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.