over a one-compartment model, showing a reduction in objective function value (OFV) of 28 points and significantly improved diagnostic plots. In the two-compartment model, the peripheral compartment was set equal to the volume of the central compartment for statistical reasons (i.e.

convergence), which resulted in adequate diagnostic plots and improvement of the fit of the data compared with a one-compartment model.

The observed delay in appearance of anti-Xa levels after subcutaneous administration of nadroparin was described with a single transit compartment (see Figure 1), which proved superior over a lag time model (20) or a model with a first order rate absorption. Incorporation of additional transit compartments did not improve the fit of the data any further. It appeared that the model improved significantly (OFV reduction = 15 points , $p<0.05$) when k_a and k_{tr} were estimated separately. Implementation of a basal anti-Xa level (BLS) into the model was found to largely improve the diagnostic plots.

The results of the systematic covariate analysis are shown in Table II and

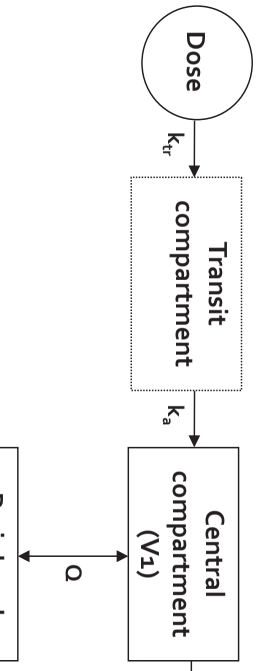


Figure 1 *Schematic representation of the pharmacodynamic model for nadroparin based on a two-compartment pharmacodynamic model with a single transit compartment with parameters k_{tr} and k_a.*

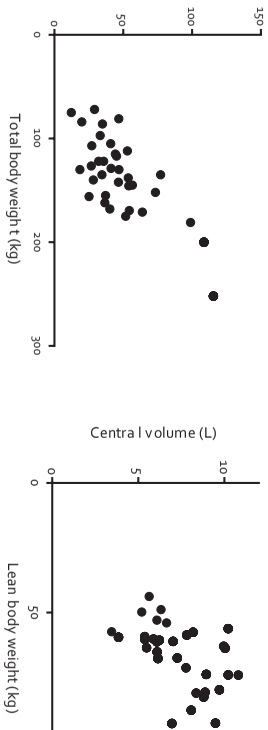


Figure 2 *Empirical Bayes estimates for clearance versus total body weight and central volume versus lean body weight for the base two-compartment pharmacodynamic model for nadroparin in twenty-eight morbidly obese patients and seven non-obese patients using anti-Xa levels as an endpoint.*

Table II *Stepwise covariate analysis for the pharmacodynamic model of nadroparin in thirty-five morbidly obese and non-obese patientst*

Parameter	Model	Relationship of covariate	No. of structural parameters	ΔOFV
-	Base model	-	10	
CL	Age	$CL_i = CL_{pop} / (1+(Age_i/40)*x)$	11	- 5.1
CL	BMI linear	$CL_i = CL_{pop} \bullet (BMI_i/25)$	10	- 10.7
CL	LBW (18) linear	$CL_i = CL_{pop} \bullet (LBW_i/60)\ (LBW_i/60)$	10	- 12.8
CL	TBW allometric	$CL_i = CL_{pop} \bullet (TBW_i/70)^{0.75}$	10	- 14.2
CL	TBW linear	$CL_i = CL_{pop} \bullet (TBW_i/70)$	10	- 17.2
CL	TBW power	$CL_i = CL_{pop} \bullet (TBW_i/70)^z$	11	- 19.1
V1	TBW linear	$V1_i = V1_{pop} \bullet (TBW_i/70)$	10	- 7.7
V1	LBW (18) linear	$V1_i = V1_{pop} \bullet (LBW_i/60)$	10	- 13.6
Final model CL and V1	TBW and LBW linear	$CL_i = CL_{pop} \bullet (TBW_i/70)$ $V1_i = V1_{pop} \bullet (LBW_i/60)$	10	- 29.1

BMI = body mass index; CL = clearance; CL_i = clearance in i^{th} individual; CL_{pop} = population mean value for clearance; CV = coefficient of variation of the parameter values; LBW = lean body weight; ΔOFV = delta objective function value compared to base model; TBW = total body weight; V1 = central volume of distribution; $V1_i$ = central volume of distribution in i^{th} individual; $V1_{pop}$ = population mean value for central volume of distribution; x = exponent for age = 4.6 (CV = 11%); z = scaling factor for clearance = 1.4 (CV = 13 %).

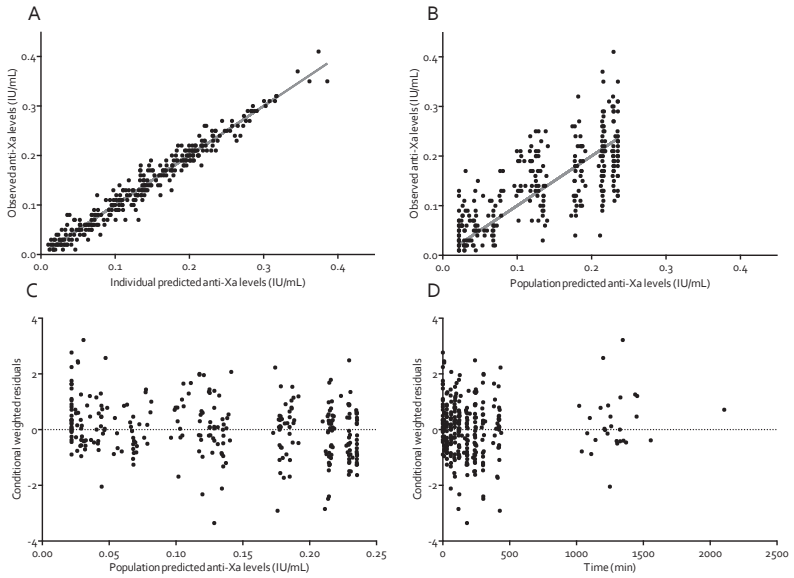
Figure 2. TBW proved the most significant covariate on the basis of a linear function (-17.2 points, 10 degrees of freedom, p<0.005) compared a power function (- 19.1 points, 11 degrees of freedom, p<0.005) given the objective function in relation to the number of structural parameters (Table II). Adding lean body weight (LBW) as a linear covariate on V1 further improved the model in a significant manner (-11.9 points, p<0.005). No covariates were identified for the other pharmacodynamic parameters. After incorporation of these two covariates, interindividual variability on clearance and volume of distribution substantially decreased (Table III), and both individual plots and goodness-of-fit plots improved (Figure 3). The pharmacodynamic parameter estimates of the base model without covariates and the final covariate model along with the results of the bootstrap analysis are shown in Table 3. Figure 4 shows the results of the NPDE validation in all patients. The histogram follows a normal distribution expected by the solid line with very limited bias over time and predicted anti-Xa levels.

Table III *Population pharmacodynamic parameters for the base model and final model for nadroparin in thirty-five morbidly patients and non-obese patients*

Parameter	Base model (CV%)	Final model (CV%)	Bootstrap final model (%)
CL/F (ml/min)	41.1 (7)		
$CL_{70\,kg}$/F (ml/min)#		23.0 (7)	99
V1/F (ml)	7380 (12)		
$V1_{60\,kg\,LBW}$/F (ml/min)*		7020 (4)	100
V2/F (ml) = V1/F			
Q/F (ml/min)	81.2 (11)	85.5 (2)	100
k_{tr} (min^{-1})	0.031 (18)	0.032 (17)	99
k_a (min^{-1})	0.0073 (7)	0.0076 (7)	103
BLS (anti-Xa IU)	0.022 (37)	0.021 (20)	100
OFV	- 1909	- 1938	101
Interindividual variability (%)			
CL	56.4 % (40)	38.9 % (29)	100
V1	35.4 % (33)	27.7 % (33)	98
k_{tr}	87.9 % (39)	82.0 % (41)	96
BLS	111.6 % (47)	109.6 % (33)	105
Additive intraindividual error	0.00041 (17)	0.00041 (13)	99

#: $CL_i = CL_{70kg} * (TBW/70)$
**: $V1_i = V1_{60kg} * (LBW/60)$*
BLS = Baseline; CL = clearance; CL_{70kg} = clearance in an individual of 70 kg; CL_i = clearance in the i^{th} individual; CV = coefficient of variation of the parameter values; k_a = absorption rate constant; k_{tr} = transit rate constant; OFV = objective function value; Q = compartmental clearance between V1 and V2; TBW = total body weight; V1 = central volume of distribution; V2 = peripheral volume of distribution.

Base model



Final model

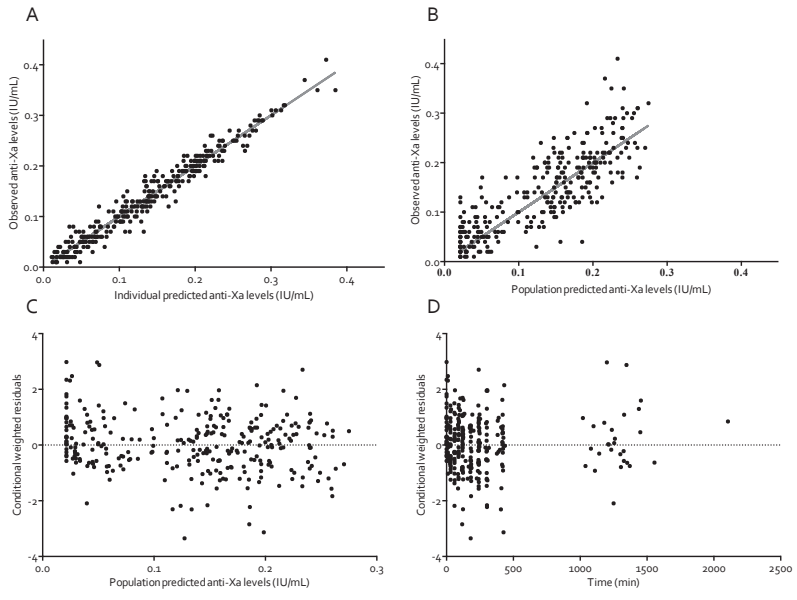


Figure 3 *Diagnostic plots for nadroparin pharmacodynamics in morbidly obese and non-obese patients showing individual anti-Xa level predictions versus observed anti-Xa levels, (A) population model anti-Xa level predictions versus anti-Xa levels (B), conditional weighted residuals versus population predicted anti-Xa levels (C) and time (D) for both the base model and final covariate model. The solid grey line represents the line of identity, x=y.*

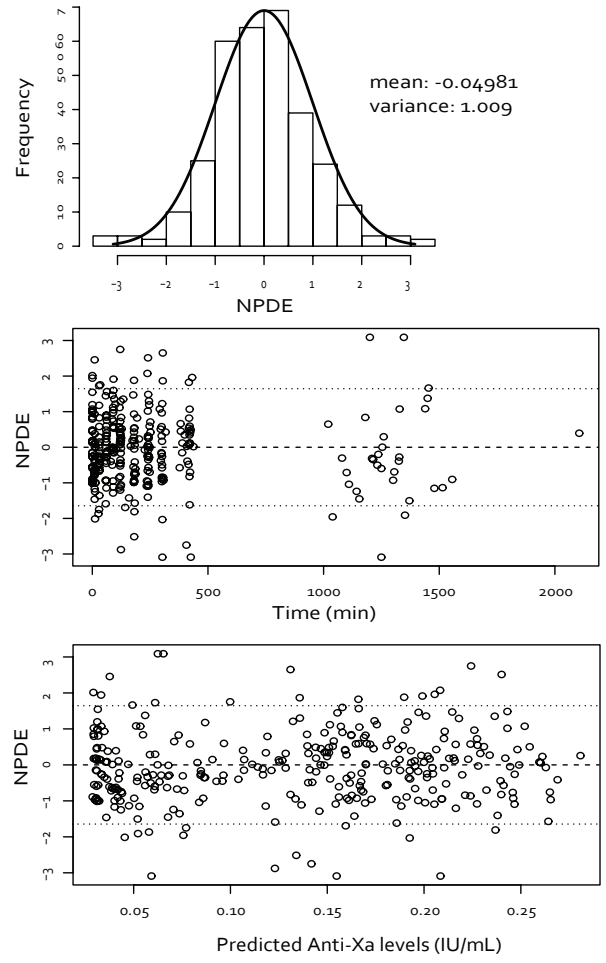


Figure 4 *Results of the internal validation with the NPDE method. The histograms show the NPDE frequency distribution for anti-Xa levels, the solid line indicates a normal distribution. The distribution of NPDE versus time and NPDE versus anti-Xa levels are also shown. The dotted lines represent the 90% distribution of the NPDE.*

Simulations

Based on the final pharmacodynamic model, simulations were performed aiming for anti-Xa levels of 0.2 IU/mL 4 hours after administration for morbidly obese patients. For these simulations, typical values without interindividual variability for all parameters were used to illustrate the influence of the covariates that were identified in this study. Supported by the results of the final covariate model, it seemed that morbidly obese patients with a lean body weight higher than 90 kg should receive 7,600 IU (0.8 ml) nadroparin and morbidly obese patients with a lean body weight lower or equal to 90 kg 5,700 IU (0.6 ml) nadroparin. Results of the simulation of the traditional dose of 5,700 IU (0.6 mL) nadroparin and the model based dose of nadroparin in three representative morbidly obese patients are depicted in Figure 5.

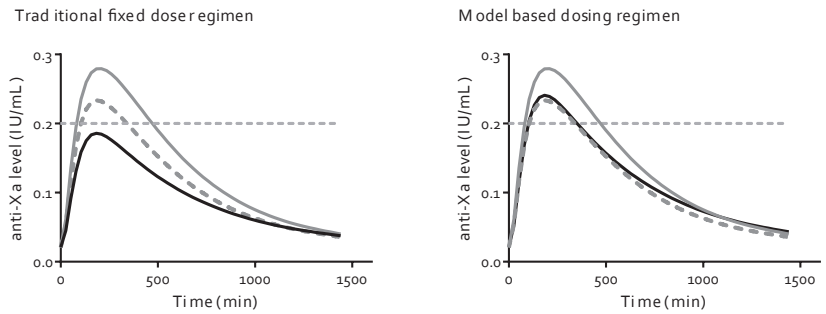


Figure 5 *Model based predictions of anti-Xa levels upon a traditional fixed dose dosing regimen of 5,700 IU =0.6 mL nadroparin for all morbidly obese patients (left panel) and upon a model based dosing regimen of 5,700 IU =0.6 mL nadroparin for patients with a lean body weight (LBW) lower than 90 kg and 7,600 IU (=0.8 mL) nadroparin for patients with a LBW higher than 90 kg (right panel). Profiles are simulated in three representative morbidly obese patients of the current study (grey solid line = total body weight (TBW) 107 kg and LBW of 53 kg, grey dotted line = TBW 135 kg and LBW = 65 kg and black solid line = TBW 162 kg and LBW = 94 kg.) . The horizontal dotted line represents the lower limit of prophylactic range (0.2 IU/mL).*

Discussion

In order to study the influence of body weight on the pharmacodynamics of low-molecular weight heparin (LMWH) nadroparin in morbidly obese and non-obese patients, a population pharmacodynamic model was developed using anti-Xa levels as endpoint. In this model, clearance proved to scale best with total body weight (TBW) and central volume of distribution with lean body weight (LBW).

As body weights are still increasing, there is high interest in the characterization of the influence of excessive body weight on pharmacokinetic and pharmacodynamics parameters of drugs in order to guide dosing in this special group of patient. For LMWHs such as nadroparin, central volume of distribution is the parameter of interest as this parameter mainly determines the maximum anti-Xa level, which is attained around 4 hours after administration, and for which a prophylactic range has been defined (27). As LMWH are assumed to mainly distribute over vascular tissue and blood, and plasma volume is known to increase in a non-linear manner with TBW (28) and most probably with LBW, it has been suggested before to guide safe and effective dosing of a LMWH on the basis of LBW (29). However, in patients up to 160 kg, TBW proved the best size descriptor for central volume of enoxaparin, which is another LMWH (15-17, 30). The current study is the first study describing the pharmacodynamics of nadroparin for patients up to 252 kg. For this wide body wide range, LBW proved the best body size descriptor for central volume in this analysis of both non-obese and morbidly obese patients.

While there are no other reports on the pharmacodynamics of nadroparin in morbidly obese patients, previous reports on enoxaparin concerning the best body size descriptor for clearance of anti-Xa in non-obese adults suggest a non-linear function for TBW (16). However, for patients up to 160 kg, the increase in clearance was described with a linear function using LBW as body size descriptor (17). However, this study used an outdated formula to calculate LBW that was found to be inconsistent at extremes of size (31). A recently reported formula for LBW that we used in our analysis, proved to be more reliable to estimate the fat free mass in both non-obese and obese patients (18) and was found to provide good predictive performance of the measured fat free mass in another study (1). Another way to describe the non-linear increase of clearance with TBW is allometric scaling (26), which has gained popularity most recently. The a priori use of allometry in obese patients is however considered to imply that obese individuals can be viewed as 'large individuals' (a different body size) instead of individuals 'having excess body fat' (a different body composition) (32). In the present study in morbidly obese and non-obese patients, we estimated an allometric scaling factor of 1.4, which was not significantly different from a linear function requiring a smaller number of structural parameters. As such, while testing all available body size descriptors, in this analysis in which a very large range in TBW (72 – 252 kg) could be evaluated, TBW was the best descriptor for clearance of anti-Xa in both morbidly obese and non-obese patients using a linear function.

In this study we found a delay in anti-Xa appearance in plasma. Different ways to describe the observed delay in effect were investigated. Using a lag

time model (20), the time of dosing shifts as if the drug was administered at a delayed time point. In a transit model, the absorption delay is described as a drug transition through one or a chain of compartments that are linked to the central compartment (22). The latter approach in which the absorption rate gradually increases was found to adequately describe the observed profile of nadroparin in blood over time and proved superior over a lag time model.

In the current study, we incorporated baseline anti-Xa activity into the structural model of nadroparin in both non-obese and morbidly obese patients. The activity of clotting factor Xa is generally used as a surrogate concentration measure as LMWH are mixture of substances (33) and therefore a kinetic assessment is complicated. It is known however that (low) endogenous anti-Xa activity may be present without the use of LMWH. While it is anticipated that this endogenous anti-Xa is due to the heparan sulfates that originate from the endothelial (34), basal activity is not often reported, even though a basal activity is obviously present in some of the reports (35-37). Although interindividual variability of BLS values was large for the entire population of morbidly obese and non-obese patients, the incorporation of a BLS as suggested by Schoemaker et al. (16) and which was also reported for tinzaparin (24), resulted in an improved description of the observations in our study.

Since there are no reports available indicating a reduced biological availability of LMWH in obese patients (38, 39), it may be anticipated that the increased apparent clearance observed in morbidly obese patients compared with non-obese patients is caused by an increased glomerular filtration in morbidly obese patients (40). Creatinine levels and age have been suggested before as covariates for anti-Xa levels after tinzaparin administration (24). In our study, we could not identify any influence of these covariates, possibly due to the small in range of age and creatinine levels.

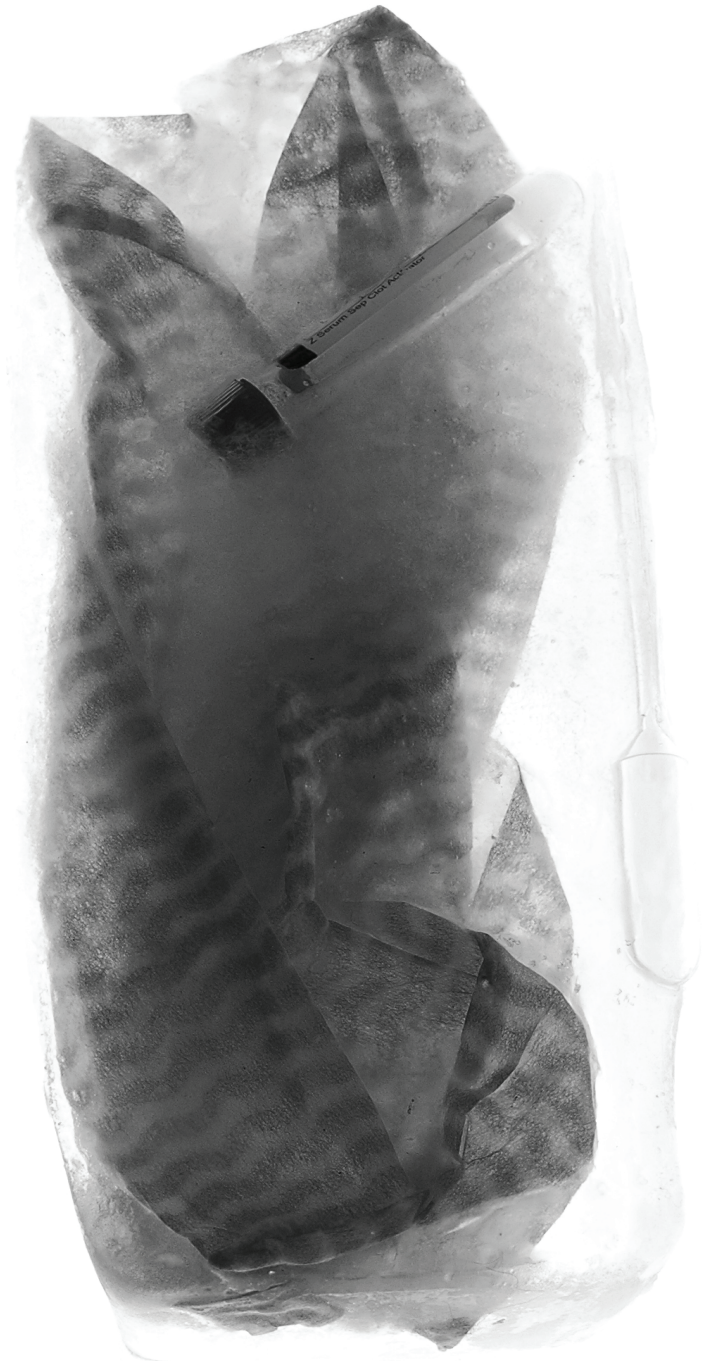
As stated before, measurement of anti-Xa levels is recommended in morbidly obese patients (41, 42) in absence of established dosing protocols for LMWH for these patients. Reports on these anti-Xa levels show that almost half of the morbidly obese patients exhibit anti-Xa levels below the prophylactic range for non-obese patients 0.2 - 0.5 IU/mL (19), suggesting that increased doses might be necessary. From the current study it seems that 5,700 IU (0.6 ml) nadroparin is appropriate for morbidly obese patients up to a LBW of 90 kg, while for morbidly obese patients with a LBW higher than 90 kg a larger dose of 7,600 IU (0.8 ml) is needed. This dosing regimen based on LBW should be explored as it aims for at least the same anti-Xa levels as non-obese patients (0.2 - 0.5 IU/mL (27)) while it is known that morbidly obese patients are at increased risk for VTE (4). The current pharmacodynamic model can be used even when in the future new target anti-Xa levels are established for thromboprophylaxis for this special group of patients. Therefore, it is advised to carefully monitor morbidly obese patients on bleedings and thrombotic events, as the exact relationship between anti-Xa levels and the occurrence of bleedings or VTE may not be known (43, 44).

Conclusion

In this study, we have developed a pharmacodynamic model for LMWH nadroparin using anti-Xa levels as endpoint in both morbidly obese and non-obese patients for a total body weight range from 72 kg until 252 kg. In the structural model, baseline anti-Xa activity was incorporated and the observed delayed effect of anti-Xa levels was described with a transit compartment. Based on the data available here, it appeared that clearance scaled with total body weight while lean body weight proved the major determinant for volume of distribution. Based on simulations using the final covariate pharmacodynamic model it appeared that a dose of 5,700 IU nadroparin will lead to target anti-Xa levels in morbidly obese patients with a LBW below 90 kg.

References

1.Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 2006;295(13):1549-55.
2.Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.
3.WorldHealthOrganisation. Obesity: Preventing and Managing the Global Epidemic. Geneva: World Health Organisation, 1997.
4.Stein PD, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. Am J Med. 2005;118(9):978-80. Epub 2005/09/17.
5.Stein PD, Matta F, Goldman J. Obesity and pulmonary embolism: The mounting evidence of risk and the mortality paradox. Thromb Res. 2011.
6.Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S-84S.
7.Rondina MT, Wheeler M, Rodgers GM, Draper L, Pendleton RC. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res. 2010;125(3):220-3.
8.Singh K, Podolsky ER, Um S, Saba S, Saeed I, Aggarwal L, et al. Evaluating the safety and efficacy of BMI-based preoperative administration of low-molecular-weight heparin in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. Obes Surg. 2012;22(1):47-51.
9.Borkgren-Okonek MJ, Hart RW, Pantano JE, Rantis PC, Jr., Guske PJ, Kane JM, Jr., et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis. 2008;4(5):625-31.
10.Kalfarentzos F, Stavropoulou F, Yarmenitis S, Kehagias I, Karamesini M, Dimitrakopoulos A, et al. Prophylaxis of venous thromboembolism using two different doses of low-molecular-weight heparin (nadroparin) in bariatric surgery: a prospective randomized trial. Obes Surg. 2001;11(6):670-6.
11.Kiang TK, Sherwin CM, Spigarelli MG, Ensom MH. Fundamentals of population pharmacokinetic modelling: modelling and software. Clin Pharmacokinet. 2012;51(8):515-25.
12.Barras MA, Duffull SB, Atherton JJ, Green B. Modelling the occurrence and severity of enoxaparin-induced bleeding and bruising events. Br J Clin Pharmacol. 2009;68(5):700-11.
13.Hulot JS, Vantelon C, Urien S, Bouzamondo A, Mahe I, Ankri A, et al. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. Ther Drug Monit. 2004;26(3):305-10.
14.Hulot JS, Montalescot G, Lechat P, Collet JP, Ankri A, Urien S. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. Clin Pharmacol Ther. 2005;77(6):542-52.
15.Green B, Greenwood M, Saltissi D, Westhuyzen J, Kluver L, Rowell J, et al. Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. Br J Clin Pharmacol. 2005;59(3):281-90.
16.Berges A, Laporte S, Epinat M, Zufferey P, Alamartine E, Tranchand B, et al. Anti-factor Xa activity of enoxaparin administered at prophylactic dosage to patients over 75 years old. Br J Clin Pharmacol. 2007;64(4):428-38.
17.Green B, Duffull SB. Development of a dosing strategy for enoxaparin in obese patients. Br J Clin Pharmacol. 2003;56(1):96-103.
18.Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
19.Diepstraten J, Hackeng CM, Van Kralingen S, Zapletal J, Van Dongen EP, Wiezer MJ, et al. Anti-Xa levels 4 hours after subcutaneous administration of 5700 IU nadroparin strongly correlate with lean body weight in morbidly obese patients. Obes Surg. 2012;Epub 1 feb.
20.Beal SL, Sheiner LB, Boeckmann A. NONMEM user's guide. San Francisco: University of California; 1999.
21.Comets E, Brendel K, Mentre F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Programs Biomed. 2008;90(2):154-66.
22.Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34(5):711-26.
23.Schoemaker RC, Cohen AF. Estimating impossible curves using NONMEM. Br J Clin Pharmacol. 1996;42(3):283-90.
24.Barrett JS, Gibiansky E, Hull RD, Planes A, Pentikis H, Hainer JW, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. Int J Clin Pharmacol Ther. 2001;39(10):431-46.
25.Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000;34(9):1066-9. Epub 2000/09/12.
26.Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36.
27.Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-83.
28.Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006;16(6):773-6.
29.Barras MA, Duffull SB, Atherton JJ, Green B. Individualized compared with conventional dosing of enoxaparin. Clin Pharmacol Ther. 2008;83(6):882-8.
30.Feng Y, Green B, Duffull SB, Kane-Gill SL, Bobek MB, Bies RR. Development of a dosage strategy in patients receiving enoxaparin by continuous intravenous infusion using modelling and simulation. Br J Clin Pharmacol. 2006;62(2):165-76.
31.Green B, Duffull S. Caution when lean body weight is used as a size descriptor for obese subjects. Clin Pharmacol Ther. 2002;72(6):743-4.
32.Eleveld DJ, Proost JH, Absalom AR, Struys MM. Obesity and allometric scaling of pharmacokinetics. Clin Pharmacokinet. 2011;50(11):751-3.
33.Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. Semin Thromb Hemost. 2000;26 Suppl 1:31-8.
34.Bourin MC, Lindahl U. Glycosaminoglycans and the regulation of blood coagulation. Biochem J. 1993;289 (Pt 2):313-30. Epub 1993/01/15.
35.Hainer JW, Barrett JS, Assaid CA, Fossler MJ, Cox DS, Leathers T, et al. Dosing in heavy-weight/obese patients with the LMWH, tinzaparin: a pharmacodynamic study. Thromb Haemost. 2002;87(5):817-23.
36.Siguret V, Pautas E, Fevrier M, Wipff C, Durand-Gasselin B, Laurent M, et al. Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. Thromb Haemost. 2000;84(5):800-4.
37.Harenberg J, Jeschek M, Acker M, Malsch R, Huhle G, Heene DL. Effects of low-molecular-weight dermatan sulfate on coagulation, fibrinolysis and tissue factor pathway inhibitor in healthy volunteers. Blood Coagul Fibrinolysis. 1996;7(1):49-56.
38.Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis. 1996;26 Suppl 2:24-38.
39.Sanderink GJ, Le Liboux A, Jariwala N, Harding N, Ozoux ML, Shukla U, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther. 2002;72(3):308-18.
40.Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. Hypertension. 1995;26(4):610-5.
41.Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):188S-203S.
42.Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost. 2004;2(4):547-50.
43.Paige JT, Gouda BP, Gaitor-Stampley V, Scalia PG, Klainer TE, Raum WJ, et al. No correlation between anti-factor Xa levels, low-molecular-weight heparin, and bleeding after gastric bypass. Surg Obes Relat Dis. 2007;3(4):469-75.
44.Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? No. J Thromb Haemost. 2004;2(4):551-4.



Section 04

Summary and perspectives

The influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs in adolescents and adults

12

Summary

Introduction

For most commonly used drugs in morbidly obese patients evidence based dosing guidelines are not available. Therefore, current dosing is based on experience of the prescriber rather than on clinical evidence. Pharmacokinetic and pharmacodynamics data in non-obese patients are extrapolated without proper exploration of influence of overweight on the dose-exposure-effect relationship.

The research described in this thesis focused on two commonly used drugs, propofol and the low-molecular-weight heparin (LMWH) nadroparin with the aim to develop weight appropriate dosing algorithms for these drugs in morbidly obese patients based on population pharmacokinetic and pharmacodynamics analysis. As an introduction to this thesis, in **Chapter 2**, a comprehensive overview is presented of clinical studies that reported on drug clearance estimates in both obese and non-obese patients. Most drug clearance values in obese patients were increased compared to non-obese patients, while clearance values of cytochrome P450 (CYP) 3A4 substrates were lower in obese as compared with non-obese patients. Very limited information was available in obese children.

The influence of morbidly obesity on the pharmacokinetics and pharmacodynamics of propofol in adults, adolescents and children

In **Chapter 3** we described that propofol clearance in morbidly obese adults can be predicted based on total body weight in an allometric function. The clearance of propofol could be predicted for a wide range of total body weights from 55 kg to 167 kg. The scaling factor of 0.72 did not change when the data in morbidly obese patients were combined with data of non-obese adults and proved to be in accordance with results from previous studies in non-obese patients (1, 2). Another aim was to explore the influence of excessive body weight on the pharmacodynamics of propofol anaesthesia

using the Bispectral index (BIS) as pharmacodynamic endpoint. A two-compartment biophase-distribution pharmacodynamic model, similar to a model described in non-obese patients (3-5), described our data well. Redistribution of propofol within the central nervous system was considered the most likely explanation for the observed biphasic distribution process. While the impact of obesity on pharmacodynamics parameters is rather unexplored, there are indications that obesity and related comorbidities can alter the pharmacodynamic response to drugs. For instance, obese patients showed an increased pain sensation as compared to non-obese patients (6). For propofol, we could not show a relationship between obesity and pharmacodynamic effect as none of the tested covariates in our morbidly obese patients significantly improved the pharmacodynamic model fit. The obtained pharmacodynamic parameters in morbidly obese patients were in accordance with previously reported pharmacodynamic parameter estimates of propofol in non-obese patients (3, 7). Therefore, our study provided the first preliminary data to suggest that there are no apparent differences between morbidly obese and non-obese patients in propofol effects as measured by the BIS. Of course, this finding has to be confirmed in a larger cohort and by analysing obese and non-obese pharmacodynamic patient data simultaneously. With the large between and within patient variability and the targeted BIS between 40 and 60 in morbidly obese patients, it is possible that more patient data covering a wider BIS range are needed to capture any influence of excessive body weight on the pharmacodynamics of propofol using the BIS. Based on the final propofol pharmacokinetic pharmacodynamic model, we derived a dosing algorithm for propofol-remifentanil anaesthesia targeting a BIS value of 40. In this model-based dosing algorithm, propofol infusion rates (in mg per kg per hour) are based on the adjusted body weight (according to ABW = 70 kg * (total body weight/70 kg)$^{0.72}$).

In addition to these results, in **Chapter 4** we showed that there are no differences in the individual pharmacokinetic or pharmacodynamic parameter estimates of propofol in morbidly obese patients receiving maintenance propofol-remifentanil or propofol-epidural anaesthesia using BIS values as pharmacodynamic endpoint. For non-obese patients, study results of the influence of remifentanil on propofol requirements are conflicting (8, 9). It cannot be excluded, however, that the exact influence of remifentanil on the level of anaesthesia may not be captured by the BIS. As the pharmacokinetic and pharmacodynamic study described in Chapter 4 was a pilot study in only six morbidly obese patients receiving epidural anaesthesia, the results have to be confirmed in a larger population.

In **Chapter 5** the model based dosing algorithm developed in Chapter 3 was prospectively evaluated in two different hospitals using BIS values as pharmacodynamic endpoint. To our knowledge this is the first study prospectively evaluating a model based dosing algorithm in morbidly obese patients. Fifty-one morbidly obese patients ranging in total body weight from 95 kg to 210 kg received stable and effective maintenance anaesthesia on the basis of BIS, blood pressure and heart rate. However, there were still concerns during the first twenty minutes after the propofol bolus dose as mean blood pressure then dropped more than 30% from pre-operative baseline values. In the study all patients received a fixed bolus dose of 350 mg propofol whereas individualisation of the induction dose might have alleviated some of these concerns. Recently, lean body weight has been suggested as a more appropriate dosing scalar to calculate propofol induction dose for morbidly obese patients and should therefore be considered instead of dose capping (10). Volumes of distribution are often used to calculate the loading dose of a drug resulting in a larger loading dose for a larger volume of distribution. In the pharmacokinetic and pharmacodynamic model derived in Chapter 3, there were no significant covariates to predict the central volume of distribution (V1), as V1 was 4.51 L (SD 13.0) when analysed in morbidly obese patients versus 3.10 L (SD 8.3) when analysed in both non-obese and morbidly obese patients. In our view, this non-significant increase in V1 may be seen as a partial explanation for the drop in blood pressures during the first twenty minutes of anaesthesia described in Chapter 5. However, the concept of a loading dose for drugs that exhibit multi-compartmental pharmacokinetics even in non-obese patients is complex, and therefore the use of V1 as the major determinant of the loading dose may not be justified. Therefore, a well-designed study is needed to determine factors predicting the optimal propofol induction dose in combination with the propofol-remifentanil maintenance dose as described in Chapter 3.

In **Chapter 6** we described the effect of excessive weight on the pharmacokinetics of propofol in children and adolescents. While the prevalence of childhood obesity increased to 17% in 2008 in the US (11), studies providing adequate pharmacokinetic and pharmacodynamic data in these patients are lacking. In accordance with the effect of morbid obesity on the pharmacokinetics of propofol in adults as described in Chapter 3, propofol clearance in morbidly obese children and adolescents proved to scale best with total body weight using an allometric function with an estimated scaling factor of 0.80. These unique results were in accordance with the observed non-linear increase of propofol clearance with total body weight in non-obese children (1, 2, 12). Based on these results, propofol maintenance dose may be based on this non-linear relationship using total body weight. This finding will have to be confirmed using a pharmacodynamic endpoint such as the BIS.

In order to fully characterize the influence of obesity and age, we performed in **Chapter 7** a population pharmacokinetic meta-analysis for propofol on the basis of data from morbidly obese adults, adolescents and children and their non-obese controls. This model was based on data with a wide total body weight range of 37 – 184 kg and an age range of 9 – 79 years. The results showed that total body weight was the most predictive covariate for propofol clearance across all patients when implemented as a power function with a scaling factor of 0.77. Increased blood volume and cardiac output in obese patients may increase liver blood flow (13) and this may explain the observed increase of both propofol clearance and other high extraction drug clearance values such as paclitaxel (14). In addition, age was identified as a significant covariate using a bilinear function with two distinct slopes, reflecting an initial increase and subsequent decrease in clearance depending on age. The potential generalizability of this pharmacokinetic model with total body weight and age as covariates of propofol clearance may increase the applicability of this type of models to scale clearance of other drugs over wide total body weight and age ranges.

Conclusions and recommendations

- The increase in propofol clearance due to obesity in adults, adolescents and children can be described using total body weight as the body size descriptor using an allometric function with a scaling factor of 0.77.
- The pharmacodynamics of propofol as measured by the BIS did not show an effect of excessive body weight in morbidly obese adults. This finding should be confirmed in a combined analysis of data obtained from both non-obese and (morbidly) obese adults, adolescents and children.
- A model based dosing algorithm using an adjusted dosing weight for propofol maintenance infusion was successfully evaluated in a prospective study in morbidly obese adults and can therefore be implemented in daily practice.
- The pharmacokinetic meta-analysis suggests to use a lower propofol maintenance dose in morbidly obese adolescents with the same body weight as morbidly obese adults.

The influence of morbidly obesity on the pharmacodynamics of low molecular weight heparins

As up to now, no dosing guidelines for low-molecular-weight heparins (LMWH) in morbidly obese patients are available, it is recommended to dose adjust based on anticoagulant effect using anti-Xa levels (15). In **Chapter 8** we showed in a morbidly obese patient with pulmonary embolism weighing 252 kg, that effective anti-thrombotic therapy can be achieved using a lower dose based on anti-Xa levels as opposed to the recommended standard units per total body weight dose. The results suggested that the pharmacodynamics of LMWH are influenced by extreme overweight and therefore we investigated current dosing strategies for LMWH dosing and monitoring for (morbidly) obese patients.

We conducted an online and telephone survey as described in **Chapter 9** among Dutch hospitals. Dosing adjustments in obese patients in Dutch hospital were found to differ widely. In the majority of the hospitals, LMWH dose was increased by body weight to a maximum dose based on a cut-off weight value (dosing cap). These cut-off weight values differed widely per institution and were based either on total body weight or BMI. Importantly, monitoring of the LMWH anticoagulant effect in morbidly obese patients using anti-Xa levels was not standard practice in any of the hospitals.

In order to determine the most appropriate dose for LMWH in morbidly obese patients, we investigated the influence of excessive body weight on the nadroparin effect following a bolus dose as described in **Chapter 10**. In morbidly obese patients anti-Xa levels four hours after drug administration strongly correlated with lean body weight. Lean body weight has been proposed previously to estimate the therapeutic dose of enoxaparin another LMWH, in patients weighing more than 100 kg (16). In accordance with the present results, it has been reported that an increase in nadroparin dose did not result in a linear increase in maximum anti-Xa levels four hours after administration in obese patients (17). We showed that lean body weight based dosing correlates well with anti-Xa levels four hours after administration in morbidly obese patients and this method therefore is suggested as a suitable dosing scalar for nadroparin dosing.

In order to fully characterize the influence of excessive body weight on the pharmacodynamics of nadroparin we also measured anti-Xa levels after a bolus dose nadroparin in non-obese patients. Population pharmacodynamic modeling was used to describe the influence of body weight on each individual PD parameter in the model in order to develop a model-based dosing algorithm. In the final pharmacodynamic model for nadroparin described in **Chapter 11** and in accordance with Chapter 10, we showed that in both non-obese and morbidly obese patients lean body weight was the best body size descriptor for the central volume of distribution. In addition, 31% of the variability of clearance between patients could be explained with total body weight as body size descriptor. The pharmacodynamic model was based on a rich anti-Xa sampling schedule in patients over a wide total body weight range from 72 kg to 252 kg. Previous reports on the influence of excessive weight on the pharmacodynamics of other LMWH (enoxaparin,

tinzaparin and dalteparin) showed that obese patients have much higher total drug clearances than non-obese patients (18). For some other renally cleared drugs such as vancomycin, daptomycin and carboplatin it is known that clearance is increased, related to higher glomerular filtration rates in obese patients as described in Chapter 2 (19-21). Renal function is affected by excessive body weight as it has been shown that obese patients have a 62% increase in estimated glomerular filtration rate (22). Therefore, the observed increased clearance values and their association with total body weight are likely due to increased glomerular filtration in (morbidly) obese patients. For LMWH, the central volume of distribution is the parameter of interest as this parameter predominantly determines the maximum anti-Xa level, which is reached around four hours after administration, and for which a therapeutic target for prophylaxis has been defined in non-obese patients (18). LMWH are assumed to mainly distribute over blood and vascular tissues, and plasma volume is known to increase in a non-linear fashion with total body weight (23) and most probably also with lean body weight. Therefore, it has been suggested to guide safe and effective dosing of a LMWH on the basis of lean body weight (16). Although the prophylactic anti-Xa target range is established for non-obese patients and not for morbidly obese patients, this model can be used as a clinically useful starting point until future research identifies alternate anti-Xa targets for safe and effective thromboprophylaxis in this special patient population.

Conclusions and recommendations

- There are large differences in the practice of thromboprophylaxis in morbidly obese surgical patients in Dutch hospitals, and current guidelines lack evidence-based dosing recommendations.
- The central volume of distribution and peak anti-Xa levels correlate with lean body weight, suggesting that lean body weight is clinically useful for nadroparin dosing.
- The developed pharmacodynamic model for nadroparin in non-obese and morbidly obese patients can be used as a starting point to further identify the appropriate anti-Xa targets in morbidly obese patients.

Perspectives

In this thesis the focus was on studying the influence of morbid obesity on the pharmacokinetics and pharmacodynamics of propofol and nadroparin with the goal to develop safe and evidence-based dosing strategies. A non-linear relationship was found between propofol clearance and total body weight in both morbidly obese and non-obese adults, adolescents and children. Furthermore, the influence of age on propofol clearance was described using a bilinear function. For nadroparin in both morbidly obese and non-obese patients, total body clearance increased linearly with total body weight whereas the central of volume distribution increased linearly with lean body weight.

As there is still an unmet clinical need for evidence based dosing algorithms for many commonly used drugs in morbidly obese patients, it should be emphasized that pharmaceutical companies need to be encouraged to start including (morbidly) obese patients in their clinical trials to identify the influence of excessive weight on the pharmacokinetics and pharmacodynamics of drugs and as part of the (early) phases of drug development. In the meantime, continued pharmacokinetic and pharmacodynamics research is desperately needed for most commonly used drugs in the morbidly obese population. These studies should focus on describing the influence of excessive overweight on the pharmacokinetic and pharmacodynamics parameters and include testing of all available body size descriptors. In this thesis, all available body size descriptors were tested and the most statistically significant covariates were incorporated into the final models. These empirical functions were based on model fit of the observed concentrations and observed effects. An alternative way to describe the influence of excessive body weight on pharmacokinetics has been proposed and entails the incorporation of lean body weight for all clearance values of all drugs using one allometric exponent of 0.66 (24). This proposal was based on a meta-analysis of covariate relationships between clearance and body size of a series of different drugs (24). This suggestion is in line with the allometric scaling principles (25). The theory of allometry is based on the empirical observation that over a wide weight range, metabolic rates in animal species increase with body weight to the power of 0.75 (26). While this empirical allometric exponent has no obvious biological or physiological meaning and even for scaling between species, the existence of one unique value for the allometric clearance exponent is widely disputed (27-30). In spite of this, allometry has gained popularity for scaling 'within' a population of a single species, i.e. the human range (25). As obesity is related to body composition and the accumulation of excess body fat, we think that one should be careful in applying the theory of allometry or to use one body size descriptor for all drugs in (morbidly) obese patients. As shown in Chapter 2 of this thesis, not all metabolic activity is increasing with body weight as for instance CYP3A mediated clearance seems to decrease. In order to develop evidence based dosing guidelines for drugs in morbidly obese patients the influence of body weight on each of the pharmacokinetic and pharmacodynamic parameter should be characterized

by testing all available obesity and body size descriptors and be based on the characteristics of a drug. Instead of the common a priori use of total body weight for dosing guidelines, detailed information on pharmacokinetics and potentially also the pharmacodynamics needs to be considered in order to define effective and safe dosing regimens over a large body weight range.
Beside the identification of predictive body size descriptors for variability pharmacokinetic and pharmacodynamic parameters, the final covariate model should be validated and prospectively be evaluated. Before the final model based dosing algorithm is prospectively tested for accuracy as described in Chapter 5, a framework for model evaluation should be used. As shown by a literature review, most pharmacokinetic and pharmacodynamic modeling papers do not adequately describe all available evaluation steps (31). Model misspecification leads to poor predictive performance and could have far-reaching consequences when such pharmacokinetic and pharmacodynamic models are used as a basis for dosing algorithms in obese patients. Therefore, the accuracy of the covariate relationships across the entire range of covariate values should be evaluated during model building. Six evaluation criteria are suggested to be performed and reported during model building using data of (morbidly) obese patients and this is adapted from guidelines for pharmacokinetic and pharmacodynamic modeling in children (32). First, the influence of each covariate on the parameters is examined separately by implementing into exploratory covariate models which are compared with the simple base model (no covariates) using the objective function value. In addition, goodness-of-fit plots are used to evaluate if the model is able to describe the data accurately and without bias. If different data sets are combined, for example non-obese and obese data, goodness-of-fit plots should be generated for each data set separately in order to evaluate if the final covariate model is able to describe the data for the different (sub)groups (33). In order to judge the accuracy of the estimated parameters, confidence intervals or standard errors should be reported. Incorporated covariates need to describe the relationship with the parameter across the entire range of covariate values. Therefore, the eta distribution of the parameter with covariates should be plotted against this covariate. Finally, at least two internal validation steps should be used, e.g. bootstrap (34), visual predictive check (35) and/or normalised prediction distribution errors (36).
The question remains how to further investigate drug dosing in obese patients in the future. As the prevalence of obesity and total body weights of both children and adults are still increasing and as this trend will persist, future studies assessing the impact of morbid obesity on specific drug elimination pathways in both children and adults are warranted. In the traditional pharmacokinetic and pharmacodynamics modeling approaches rather empirical models such as the Hill equation are used to describe in vivo dose-concentration-effect relationships. These equations do not provide insight into physiology or factors determining the concentration-effect relationship. In theory, the relationship between drug concentration and biological response depends on drug and biological system specific factors (37). The classical modeling can ultimately lead to physiological based pharmacokinetic modeling as can be done using software such as the Simcyp software (Simcyp Ltd, UK) (38, 39). Using this software the obesity related (patho)-physiological changes such as for example blood volume, liver blood flow, kidney function and metabolic processes can be incorporated in the model. Furthermore, physicochemical drug properties like the molecular mass, the octanol/water partition coefficient (logP) and the acid dissociation constant (pKa) are taken into account. As data of specific (patho)-physiological processes in (morbidly) obese patients may not all be available, these models currently also rely on assumptions and on in vitro parameters. Therefore, information generated using traditional pharmacokinetic and pharmacodynamic modeling may be of added value to obtain evidence based dosing guidelines and to gain information about the influence of excessive body weight on the pharmacokinetics and pharmacodynamics. However, it is unlikely that thoroughly validated pharmacokinetic covariate models will be developed for every existing drug prescribed for (morbidly) obese patients across the entire weight range. Therefore, more efficient approaches have to be set up to develop safe and effective dosing regimens for this special group of patients. In Chapter 2, we described the current knowledge of the impact of obesity on drug metabolism and elimination and how it differs per drug based on metabolic or elimination pathway. This implies that covariate relationships describing the influence of obesity on the clearance of a specific drug may be extrapolated to other drugs if cleared through the same pathway, which has been described before in children (40, 41). The extrapolation of covariate models between drugs would expedite the development of obesity pharmacokinetic and pharmacodynamics models, which in its turn could help with the individualization of drug dosing in first-in-obese studies and in facilitating the development of evidence-based dosing recommendations for obese patients.

References

1.Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. Anesthesiology. 2000;92(3):727-38.
2.Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010;49(4):269-75.
3.Bjornsson MA, Norberg A, Kalman S, Karlsson MO, Simonsson US. A two-compartment effect site model describes the bispectral index after different rates of propofol infusion. J Pharmacokinet Pharmacodyn. 2010;37(3):243-55.
4.Wiczling P, Bienert A, Sobczynski P, Hartmann-Sobczynska R, Bieda K, Marcinkowska A, et al. Pharmacokinetics and pharmacodynamics of propofol in patients undergoing abdominal aortic surgery. Pharmacol Rep. 2012;64(1):113-22.
5.Upton RN, Ludbrook G. A physiologically based, recirculatory model of the kinetics and dynamics of propofol in man. Anesthesiology. 2005;103(2):344-52.
6.Stone AA, Broderick JE. Obesity and pain are associated in the United States. Obesity (Silver Spring). 2012;20(7):1491-5. Epub 2012/01/21.
7.Struys MM, Coppens MJ, De Neve N, Mortier EP, Doufas AG, Van Bocxlaer JF, et al. Influence of administration rate on propofol plasma-effect site equilibration. Anesthesiology. 2007;107(3):386-96.
8.Wang LP, McLoughlin P, Paech MJ, Kurowski I, Brandon EL. Low and moderate remifentanil infusion rates do not alter target-controlled infusion propofol concentrations necessary to maintain anesthesia as assessed by bispectral index monitoring. Anesth Analg. 2007;104(2):325-31.
9.Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology. 2004;100(6):1353-72.
10.Ingrande J, Brodsky JB, Lemmens HJ. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. Anesth Analg. 2011;113(1):57-62.
11.Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. Jama. 2010;303(3):242-9.
12.Wang C, Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Krekels EH, Tibboel D, et al. A Bodyweight-Dependent Allometric Exponent for Scaling Clearance Across the Human Life-Span. Pharm Res. 2012.
13.Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. J Clin Anesth. 2005;17(2):134-45.
14.Sparreboom A, Wolff AC, Mathijssen RH, Chatelut E, Rowinsky EK, Verweij J, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol. 2007;25(30):4707-13.
15.Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost. 2004;2(4):547-50.
16.Barras MA, Duffull SB, Atherton JJ, Green B. Individualized compared with conventional dosing of enoxaparin. Clin Pharmacol Ther. 2008;83(6):882-8.
17.Heizmann M, Baerlocher GM, Steinmann F, Horber FF, Wuillemin W. Anti-Xa activity in obese patients after double standard dose of nadroparin for prophylaxis. Thromb Res. 2002;106(4-5):179-81.
18.Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-83.
19.Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol. 1998;54(8):621-5.
20.Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. J Clin Pharmacol. 2005;45(1):48-56.
21.Schmitt A, Gladieff L, Lansiaux A, Bobin-Dubigeon C, Etienne-Grimaldi MC, Boisdron-Celle M, et al. A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. Clin Cancer Res. 2009;15(10):3633-9.
22.Pai MP. Estimating the Glomerular Filtration Rate in Obese Adult Patients for Drug Dosing. Adv Chronic Kidney Dis. 2010;17(5):e53-e62.
23.Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006;16(6):773-6.
24.McLeay SC, Morrish GA, Kirkpatrick CM, Green B. The Relationship between Drug Clearance and Body Size: Systematic Review and Meta-Analysis of the Literature Published from 2000 to 2007. Clin Pharmacokinet. 2012;51(5):319-30.
25.Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32.
26.Kleiber M. Energy Metabolism. Annu Rev Physiol. 1944;6:123-54.
27.Kolokotrones T, Van S, Deeds EJ, Fontana W. Curvature in metabolic scaling. Nature. 2010;464(7289):753-6.
28.White CR, Cassey P, Blackburn TM. Allometric exponents do not support a universal metabolic allometry. Ecology. 2007;88(2):315-23.
29.Glazier DS. Beyond the '3/4-power law': variation in the intra- and interspecific scaling of metabolic rate in animals. Biol Rev Camb Philos Soc. 2005;80(4):611-62.
30.Packard GC, Birchard GF. Traditional allometric analysis fails to provide a valid predictive model for mammalian metabolic rates. J Exp Biol. 2008;211(Pt 22):3581-7.
31.Brendel K, Dartois C, Comets E, Lemenuel-Diot A, Laveille C, Tranchand B, et al. Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004. Clin Pharmacokinet. 2007;46(3):221-34.
32.De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol. 2011;67 Suppl 1:5-16.
33.Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007;82(1):17-20.
34.Beal SL, Sheiner LB, Boeckmann A. NONMEM user's guide. San Francisco: University of California; 1999.
35.Yano Y, Beal SL, Sheiner LB. Evaluating pharmacokinetic/pharmacodynamic models using the posterior predictive check. J Pharmacokinet Pharmacodyn. 2001;28(2):171-92.
36.Comets E, Brendel K, Mentre F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Programs Biomed. 2008;90(2):154-66.
37.Danhof M, de Lange EC, Della Pasqua OE, Ploeger BA, Voskuyl RA. Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. Trends in pharmacological sciences. 2008;29(4):186-91.
38.Ghobadi C, Johnson TN, Aarabi M, Almond LM, Allabi AC, Rowland-Yeo K, et al. Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients: expected variations in clearance. Clin Pharmacokinet. 2011;50(12):809-22.
39.Darwich AS, Pade D, Ammori BJ, Jamei M, Ashcroft DM, Rostami-Hodjegan A. A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution. J Pharm Pharmacol. 2012;64(7):1008-24.
40.Krekels EHJ, Neely M, Panoilia E, Tibboel D, Capparelli E, Danhof M, et al. From Pediatric Covariate Model to Semiphysiological Function for Maturation: Part I-Extrapolation of a Covariate Model From Morphine to Zidovudine. CPT: pharmacomet syst pharmacol. 2012;1:e9.
41.Krekels EHJ, Johnson TN, den Hoedt SM, Rostami-Hodjegan A, Danhof M, Tibboel D, et al. From Pediatric Covariate Model to Semiphysiological Function for Maturation: Part II-Sensitivity to Physiological and Physicochemical Properties. CPT: pharmacomet syst pharmacol. 2012;1:e10.

Dutch summary

Introductie

Voor morbide obese patiënten zijn voor de meest gebruikte geneesmiddelen geen wetenschappelijk onderbouwde doseringsrichtlijnen beschikbaar. De gekozen dosering wordt met name gebaseerd op de ervaring van de voorschrijver in plaats van op klinisch bewijs. Daarnaast worden farmacokinetische en farmacodynamische gegevens van niet-obese patiënten geëxtrapoleerd zonder een goede verkenning van de invloed van overgewicht op de dosis-blootstelling-effect relatie.

Het onderzoek beschreven in dit proefschrift richt zich op twee veelgebruikte geneesmiddelen rondom chirurgische ingrepen: propofol en de laagmoleculair gewicht heparine (LMWH) nadroparine. Het doel is om voor morbide obese patiënten onderbouwde doseringsalgoritmen te ontwikkelen met behulp van populatie farmacokinetische en farmacodynamische analyses. Als inleiding op dit proefschrift wordt in **hoofdstuk 2** een uitgebreid overzicht gegeven van de klinische studies waarin schattingen van de geneesmiddelklaring in zowel obese als niet-obese patiënten worden beschreven. Voor obese kinderen was slechts zeer beperkte informatie beschikbaar.

De invloed van morbide obesitas op de farmacokinetiek en farmacodynamiek van propofol in volwassenen, adolescenten en kinderen

In **hoofdstuk 3** beschreven we dat de propofol klaring van morbide obese volwassenen kan worden voorspeld op basis van het totale lichaamsgewicht met behulp van een allometrische functie met een exponent van 0,72. Dit was van toepassing voor patiënten met een totaal lichaamsgewicht variërend van 55 kg tot 167 kg. De gevonden exponent van 0,72 veranderde niet wanneer de gegevens van morbide obese patiënten werden gecombineerd met gegevens van niet-obese volwassenen. Tevens werd in dit hoofdstuk de invloed van overgewicht op de farmacodynamiek van propofol anesthesie, gemeten met behulp van de Bispectral index (BIS), verkend. Een twee-compartimenten farmacodynamisch model, vergelijkbaar met een model beschreven in niet-obese patiënten (1-3), bleek de data goed te beschrijven. Herverdeling van propofol binnen het centrale zenuwstelsel werd beschouwd als de meest waarschijnlijke verklaring voor het waargenomen effectiviteitsverloop in de tijd. Terwijl de

invloed van obesitas op farmacodynamische parameters een onontgonnen onderzoeksgebied is, waren er aanwijzingen dat obesitas en gerelateerde comorbiditeiten de farmacodynamische respons op geneesmiddelen kunnen veranderen. Zo bleken obese patiënten bijvoorbeeld een verhoogde pijnsensatie te vertonen in vergelijking tot niet-obese patiënten (4). Aangezien geen van de geteste covariaten het beschrijvend vermogen van het farmacodynamische model verbeterde, werd er geen invloed van overgewicht op de farmacodynamiek van propofol in morbide obese patiënten aangetoond. De verkregen farmacodynamische parameters in morbide obese patiënten waren in overeenstemming met eerder gerapporteerde farmacodynamische parameters van propofol in niet-obese patiënten (1, 5). Dit is de eerste analyse die erop wijst dat er geen duidelijke verschillen zijn in de concentratie-effect relatie van propofol gemeten met behulp van de BIS tussen morbide obese en niet-obese patiënten. Het lijkt van belang deze bevindingen te bevestigen in een groter cohort en door het tegelijkertijd analyseren van obese en niet-obese farmacodynamische patiëntgegevens. Op basis van het uiteindelijke propofol farmacokinetisch en farmacodynamisch model hebben we een doseeralgoritme voor propofol-remifentanil anesthesie afgeleid, gericht op een BIS waarde van 40. In dit doseringsalgoritme worden propofol infusiesnelheden (in mg/kg/uur) berekend op een gecorrigeerd lichaamsgewicht (= 70 kg * (totaal lichaamsgewicht/70 kg)^{0,72}).

In aansluiting op deze resultaten hebben we in **hoofdstuk 4** laten zien dat er geen verschillen zijn in de farmacokinetische en farmacodynamische parameters van propofol in morbide obese patiënten die onderhoud propofol-remifentanil of propofol-epidurale anesthesie kregen met BIS-waarden als farmacodynamische eindpunt. Terwijl we in morbide obese patienten geen aanwijzingen vonden voor invloed van remifentanil op de farmacokinetische en farmacodynamische parameters, zijn de studieresultaten voor niet-obese patiënten conflicterend en afhankelijk van het gekozen eindpunt (6, 7). Van belang hierbij is dat niet kan worden uitgesloten dat de precieze invloed van remifentanil op het niveau van anesthesie mogelijk niet goed kan worden beschreven met behulp van de BIS. Daarom moeten de resultaten van deze pilot in zes morbide obese patiënten worden bevestigd in een groter cohort waarbij verschillende eindpunten worden meegenomen.

In **hoofdstuk 5** is het op het farmacokinetische en farmacodynamische model gebaseerde doseringsalgoritme zoals beschreven in hoofdstuk 3 prospectief geëvalueerd in twee verschillende ziekenhuizen met behulp van BIS waarden als farmacodynamische eindpunt. Voor zover ons bekend is dit de eerste studie, die prospectief een doseringsalgoritme gebaseerd op een farmacokinetiek en farmacoynamiek model bij morbide obese patiënten, evalueert. In 51 morbide obese patiënten variërend in totaal lichaamsgewicht van 95 kg tot 210 kg werd stabiele en effectieve onderhoudsanesthesie verkregen gemeten op basis van de BIS, bloeddruk en hartslag. Tijdens de eerste twintig minuten na de bolusinjectie van propofol daalde de gemiddelde bloeddruk echter met meer dan 30% ten opzichte van de preoperatieve bloeddruk. Dit kan wellicht verklaard worden doordat in de studie alle patiënten een bolus dosis van 350 mg propofol kregen, terwijl individualisering van de inductiedosis deze bloeddrukdaling mogelijk zou hebben kunnen verminderd. Onlangs is lean body weight voorgesteld als een meer geschikte doseermaat om de propofol inductie dosis te berekenen in morbide obese patiënten (8). Verdelingsvolumina worden vaak gebruikt om de initiële dosis van een geneesmiddel te berekenen, resulterend in een grotere oplaaddosis voor een groter verdelingsvolume. In het farmacokinetische en farmacodynamische model beschreven in hoofdstuk 3 werden geen significante covariaten gevonden voor het centrale verdelingsvolume (V1). Wel was het geschatte V1 in morbide obese patiënten groter dan het V1 in de analyse van de gezamenlijke data van niet-obese en morbide obese patiënten (4,51 L (SD 13,0) versus 3,10 L (SD 8,3)). Naar onze mening kan deze niet-significante toename in V1 worden gezien als een gedeeltelijke verklaring voor de daling van de bloeddruk tijdens de eerste twintig minuten van de anesthesie beschreven in hoofdstuk 5. Het concept van een bolus dosis voor geneesmiddelen die meerdere compartimenten farmacokinetiek vertonen is complex en daarom is het gebruik van V1 als de belangrijkste determinant van de oplaaddosis mogelijk niet geheel gerechtvaardigd. Een studie is nodig om voorspellende factoren van de optimale propofol inductiedosis in combinatie met de propofol-remifentanil onderhoudsdosering als beschreven in hoofdstuk 3 nader te bepalen.

In **hoofdstuk 6** beschrijven we de effecten van overgewicht op de farmacokinetiek van propofol in kinderen en adolescenten. Terwijl in de VS in 2008 de prevalentie van obesitas onder kinderen steeg tot 17% (9), ontbreken er adequate farmacokinetische en farmacodynamische gegevens in deze patiënten. Analoog aan het effect van morbide obesitas op de farmacokinetiek van propofol bij volwassenen zoals beschreven in hoofdstuk 3, bleek de propofol klaring van morbide obese kinderen en adolescenten het beste te schalen met totale lichaamsgewicht in een allometrische functie met een exponent van 0,80. Deze unieke resultaten waren in overeenstemming met de waargenomen niet-lineaire stijging van de propofol klaring met het totale lichaamsgewicht in niet-obese kinderen (10-12). Op basis van de huidige resultaten kan de propofol onderhoudsdosering worden gebaseerd op deze niet-lineaire relatie tussen de klaring van propofol en het totale lichaamsgewicht. Deze bevinding moet worden bevestigd met behulp van evaluaties van farmacodynamische eindpunten, zoals de BIS, zodat de farmacokinetiek farmacodynamiek relatie in morbide obese kinderen kan

worden vastgesteld.
Om de gehele invloed van obesitas en leeftijd op de farmacokinetiek van propofol te kunnen karakteriseren, voerden we in **hoofdstuk 7** een populatie farmacokinetische meta-analyse uit met gegevens van morbide obese volwassenen, adolescenten en kinderen en hun niet-obese controle patiënten. Het uiteindelijke model is gebaseerd op gegevens van patiënten met een brede spreiding aan totale lichaamsgewichten (37 - 184 kg) en leeftijden (9 - 79 jaar). De resultaten lieten zien dat het totale lichaamsgewicht met behulp van een allometrische functie met een exponent van 0,77 de meest voorspellende covariaat is om de verandering in propofol klaring voor alle patiënten te beschrijven. Een mogelijke verklaring voor deze toename van de propofol klaring met het totale lichaamsgewicht is, net als voor andere "high extraction drugs", zoals paclitaxel (13), een verhoogd bloedvolume en cardiale output, waardoor de bloedtoevoer naar de lever vergroot is (14). Daarnaast werd leeftijd als significante covariaat beschreven met een bilineaire functie met twee verschillende hellingen: een aanvankelijke stijging met daaropvolgend een afname in klaring met de leeftijd. Het verdient aanbeveling dat dit farmacokinetische model met totaal lichaamsgewicht en leeftijd als covariaten voor klaring nader te onderzoeken bij data analyse van andere geneesmiddelen in patiënten cohorten met sterk uiteenlopende gewichten en leeftijden.

Conclusies en aanbevelingen
- De toename in propofol klaring als gevolg van (morbide) obesitas bij volwassenen, adolescenten en kinderen kan worden beschreven met behulp van het totale lichaamsgewicht als de gewichtsmaat in een allometrische functie met een exponent van 0,77.
- De farmacodynamiek van propofol gemeten met de BIS liet geen effect van overgewicht in morbide obese volwassenen zien. Deze bevinding moet worden bevestigd in een gecombineerde analyse van gegevens van zowel niet-obese als (morbide) obese volwassenen, adolescenten en kinderen.
- De propofol onderhoudsdosering gebaseerd op het farmacokinetiek en farmacodynamiek model, gebruikmakend van een gecorrigeerd lichaamsgewicht werd met succes geëvalueerd in een prospectieve studie in morbide obese volwassenen en kan daarom worden toegepast in de dagelijkse praktijk.
- De farmacokinetische meta-analyse laat zien dat een lagere propofol onderhoudsdosis gebruikt moet worden in een morbide obese adolescent met hetzelfde lichaamsgewicht als een morbide obese volwassene.

De invloed van morbide obesitas op de farmacodynamiek van laagmoleculair gewicht heparines

Aangezien er op dit moment geen richtlijnen beschikbaar zijn voor het doseren van laagmoleculair gewicht heparines (LMWHs) bij morbide obese patiënten, wordt aanbevolen de dosis te baseren op het antistollingseffect, gemeten met behulp van anti-Xa spiegels (15). In **hoofdstuk 8** hebben we laten zien, dat in een morbide obese patiënt van 252 kg met een gediagnostiseerde longembolie, effectieve anti-Xa spiegels worden bereikt met een lagere dosis dan de aanbevolen dosis op basis van het totale lichaamsgewicht. Het resultaat suggereerde dat de farmacodynamiek van LMWHs wordt beïnvloed door extreem overgewicht. Dit was voor ons de aanleiding om het huidige beleid voor het doseren van LMWHs in (morbide) obese patiënten in kaart te brengen. Daarvoor hebben wij in **hoofdstuk 9** online en telefonisch een enquête uitgevoerd onder alle Nederlandse ziekenhuizen. Dosisaanpassingen in obese patiënten in de Nederlandse ziekenhuizen bleken sterk uiteen te lopen. In het merendeel van de ziekenhuizen werd de LMWH dosis verhoogd boven een bepaalde cut-off waarde van het gewicht. Deze waarde was gebaseerd op het totale lichaamsgewicht of BMI en verschilde per instelling. Opvallend was dat controle van het antistollingseffect door LMWHs in morbide obese patiënten met behulp van anti-Xa spiegels niet gangbaar was in de ziekenhuizen.
Om de meest geschikte dosis LMWH in morbide obese patiënten te bepalen, onderzochten we in **hoofdstuk 10** de invloed van overgewicht op het effect van een bolus dosis nadroparine. De anti-Xa spiegels vier uur na toediening bleken te correleren met lean body weight. Lean body weight is eerder voorgesteld als doseermaat voor de therapeutische dosis van enoxaparine, een ander LMWH, bij patiënten met een gewicht boven de 100 kg (16). In overeenstemming met onze resultaten, is eerder beschreven dat het verhogen van de nadroparine dosering resulteerde in een niet-lineaire toename van de maximale anti-Xa spiegel vier uur na toediening in obese patiënten (17). Wij stellen daarom voor lean body weight te gebruiken als doseermaat voor nadroparine.
Om de invloed van overgewicht op de farmacodynamiek van nadroparine volledig te karakteriseren, zijn ook anti-Xa spiegels gemeten na een bolusdosis nadroparine in niet-obese patiënten. Een farmacodynamische populatie analysemethode werd gebruikt om de invloed van het lichaamsgewicht op elke afzonderlijke farmacodynamische parameter te beschrijven om zo een onderbouwd doseringsalgoritme te ontwikkelen. In het farmacodynamische model voor nadroparine beschreven in **hoofdstuk**

11 hebben we laten zien dat zowel in niet-obese als morbide obese patiënten lean body weight de beste gewichtsmaat voor het centrale verdelingsvolume was. Bovendien kon 31% van de interindividuele variatie in de klaring worden verklaard met het totale lichaamsgewicht. Het farmacodynamische model is gebaseerd op een groot aantal anti-Xa spiegels per patiënt uit patiënten die sterk varieerden in lichaamsgewicht (72 kg tot 252 kg). Eerdere publicaties over de invloed van overgewicht op de farmacodynamiek van andere LMWHs (enoxaparine, tinzaparin en dalteparine) toonden aan dat patiënten met obesitas een hogere totale geneesmiddel klaring hebben dan niet-obese patiënten (18). Voor enkele andere renaal geklaarde geneesmiddelen zoals vancomycine, daptomycine en carboplatine is bekend dat de klaring is verhoogd, wat gerelateerd wordt aan een hogere glomerulaire filtratiesnelheid bij obese patiënten, zoals ook is beschreven in hoofdstuk 2 (19-21). De nierfunctie wordt beïnvloed door overgewicht, omdat obese patiënten een 62% toename van de geschatte glomerulaire filtratiesnelheid hebben (22). Daarom wordt de verhoogde klaring van nadroparine met het totale lichaamsgewicht waarschijnlijk veroorzaakt door een toegenomen glomerulaire filtratie in (morbide) obese patiënten. Voor LMWH is het centrale verdelingsvolume de belangrijkste parameter, omdat deze parameter voornamelijk de maximale anti-Xa spiegel vier uur na toediening, bepaalt en waarvoor een profylactische range is gedefinieerd in niet-obese patiënten (18). Er wordt verondersteld dat LMWH zich voornamelijk verdelen over bloed en vasculaire weefsels. Daarnaast is bekend dat het plasmavolume niet-lineair toeneemt met het totale lichaamsgewicht (23) en waarschijnlijk lineair met lean body weight. Daarom is eerder al lean body weight voorgesteld als doseermaat voor het doseren van LMWH (16). Omdat de profylactische anti-Xa streefspiegels zijn vastgesteld voor niet-obese patiënten, kan het zijn dat in de toekomst andere anti-Xa streefspiegels voor morbide obese patiënten worden vastgesteld. Het huidige model kan dan gebruikt worden om veilige en effectieve doseringen voor tromboseprofylaxe in deze bijzondere patiëntenpopulatie te bepalen waarbij deze streefspiegels daadwerkelijk in alle morbide obese patiënten met variërende lichaamsgewichten worden bereikt.

Conclusies en aanbevelingen

- Er zijn grote verschillen in de praktijk van tromboseprofylaxe in (morbide) obese chirurgische patiënten in Nederlandse ziekenhuizen. In de huidige richtlijnen ontbreken onderbouwde dosis aanbevelingen.
- Het centrale distributievolume en de maximale anti-Xa spiegel zijn gecorreleerd met lean body weight, hetgeen suggereert dat lean body weight gebruikt kan worden voor het doseren van nadroparine.
- Het ontwikkelde farmacodynamische model voor nadroparine kan in de toekomst worden gebruikt om met de juiste anti-Xa streefspiegels voor morbide obese patiënten veilige en effectieve doseringen voor tromboseprofylaxe in deze bijzondere patiëntenpopulatie te bepalen.

De invloed van obesitas op de farmacokinetiek en farmacodynamiek van geneesmiddelen in adolescenten en volwassenen: perspectieven van het onderzoek

In dit proefschrift lag de nadruk op het bestuderen van de invloed van morbide obesitas op de farmacokinetiek en farmacodynamiek van propofol en nadroparine met als doel veilige en wetenschappelijk onderbouwde doseringsrichtlijnen te ontwikkelen. Aangezien er grote klinische behoefte is aan onderbouwde doseringsrichtlijnen voor veel gebruikte geneesmiddelen in morbide obese patiënten zou er niet alleen onderzoek zoals beschreven in dit proefschrift uitgevoerd moeten worden, de farmaceutische industrie zou tevens moeten worden aangemoedigd deze patiënten in klinische studies te includeren. Alleen dan kan de invloed van overgewicht op de farmacokinetiek en farmacodynamiek van geneesmiddelen tijdens de eerste fasen van geneesmiddelontwikkeling worden geïdentificeerd. In de uit te voeren farmacokinetische en farmacodynamische studies in deze patientengroep zouden alle beschikbare gewichtsmaten zoals totaal lichaamsgewicht, BMI en lean body weight moeten worden onderzocht. In dit proefschrift werden deze gewichtsmaten getest en de meest significante gewichtsmaat werd opgenomen in het uiteindelijke model. Alternatieve methoden om de invloed van overgewicht op de farmacokinetiek te beschrijven zijn lean body weight met een exponent van 0,66 voor alle geneesmiddelklaringen te gebruiken (24) of het hanteren van de allometrische theorie (25). Laatstgenoemde theorie is gebaseerd op empirische observaties dat de stofwisseling tussen diersoorten toeneemt met het lichaamsgewicht met een exponent van 0,75 (26). Zoals beschreven in hoofdstuk 2 van dit proefschrift, nemen niet alle metabolische activiteiten tussen mensen toe met het lichaamsgewicht. CYP3A gemedieerde geneesmiddelklaringen lijken daarbij zelfs af te nemen. Daarbij is obesitas, naast de ophoping van overtollig vet, een aandoening die de (patho)fysiologie beïnvloedt, waardoor men voorzichtig moet zijn bij het gebruik van de allometrische theorie of het gebruik van één lichaamsmaat voor alle geneesmiddelen in (morbide) obese patiënten. Naast de identificatie van voorspellende gewichtsmaten voor de variabiliteit van de farmacokinetische en farmacodynamische parameters, moet het uiteindelijke model worden gevalideerd en prospectief geëvalueerd, zoals beschreven in hoofdstuk 5. Uit de literatuur blijkt dat de meeste farmacokinetische en farmacodynamische studies niet adequaat alle beschikbare evaluatie- en validatiestappen te beschrijven (27). Misspecificatie van modellen kan leiden tot slechte voorspellende waarden van het model en het kan verstrekkende gevolgen hebben wanneer deze

farmacokinetische en farmacodynamische modellen worden gebruikt als basis voor het doseren van geneesmiddelen in morbide obese patiënten. De nauwkeurigheid van de gewichtsmaten in het uiteindelijke model moeten daarom worden geëvalueerd over de gehele gewichtsrange. In hoofdstuk 12 worden zes evaluatiecriteria voorgesteld om te worden uitgevoerd en gerapporteerd bij de validatie van farmacokinetische en farmacodynamische modellen voor morbide obese patienten. Deze criteria zijn een bewerking van richtlijnen voor farmacokinetisch en farmacodynamisch onderzoek in kinderen (28). De vraag blijft hoe de dosering voor geneesmiddelen in morbide obese patiënten in de toekomst moeten worden onderzocht. Aangezien de prevalentie van obesitas en de totale lichaamsgewichten van zowel kinderen als volwassenen nog steeds toenemen, zijn studies naar de impact van morbide obesitas op specifieke geneesmiddel eliminatieroutes in zowel kinderen als volwassenen gerechtvaardigd. De traditionele farmacokinetische en farmacodynamische modellen hanteren veelal empirische modellen zoals de Hill vergelijking die wordt gebruikt om in vivo dosis-concentratie-effect relaties te beschrijven. Deze vergelijkingen geven niet altijd inzicht in de fysiologie of in factoren die de concentratie-effect relatie beïnvloeden. In theorie is de relatie tussen geneesmiddelconcentratie en biologische respons afhankelijk van geneesmiddelfactoren en biologische factoren (29). De klassieke farmacokinetische en farmacodynamische modellen kunnen uiteindelijk wel leiden tot een fysiologisch model, al dan niet ondersteund met behulp van de Simcyp software (Simcyp Ltd, UK) (30, 31). Met deze software kunnen naast de obesitas gerelateerde (patho)fysiologische veranderingen zoals bijvoorbeeld bloedvolume en metabole processen ook fysische eigenschappen van het geneesmiddel worden opgenomen in het model. Het is onwaarschijnlijk dat voor elk bestaand geneesmiddel in (morbide) obese patiënten grondig gevalideerde farmacokinetische modellen zullen worden ontwikkeld. Een efficiëntere benadering moet daarom worden opgezet om veilige en effectieve doseringsschema's voor deze speciale groep patiënten te ontwikkelen. In hoofdstuk 2 werd beschreven hoe de invloed van obesitas op het metabolisme en de eliminatie van geneesmiddelen per route verschilt. Voorgesteld wordt om de gewichtsmaat en functie die de invloed van obesitas op de klaring van een bepaald geneesmiddel beschrijft, te extrapoleren naar andere geneesmiddelen die via dezelfde route worden geklaard uit het lichaam. De extrapolatie van deze modellen kan de ontwikkeling van farmacokinetische en farmacodynamische modellen voor geneesmiddelen in (morbide) obese patiënten versnellen en kan helpen bij de individualisering van de dosering van geneesmiddelen.

Referenties

1. Bjornsson MA, Norberg A, Kalman S, Karlsson MO, Simonsson US. A two-compartment effect site model describes the bispectral index after different rates of propofol infusion. J Pharmacokinet Pharmacodyn. 2010;37(3):243-55.
2. Wiczling P, Bienert A, Sobczynski P, Hartmann-Sobczynska R, Bieda K, Marcinkowska A, et al. Pharmacokinetics and pharmacodynamics of propofol in patients undergoing abdominal aortic surgery. Pharmacol Rep. 2012;64(1):113-22.
3. Upton RN, Ludbrook G. A physiologically based, recirculatory model of the kinetics and dynamics of propofol in man. Anesthesiology. 2005;103(2):344-52.
4. Stone AA, Broderick JE. Obesity and pain are associated in the United States. Obesity (Silver Spring). 2012;20(7):1491-5.
5. Struys MM, Coppens MJ, De Neve N, Mortier EP, Doufas AG, Van Bocxlaer JF, et al. Influence of administration rate on propofol plasma-effect site equilibration. Anesthesiology. 2007;107(3):386-96.
6. Wang LP, McLoughlin P, Paech MJ, Kurowski I, Brandon EL. Low and moderate remifentanil infusion rates do not alter target-controlled infusion propofol concentrations necessary to maintain anesthesia as assessed by bispectral index monitoring. Anesth Analg. 2007;104(2):325-31.
7. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology. 2004;100(6):1353-72.
8. Ingrande J, Brodsky JB, Lemmens HJ. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. Anesth Analg. 2011;113(1):57-62.
9. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. Jama. 2010;303(3):242-9.
10. Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. Anesthesiology. 2000;92(3):727-38.
11. Wang C, Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Krekels EH, Tibboel D, et al. A Bodyweight-Dependent Allometric Exponent for Scaling Clearance Across the Human Life-Span. Pharm Res. 2012.
12. Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010;49(4):269-75.
13. Sparreboom A, Wolff AC, Mathijssen RH, Chatelut E, Rowinsky EK, Verweij J, et al. Evaluation of alternate size descriptors for dose calculation of anticancer drugs in the obese. J Clin Oncol. 2007;25(30):4707-13.
14. Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. J Clin Anesth. 2005;17(2):134-45.
15. Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? Yes. J Thromb Haemost. 2004;2(4):547-50.
16. Barras MA, Duffull SB, Atherton JJ, Green B. Individualized compared with conventional dosing of enoxaparin. Clin Pharmacol Ther. 2008;83(6):882-8.
17. Heizmann M, Baerlocher GM, Steinmann F, Horber FF, Wuillemin W. Anti-Xa activity in obese patients after double standard dose of nadroparin for prophylaxis. Thromb Res. 2002;106(4-5):179-81.
18. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064-83.
19. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol. 1998;54(8):621-5.
20. Dvorchik BH, Damphousse D. The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. J Clin Pharmacol. 2005;45(1):48-56.
21. Schmitt A, Gladieff L, Lansiaux A, Bobin-Dubigeon C, Etienne-Grimaldi MC, Boisdron-Celle M, et al. A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. Clin Cancer Res. 2009;15(10):3633-9.
22. Pai MP. Estimating the Glomerular Filtration Rate in Obese Adult Patients for Drug Dosing. Adv Chronic Kidney Dis. 2010;17(5):e53-e62.
23. Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006;16(6):773-6.
24. McLeay SC, Morrish GA, Kirkpatrick CM, Green B. The Relationship between Drug Clearance and Body Size: Systematic Review and Meta-Analysis of the Literature Published from 2000 to 2007. Clin Pharmacokinet. 2012;51(5):319-

30.
25.Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32.
26.Kleiber M. Energy Metabolism. Annu Rev Physiol. 1944;6:123-54.
27.Brendel K, Dartois C, Comets E, Lemenuel-Diot A, Laveille C, Tranchand B, et al. Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004. Clin Pharmacokinet. 2007;46(3):221-34.
28.De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol. 2011;67 Suppl 1:5-16.
29.Danhof M, de Lange EC, Della Pasqua OE, Ploeger BA, Voskuyl RA. Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. Trends in pharmacological sciences. 2008;29(4):186-91.
30.Ghobadi C, Johnson TN, Aarabi M, Almond LM, Allabi AC, Rowland-Yeo K, et al. Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients: expected variations in clearance. Clin Pharmacokinet. 2011;50(12):809-22.
31.Darwich AS, Pade D, Ammori BJ, Jamei M, Ashcroft DM, Rostami-Hodjegan A. A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution. J Pharm Pharmacol. 2012;64(7):1008-24.

List of co-authors

(in order of appearance in the manuscript)

MJE Brill
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands

A van Rongen
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands

S van Kralingen
Department of Anaesthesiology, St Lucas Andreas Hospital, Amsterdam, the Netherlands

JN van den Anker
Division of Pediatric Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA

CAJ Knibbe
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands
Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden University, Leiden, the Netherlands

MYM Peeters
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands

VHM Deneer
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands

B van Ramshorst
Department of Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands

RJ Wiezer
Department of Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands

HPA van Dongen
Department of Anesthesiology, Intensive Care and Pain Management, St. Antonius Hospital, Nieuwegein, the Netherlands

M Danhof
Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden University, Leiden, the Netherlands

CJ van Sasse van Ysselt
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands

EMW van de Garde
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands

BA van Wagensveld
Department of Surgery, St Lucas Andreas Hospital, Amsterdam, the Netherlands

V Chidambaran
Division of Anesthesiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, OH, USA

S Sadhasivam
Division of Anesthesiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, OH, USA

HR Esslinger
Division of Anesthesiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

SL Cox
Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

TH Inge
Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

AA Vinks
Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, OH, USA

HJ Blussé van Oud-Alblas
Department of Anesthesiology, Erasmus Medical Center, Rotterdam, the Netherlands

RJ Snijder
Department of Pulmonology, St. Antonius Hospital, Nieuwegein, the Netherlands

CM Hackeng
Department of Clinical Chemistry, St. Antonius Hospital, Nieuwegein, the Netherlands

J Zapletal
Department of Radiology, St. Antonius Hospital, Nieuwegein, the Netherlands

EJH Janssen
Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, the Netherlands

J Boer
Department of Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands

M Russcher
Department of Clinical Pharmacology, Meander Medical Centre, Amersfoort, the Netherlands

List of publications

Appelo DA, Bouwman SN, **Diepstraten J**, Diemont WL, Derijks HJ; Achterliggend mechanisme van fototoxiciteit bij fluorchinolonen. Pharm Weekbl; 2005;17: 563-564 (article in Dutch).

Boon WC, **Diepstraten J**, Van der Burg J, Jones ME, Simpson ER, van den Buuse M; Hippocampal NMDA receptor subunit expression and watermaze learning in estrogen deficient female mice. Mol Brain Res; 2005; 140:127-132.

Diepstraten J, Van de Garde EMW, Wiltink EHH; Lage doseringen zijn effectief. Eptacog alfa in de cardiochirurgie. Pharm Weekbl; 2006; 20:681-684 (article in Dutch).

Diepstraten J, Van Kralingen S, Snijder RJ, Hackeng CM, Van Ramshorst B, Knibbe CAJ; Treatment of pulmonary embolism in an extremely obese patient. Obesity Surgery; 2009; 19:1186-9.

Van Kralingen S, **Diepstraten J**, Van de Garde, Van de EMW, Van der Lely AJWJ, Van Dongen EP, Van Ramshorst B, Knibbe CAJ; Comparative evaluation of propofol 350 mg and 200 mg for induction of anaesthesia in morbidly obese patients:a randomised double blind pilot study. Eur J Anaesthesiol. 2010; 27:572-4.

Van Kralingen S, Van de Garde EM, Knibbe CA, **Diepstraten J**, Wiezer MJ, Van Ramshorst B, Van Dongen EP; Comparative evaluation of atracurium dosed on ideal body weight vs. total body weight in morbidly obese patients. Br J Clin Pharmacol. 2011; 71:34-40.

Van Kralingen S, Taks M, **Diepstraten J**, Van de Garde EM, Van Dongen EP, Wiezer MJ, Van Ramshorst B, Vlaminckx B, Deneer VH, Knibbe CA. Pharmacokinetics and protein binding of cefazolin in morbidly obese patients. Eur J Clin Pharmacol. 2011; 67:985-92.

Van Kralingen S, Van de Garde EM, Van Dongen EP, **Diepstraten J**, Deneer VHM, Van Ramshorst B, Knibbe CAJ; Maintenance of anesthesia in morbidly obese patients using propofol with continuous BIS-monitoring: a comparison of propofol-remifentanil and propofol-epidural anesthesia. Acta Anaesthesiol Belg. 2011; 62:73-82.

Van Kralingen S, **Diepstraten J**, Peeters MYM, Deneer VHM, Van Ramshorst B, Wiezer MJ, Van Dongen EP, Danhof M, Knibbe CAJ; Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. Clin Pharmacokin. 2011; 50:739-50.

Diepstraten J, Knibbe CAJ, The authors' reply: obesity and allometric scaling of pharmacokinetics. Clin Pharmacokin. 2011; 50:755-6.

Diepstraten J, Hackeng CM, Van Kralingen S, Zapletal J, Van Dongen EP, Wiezer MJ, Van Ramshorst B, Knibbe CA. Anti-Xa levels 4 hours after subcutaneous administration of 5700 IU nadroparin strongly correlate with lean body weight in morbidly obese patients. Obes Surg. 2012; Epub 1 feb.

Diepstraten J, Van Kralingen S, Peeters MYM, Deneer VHM, Van Ramshorst B, Van Dongen EP, Danhof M, Knibbe CAJ. Farmacokinetiek en farmacodynamiek van propofol bij morbide obese patiënten. Pharm Weekbl. 2012; 6:68-72 (article in Dutch).

Brill MJ, **Diepstraten J**, Van Rongen A, Van Kralingen S, Van den Anker JN, Knibbe CA. Impact of Obesity on Drug Metabolism and Elimination in Adults and Children. Clin Pharmacokinet. 2012; 51:277-30.

Diepstraten J, Chidambaran V, Sadhasivam S, Esslinger H, Cox S, Inge T, Knibbe CAJ, Vinks AA. Propofol clearance in morbidly obese children and adolescents is influenced by total body weight. Clin Pharmacokinet. 2012; 51:543-51.

Acknowledgements

(in Dutch)

De tocht van het promoveren doet me denken aan mijn hobby wielrennen. Onderweg kom je allerlei hindernissen tegen die je wil en moet overwinnen: lekke banden maar ook beklimmingen naar de top en als je het lukt is de afdeling daarna heerlijk genieten. Met doorzettingsvermogen bereik je de finish: moe maar voldaan. Naast dat alleen promoveren onmogelijk is, is het net zoals alleen fietsen ook heel erg saai. Ik ben blij dat ik dit proefschrift samen met velen heb weten te realiseren. Iedereen die heeft bijgedragen aan de totstandkoming van dit proefschrift wil ik bedanken waarbij ik een aantal bijzondere mensen specifiek wil benoemen.

Beste Catherijne, jij bent degene die mij de mogelijkheid heeft gegeven dit project te realiseren. Ik kwam het St. Antonius binnen met een passie voor het vak ziekenhuisapotheker en ga nu weg met een extra passie; PKPD onderzoek. Tijdens mijn opleiding tot ziekenhuisapotheker kwam ik er achter dat ik alleen bij jou zou willen promoveren. Je steun gedurende dit traject heeft mij er doorheen getrokken. Ik heb erg veel waardering voor de manier waarop je mensen kan motiveren met je enthousiasme voor het onderzoek.

Beste Sander, jij hebt mij de kans geboden om 3 maanden onderzoek te kunnen doen in het Cincinnati Children's Hospital en dit heeft unieke data van obese kinderen opgeleverd. Daarnaast heb je mij tijdens mijn bezoek aan de VS aangespoord om vol te houden tot het einde en zie daar. De goede en unieke samenwerking tussen Nieuwegein en Cincinnati blijft hopelijk in stand.

Beste Eric, je gedreven uitleg over de vier pijlers van de anesthesie en je onvoorwaardelijke hulp tijdens de voorbereidingen en ook tijdens het includeren hebben er voor gezorgd dat er in korte tijd veel data kon worden verzameld.

Beste Bert, ik werd aangestoken door het enthousiasme van je om de onderzoekslijn bariatrie in het St. Antonius Ziekenhuis uit te breiden en overal nieuwe mogelijkheden te zien voor vervolg onderzoeken. Jij maakt ons onderzoek mogelijk door ons te 'gedogen' tijdens jouw operaties.

Beste Mathieu, ten eerste ben ik natuurlijk heel dankbaar dat jij mij ooit hebt aangenomen in het St. Antonius Ziekenhuis voor de opleiding tot ziekenhuisapotheker. De kracht om met plezier nieuwe ontwikkelingen en uitdagingen aan te gaan hebben mij geïnspireerd, zeker ook bij dit onderzoek. Als niet academisch ziekenhuis zo veel onderzoek doen, maakt promoveren in het St. Antonius Ziekenhuis bijzonder. Dank voor je onvoorwaardelijke steun en je humor. Hopelijk blijven we elkaar zien in het kleine wereldje van de ziekenhuisfarmacie.

Ik wil alle medewerkers van de afdelingen Anesthesie, Heelkunde, Klinische Chemie en het Farmaceutisch Tox Lab bedanken voor hun hulp tijdens dit onderzoek wat veelal naast de reguliere werkzaamheden werd uitgevoerd.

In het bijzonder dank ik Brigitte, Silvia, Koos en Lilian voor hun hulp. Ook alle patiënten die toestemming hebben gegeven om mee te doen aan dit onderzoek dank ik. Zonder data geen onderzoek. Het PK-PD modelleren heb ik ook zeker geleerd van de medewerkers van LAP&P Consultants. In het bijzonder Tamara van Steeg bedankt voor je enthousiaste en duidelijke uitleg. De studenten die mij hebben geholpen met allerlei klussen en onderzoeken en het ook gezellig hebben gemaakt, wil ik hier graag noemen: Margot, Esther en Christine. De interactie hield mij scherp. Simone en Aletta, jullie wil ik danken voor alle hulp vooral tijdens de inclusie.

tCollega's van de Klinische Farmacie met in het bijzonder mijn onderzoeksmaatjes Rifka, Magreke en Anne en de apothekers waarmee ik mijn opleiding tot ziekenhuisapotheker heb gedaan Ewoudt, Ankie, Roeland, Bas en Tanja: ik heb genoten van alle inhoudelijke discussies maar ook van al het plezier op de afdeling. Hopelijk houden we de etentjes en de kleine biertjes drinken erin. I, I follow...

Marly na het zien van je afstuurprojecten van de Design Academy wist ik dat jij voor mij het boekje moest vormgeven. Ik ben super tevreden met het resultaat en zal reclame voor je blijven maken. Al jouw werk maakt het boekje voor mij nog persoonlijker.

Ik ben gezegend met een vriendengroep die me erg dierbaar is. Jullie zorgen voor de ontspanning naast het werk. Zonder iedereen te noemen wil ik jullie wel allemaal bedanken. Maar in het bijzonder de Boys, we zijn met z'n achten al vanaf de middelbare school bij elkaar. Dat is zo uniek en ik geniet van alle feestjes, etentjes en vakanties samen. Hopelijk volgen er nog veel.

Lieve Sabine, ik vond het super om jouw paranimf te zijn maar ben nog trotser dat jij dadelijk naast mij staat. Hopelijk volgen er nog veel etentjes en vinden we altijd wel weer een reden om bubbels te schenken.

Boertje, naast je aanstekelijke humor ben ik ook erg blij met onze gezamenlijke passie voor de zorg. Hopelijk krijgen we het een keer voor het zeggen in de zorg: dan wordt alles beter. Ik ben erg trost dat jij mijn paranimf bent.

Lieve pap en mam, de eeuwige steun en liefde die jullie uitstralen naar mij doet al 34 jaar heel goed. Dank voor alles.

Nu nog het beste van het stel: Marieke. Je Rotterdamse nuchtere humor en je liefde voor mij zijn onbetaalbaar. We hebben zo veel gemeen maar zijn soms ook zo anders. Daarom zijn we het beste stel. Ik verheug me op ons verdere leven samen en de avonturen die we samen gaan beleven.

Curriculum vitae

Jeroen Diepstraten was born on April 8th, 1979 in Eindhoven, The Netherlands. In 1997 he finished the secondary school (VWO) at the Van Maerlantlyceum in Eindhoven. After obtaining his propaedeutics of Architecture at Delft University of Technology, he started studying Pharmacy at the Utrecht University in 1998. In 2003 he obtained his doctoral exam, followed by his PharmD exam in 2005. As part of his doctoral program he worked for 6 months on a research project analyzing the effects of estrogen on NMDA receptor subunits and 5-HT2AR transcriptions at Prince Henry's Institute of Medical Research in Melbourne, Australia. From December 2005 to December 2006, he developed a clinical pharmacy benchmark tool for the Dutch Society of Hospital Pharmacy (NVZA) and carried out the research project "Hospital Admission Related to Medication (HARM)" for the Department of Clinical Pharmacy & Toxicology of the Leiden University Medical Center (supervisor Prof. dr. H.J. Guchelaar). In 2007 he started his training as clinical pharmacist which was completed in December 2010 in the Department of Clinical Pharmacy at the St. Antonius Hospital Nieuwegein , The Netherlands (supervisor M.M. Tjoeng). At the same time he started working on the studies presented in this PhD thesis (supervisors Prof. dr. C.A.J. Knibbe, Prof. dr. A.A. Vinks, dr. H.P.A. van Dongen, dr. B. van Ramshorst). As part of his PhD project he spent 3 months for setting up a research project in (morbidly) obese children at the Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA (supervisor Prof. dr. A.A. Vinks). Jeroen is now working as a clinical pharmacist at the Onze Lieve Vrouwe Gasthuis in Amsterdam, The Netherlands and after completion of his PhD he will continue his career as clinical pharmacist at the Reinier de Graaf Gasthuis in Delft, The Netherlands.

Jeroen Diepstraten lives together with Marieke Ezinga in Utrecht.