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Pharmacokinetics and/or pharmacodynamics of propofol, atracurium and cefazolin in morbidly obese patients

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Section I

General introduction

Chapter 1

**Pharmacokinetics and/or
pharmacodynamics of propofol,
atracurium and cefazolin in
morbidly obese patients**

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1. Introduction

In the last decade there has been a worldwide increase in the prevalence of obesity. In the United States 35% of the population is obese (BMI = body mass index $> 30 \text{ kg m}^{-2}$) and 2.8% of men and 6.9% of women suffer from morbid obesity (BMI $> 35 \text{ kg m}^{-2}$) [1, 2]. Bariatric surgery or weight-reducing surgery is not only effective in achieving weight reduction in morbidly obese patients, but has been shown to improve or even resolve the associated health problems, such as diabetes mellitus, hyperlipidaemia, hypertension, and obstructive sleep apnoea [3]. As a consequence of the rise in prevalence of obesity, health services will be treating a growing number of obese patients for concomitant illnesses and, therefore, medical personnel will have to be well informed on the physical and physiological changes in obesity. Surgery in morbidly obese patients 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 (cardiomyopathy, increased cardiac output and blood volume). In addition, they are at increased risk of developing thrombo-embolism, postoperative apnoea and wound infections. Knowledge of optimal dosing schemes of anaesthetics, analgesics, neuromuscular blocking agents, antibiotics and a variety of other drugs administered peri-operatively is a prerequisite and of specific relevance for the anaesthesiologist taking care of these patients in bariatric surgery programs. The existing literature on this topic is scarce and most studies included patients with lower body mass indices than patients currently undergoing bariatric surgery. Obesity and morbid obesity are associated with many physiological changes, which may influence the pharmacokinetics and pharmacodynamics of drugs. In the next section we will first describe the pathophysiological changes associated with obesity and then discuss, from this perspective, what is known on the pharmacokinetics and/or pharmacodynamics of propofol, atracurium and cefazolin in morbidly obese patients.

2. Pathophysiological changes in morbidly obese patients

Obesity is associated with increases in both fat and lean body masses compared to non-obese subjects. Lean body mass is a size descriptor of weight devoid of all adipose tissue, consisting of extra-cellular fluid, muscle, bone and the vital organs. In morbidly obese patients the increase in lean body mass represents 20% to 40% of total weight excess. The percentage of fat mass per kilogram of total body weight increases more than lean body mass in obese patients compared to non-obese patients, resulting in a relative decrease of the percentage of lean body mass and total body water [4, 5]. Other changes related to obesity are an absolute increase in blood volume and cardiac output [6, 7]. Blood volume and capillary flow are increased to supply the excess body mass, and there is a concomitant increase in preload and, often, afterload. The heart compensates for the expanded blood volume by increasing stroke volume and cardiac work, resulting in an increased cardiac output [8]. Total blood volume increases with overweight, but not in a linear manner [9]. Systemic hypertension, due to an increase in cardiac output and blood volume and pulmonary hypertension, due to hypoxic pulmonary vasoconstriction and increased cardiac output, are often associated with morbid obesity. As a result, left and right ventricular hypertrophy may develop. Obesity leads to fatty infiltration of the cardiac conduction system, which can lead to sudden cardiac death due to conduction disorders [10, 11].

Pulmonary function tests are uniformly altered in obesity. The tidal volume is normal or increased and the inspiratory reserve volume is decreased. The expiratory reserve volume is decreased, because the normal expansive tendency of the rib cage is reduced due to the increased weight of the torso and abdomen. The forced vital capacity and forced expiratory volume are reduced, an effect which is more explicit in central compared to peripheral obesity. Total respiratory system compliance is reduced because of the increase in weight of the torso and abdominal contents pressing against the diaphragm, creating a restrictive component. Lung compliance is often normal, but is decreased when pulmonary and circulatory comorbidities such as pulmonary hypertension are present. The functional residual capacity is reduced in obese patients, and may be below the closing capacity,

resulting in small airway closure, ventilation-perfusion mismatch, right-to-left shunting and the occurrence of hypoxemia. Morbid obesity is associated with a 70% increase in work of breathing, and a fourfold increase in the oxygen cost of breathing [12]. Finally, there is a high incidence of obstructive sleep apnoea syndrome (OSAS) in morbidly obese patients.

Non-alcoholic steatohepatitis is very common in morbidly obese patients [13]. Histological abnormalities as fatty infiltration are present in the liver in 87% of this population [14] and the accumulation of fat in the liver of obese individuals may alter hepatic blood flow [15]. Increased fat deposition in the liver causing sinusoidal narrowing and altered functional morphology has been described [16]. Due to the increased blood volume, hepatic clearance is not necessarily reduced in obesity [17]. Liver function tests often do not reflect the severity of liver dysfunction. The effect of liver dysfunction on clearance of drugs is conflicting, as unchanged clearance (CL) values, increased CL values and reduced CL values have been reported [4].

Renal clearance, in the early stages of obesity, is increased in obese patients due to the increased renal blood flow and glomerular filtration rate. The glomerular filtration rate and effective renal plasma flow have been reported to be increased in overweight compared with lean subjects irrespective of the presence of hypertension [18]. Obesity is related to a state of glomerular hyperfiltration, which resembles that seen in early-stage diabetic nephropathy [19]. A decreased afferent arteriolar tone is present, which allows for a larger transmission of the systemic arterial pressure to the glomerular capillary bed and an increase in filtration as well as perfusion. The combined effects of afferent vasodilatation with impaired protection against elevated systemic arterial pressure and an increased efferent vascular tone that further augments glomerular pressure increases the renal susceptibility to hypertensive damage [20]. Estimates of the creatinine clearance from standard formulas tend to be inaccurate in obese patients with renal impairment, as these formulas include age, weight and gender to account for inter-individual differences in muscle mass and the resulting differences in creatinine generation. As the factor body weight is assumed to reflect muscle mass instead of fat mass, the higher fat mass in obesity influences the factor body weight

in the equation, thereby overestimating creatinine clearance. Creatinine clearance should thus be measured instead of estimated [20, 21]. In Zucker rats with genetic obesity, initially, an increased glomerular filtration rate was observed, mainly in superficial nephrons and in association with expansion of glomerular area and mesangial matrix [22]. In the later stages of obesity, glomerular filtration rate was found to normalize and subsequently decrease, together with the development of progressive albuminuria and glomerulosclerosis [23, 24]. Also in human studies it has been argued that overweight may lead to end-stage renal disease. Focal glomerular sclerosis and/or diabetic nephropathy have been observed in morbidly obese patients who presented with proteinuria [25].

Although most obese patients are not diabetic, 80-90% of non-ketotic diabetics are obese. Increased insulin secretion and insulin resistance resulting from peripheral tissue insensitivity are well-characterized features of obesity. Obesity exacerbates the diabetic state; there is a more than 40-fold increase in adult onset diabetes mellitus in patients with a body mass index of more than 35 kg m^{-2} [26]. Recent studies suggest that bariatric surgery improves or even effectuates resolution of type II diabetes mellitus [27] in up to 80% of patients. This effect was initially described in 1995 by Pories *et al.* following gastric bypass surgery [28] and similar rates have been repeatedly demonstrated since [3, 29]. The initial assumption was that the mechanism causing this effect was through weight loss. It is becoming evident that the anti-diabetic effect is not entirely due to weight loss, as there is a consistent observation that the improvement of glucose and insulin levels occurs within days after gastric bypass surgery before a significant weight reduction has been achieved [28, 30]. There are two theories attempting to explain this weight-independent anti-diabetic effect after gastric bypass surgery. First, the rapid delivery of partially digested nutrients to the distal bowel may up-regulate the secretion of incretins such as glucagon-like peptide-1 (GLP-1). The result of the increased incretin secretion is an enhanced glucose-dependent insulin secretion, as well as a number of other changes causing improved glucose tolerance [30]. Second, the exclusion of the duodenum may result in the inhibition of a 'putative' signal that is responsible for insulin resistance and/or abnormal glycaemic control. In a non-obese diabetic rat model, surgical diversion of the proximal

bowel caused rapid improvement of diabetes without reduction of food intake or change in weight [31].

Morbidly obese patients are exposed to an increased risk of developing post-operative wound infections compared to non-obese patients [32, 33]. Local changes, such as an increase in adipose tissue, increase in local tissue trauma related to retraction, lengthened operative time, and a disturbance of body homeostatic balance may contribute to the reported increased incidence of surgical-site infections in obesity [34]. Subcutaneous tissue oxygenation is said to be reduced in obese patients and this may predispose to wound infection, particularly after laparoscopic procedures [35]. Obesity is independently associated with *Staphylococcus aureus* nasal carriage, which is a risk factor for surgical-site infections [36].

It has recently been recognized that adipose tissue participates actively in inflammation and immunity, producing and releasing a variety of pro-inflammatory and anti-inflammatory factors, including the adipokines leptin and adiponectin, as well as cytokines and chemokines [37]. Levels of adiponectin, which has potent immunosuppressive properties and is known for its role in the regulation of insulin sensitivity, are reported to be reduced in obese subjects [37, 38]. Leptin exerts a pro-inflammatory role, but at the same time protects against infections. While control of appetite is the primary role of leptin, circulating leptin levels are reported to correlate directly with adipose tissue mass [37]. Levels of TNF- α , which is considered a likely mediator of the insulin resistance and type II diabetes associated with high visceral obesity, are increased in obese patients [37]. The association of the pro-inflammatory state of obesity with the risk of infection has not been precisely determined, but, as already mentioned, leptin seems to play an important role in the immune response.

Finally, increased concentrations of triglycerides, lipoproteins, cholesterol and free fatty acids [39] have been reported in morbidly obese patients, which may inhibit plasma protein binding of some drugs, and thereby increase free plasma concentrations [39]. In contrast, elevated concentrations of acute phase proteins as α_1 acid glycoprotein have been observed in obese patients [40] and this may increase the degree of plasma protein binding of other drugs (e.g. local

anaesthetics), reducing the free plasma fraction [40]. Regarding plasma protein binding, obesity does not appear to have an impact on drug binding to albumin [41, 42].

In summary, there are numerous physiological changes associated with (morbid) obesity. There is an increase in both fat and lean body masses, with a relative decrease in the percentage of lean body mass and total body water. Blood volume and cardiac output are increased and systemic hypertension, as well as pulmonary hypertension, is often associated with morbid obesity. Pulmonary function tests are uniformly altered in obesity and there is a high incidence of obstructive sleep apnoea syndrome (OSAS) in morbidly obese patients. In the early stages of obesity an increase in glomerular filtration and perfusion in the kidneys is described, while in the later stages of obesity, glomerular filtration rate was found to normalize and subsequently decrease. Non-alcoholic steatohepatitis is very common in morbidly obese patients but due to the increased blood volume, hepatic clearance is not necessarily reduced in obesity. Obesity exacerbates the diabetic state and recent studies suggest that bariatric surgery improves or even effectuates resolution of type II diabetes mellitus. The excess of adipose tissue may be poorly perfused, which may affect the penetration of medication into this tissue. Together with the altered immune system associated with obesity this may lead to an increased risk of infection. Due to increased concentrations of triglycerides, lipoproteins, cholesterol and free fatty acids and acute phase proteins as α_1 acid glycoprotein, plasma protein binding of different drugs can be altered.

3. The influence of (morbid) obesity on the pharmacokinetics and/or pharmacodynamics of propofol, atracurium and cefazolin.

The physiological changes associated with obesity as described above under 2. can be expected to lead to alterations in the distribution, plasma protein binding and elimination of many drugs [19, 43, 44]. The net pharmacokinetic effect in any patient is often uncertain as there is little knowledge on the pharmacodynamics of drugs in morbidly obese patients.

Factors that affect the apparent volume of distribution of a drug in obese patients include the size of the fat organ, the increased lean body mass, the increased blood volume and cardiac output, the reduced percentage of total body water and lean body mass, the alterations in plasma protein binding and the lipophilicity of the drug [45]. For highly lipophilic substances such as barbiturates and benzodiazepines significant increases in volume of distribution for obese individuals relative to non-obese individuals have been reported [46-48]. In the case of an increased central volume of distribution, this could lead to the conclusion that lipophilic medication administered as a bolus should be dosed on a total body weight basis. However, this is not consistently reported in the existing pharmacological literature [49, 50]. This suggests the involvement of other mechanisms, such as plasma protein-binding.

When drugs are administered as a continuous infusion, clearance is the main determinant of the dose administered. Despite the high incidence of non-alcoholic steatohepatitis, hepatic clearance is not necessarily reduced in obesity [17]. The effect of liver dysfunction on clearance of drugs is conflicting. Unchanged clearance (CL) values, increased CL values and reduced CL values have been reported [4]. Regarding glomerular filtration rate, in preclinical studies an initial increase is reported in obese subjects [22], but in the later stages of obesity, glomerular filtration rate was found to normalize and subsequently decrease [23, 24]. Also in human studies the increase in glomerular filtration as well as perfusion in the kidneys result in a normal or even slightly increased renal function in young obese patients [18], but it has been argued that overweight with increasing age may ultimately lead to end-stage renal disease [25].

Due to the increased concentrations of lipids and acute phase proteins as α_1 acid glycoprotein observed in obese patients [51] the degree of protein binding of drugs may be altered. Drugs that mainly bind to albumin are considered to have an unchanged level of unbound fraction, although little is known on this subject. In the next section the general pharmacokinetics and pharmacodynamics of propofol, atracurium and cefazolin are summarized based on the existing literature, with special emphasis on (morbidly) obese patients.

3.a *Propofol*

3.a.i *General characteristics of propofol*

3.a.i.1 *Pharmacokinetic characteristics of propofol*

Propofol is 2,6-di-isopropylphenol, a derivative of phenol, which is an extensively used intravenous agent for induction and maintenance of anaesthesia. It is highly lipophilic, 98% is protein-bound (mainly albumin) and clearance is mostly hepatic and for a small part extra-hepatic. Propofol has a rapid onset of action and fast recovery and the incidence of nausea and vomiting is the least of all anaesthetic agents [52]. An induction dose of 2-3 mg kg⁻¹ is given to healthy patients, but co-existing factors such as premedication, advanced age or presence of concurrent disease (hypovolemia or cardiac dysfunction) will decrease the required dose of propofol [53]. For maintenance of anaesthesia a dose of 3-12 mg kg⁻¹ hr⁻¹ is given to healthy patients [54].

The pharmacokinetics of propofol are best described by a three-compartment pharmacokinetic model with a rapid initial distribution from blood into highly perfused tissues such as brain, heart, lung and liver ($t_{1/2\alpha} = 2 - 4.6$ min), redistribution and metabolic clearance ($t_{1/2\beta} = 22 - 166$ min) and a slow return from poorly perfused tissues to blood ($t_{1/2\gamma} = 164 - 355$ min) [55-60]. Plasma clearance of propofol is estimated to range from 1.4 to 2.2 L min⁻¹ [55-57, 60, 61], exceeding hepatic blood flow suggesting extra-hepatic elimination of propofol. The alimentary canal, kidneys and in particular the lungs have been mentioned as the most probable sites where this process occurs [62]. Propofol has a relatively small initial volume of distribution (2-5 L kg⁻¹) [55-57, 63] and a high apparent volume of distribution at steady-state (159 – 322 liters), reflecting extensive tissue distribution [55-57, 60, 61].

Propofol is eliminated in urine as the glucuronic acid conjugate of propofol, which is the major metabolite in plasma and urine, and the glucuronic acid- and sulphate conjugates of the hydroxylated derivative, 2,6-di-isopropyl-1,4-quinol. None of these metabolites possess biological activity [64].

3.a.i.2 Pharmacodynamic characteristics of propofol

Propofol induces anaesthesia usually within 40 seconds after a therapeutic dose [65]. The onset of action or induction time is shortened by rapid injection of the dose [66-68]. The quick onset of action is facilitated by the rapid penetration of the blood-brain barrier. Propofol appears to enhance γ -aminobutyric acid (GABA)-mediated transmission by binding to a specific site independent of the benzodiazepine receptor site [69], while there is also evidence that propofol may interact with sodium channels in the central nervous system [70]. Propofol is rapidly redistributed from the central nervous system to inactive tissue depots and together with its high clearance from blood this leads to rapid recovery from anaesthesia. Renal failure does not markedly affect the pharmacodynamic profiles of propofol [71]. Although conjugates of propofol accumulate in blood of patients with renal disease and in patients after prolonged administration, no difference in time to eye opening was found, confirming the absence of clinical effects of these metabolites [72].

Propofol causes 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 decreases of pre –and afterload [73]. Propofol exerts respiratory depressant effects comparable to other sedatives such as midazolam [74, 75].

3.a.i.3 Pharmacokinetic-pharmacodynamic relation of propofol

The effects of propofol in conjunction with plasma or blood concentrations have been determined in several studies and it appears that the effects can be related to propofol concentrations, while inter –and intra-individual variability is large. Elderly patients are found to be nearly twice as sensitive to the hypnotic effects of propofol as younger patients and the plasma concentration associated with a 50% probability of being asleep at the end of propofol infusion was significantly correlated with age [76]. Finally, disease severity seems to be a major determinant for the pharmacodynamics of propofol in critically ill patients. Intensive care

patients with higher Sequential Organ Failure Assessment (SOFA) scores appear to have lower Ramsay scores and Bispectral Index values than patients with lower SOFA scores [77].

3.a.i.4 Propofol-remifentanil combination

From the study of Bouillon *et al.* there is evidence that remifentanil does not interact with the dose-concentration relation (pharmacokinetics) of propofol [78]. They also concluded that co-administration of propofol decreases the central volume of distribution and distributional clearance of remifentanil by 41% and elimination clearance by only 15%, so that maintenance infusion rates do not need adjustment for pharmacokinetic reasons [79].

The current opinion is that opioids such as remifentanil exert a propofol-sparing effect when given in combination with propofol. Some studies did show reductions in Bispectral Index values (measure of the level of consciousness by algorithmic analysis of a patient's electroencephalogram during general anaesthesia) when an opioid was given during anaesthesia with propofol [78, 80-82]. However, as Ferreira [82] pointed out, this influence may be due to the decrease in blood pressure and heart rate when an opioid is co-administered, which can lead to a reduction of cerebral blood flow and thus a decrease in Bispectral Index values, and this indicates there may not be a hypnotic effect of opioids. On the other hand, Guignard *et al.* demonstrated that remifentanil does not affect Bispectral Index values but that the increases in Bispectral Index values associated with laryngoscopy and orotracheal intubation are prevented by remifentanil in a dose-dependent fashion [83]. Other studies did demonstrate a deeper level of anaesthesia or loss of consciousness at lower propofol effect-site concentrations when an opioid was co-administered with propofol which was not reflected by lower Bispectral Index values [84, 85]. An explanation for the results of these last studies, that showed no effects of opioids on Bispectral Index values but did observe an increased hypnotic effect when co-infused with propofol, is that hypnotics affect the EEG by an action on the cerebral cortex, whereas opioids exert their analgesic action through an inhibition of subcortical structures, including the

spinal cord. These last structures may not be integrated in the Bispectral Index monitor.

In summary, adding an opioid to propofol-anaesthesia had no effect on the pharmacokinetics of propofol, but results in an increased clinical hypnotic effect which may not be captured by lower Bispectral Index values.

3.ii Propofol in morbidly obese patients

Due to its rapid onset of action and early recovery, propofol has suitable pharmacological properties for the use of induction and maintenance of anaesthesia in morbidly obese patients undergoing surgery. Morbidly obese patients are prone to desaturation due to a decreased expiratory reserve volume and functional residual capacity and the high incidence of obstructive sleep apnoea syndrome (OSAS), rendering it of utmost importance to induce a rapid onset of anaesthesia, in order to prevent desaturation. Prompt emergence is, in this perspective, a pharmacological advantage of propofol as it was reported not to accumulate in obese patients [86], making it suitable for use in morbidly obese patients.

When considering the known physiological changes associated with morbid obesity together with the pharmacological properties of propofol, some interpretations can be made. The increase in both fat and lean body masses may lead to speculations that the volume of distribution of propofol increases with increasing body weight, due to the lipophilicity of propofol. However, the initial volume of distribution of propofol is reported to be relatively small and similar in obese and non-obese patients [87], which is in contrast to the apparent and peripheral volumes of distribution, which are more dependent on fat and muscle tissue [44-46].

While blood volume and cardiac output are known to be increased, Kurita and co workers [88] showed in swine that cardiac output is the determinant for the concentration of propofol during continuous infusion. A higher cardiac output resulted in lower systemic arterial concentrations of propofol and a lower cardiac output resulted in higher systemic arterial concentrations [88]. From the results of

this preclinical study it can be hypothesized that the maintenance dose of propofol should be adjusted on the basis of the increased cardiac output associated with obesity.

In contrast, the commonly reported non-alcoholic steatohepatitis in morbidly obese patients is not expected to influence propofol clearance, as, due to the increased blood volume in obesity, hepatic blood flow, which is the main determinant for propofol clearance, is not decreased. Similarly, plasma protein binding of propofol is not expected to be influenced by obesity, as propofol is mainly albumin-bound. The existing literature is conflicting in their recommendations for dosing of propofol in morbidly obese patients. Some studies recommend dosing of propofol for induction and maintenance to be calculated on a total body weight basis [17], but point at the risk of deleterious haemodynamic effects caused by these large amounts of propofol administered. In order to prevent dose-related cardiovascular complications, other dosing regimen have been proposed, based either on an empirical formula (corrected weight = ideal weight + $[0,4 \times \text{excess weight}]$) or lean body mass [89, 90]. Lemmens *et al.* refer to reports suggesting that the induction dose of propofol should be based on total body weight, but conclude that due to the fear of cardiovascular collapse it seems prudent to titrate propofol based on lean body mass [89]. Servin, who proposed the above mentioned empirical formula, concluded, similar to Casati *et al.* [17], that dosing of propofol for maintenance of anaesthesia should be based on actual body weight while mentioning the risk of haemodynamic complications [90]. Albertin *et al.* concludes after evaluating Servin's formula when used for Bispectral Index (BIS)-guided propofol-remifentanyl target-controlled infusion (TCI) in morbidly obese patients, that TCI system performance should be significantly improved when total body weight is used as weight input [91]. However, a more recent paper actually studied total body weight in the TCI device and concluded that both dosing on total body weight and adjusted body weight using Servin's formula in TCI leads to performance error in predicted propofol concentrations. Based on these incorrectly predicted propofol concentrations, they finally concluded that propofol should be dosed by titration to processed-EEG values [92].

In summary, there is controversy in the current literature on dosing of propofol for induction as well as maintenance of anaesthesia in morbidly obese patients. In the meantime, body weights and body mass indices of obese patients undergoing bariatric surgery are still increasing.

4.b *Atracurium*

3.b.i General characteristics of atracurium

Atracurium is a bisquaternary benzyloisoquinoline di-ester and a commonly used non-depolarizing neuromuscular blocking agent due to its organ-independent elimination. It degrades spontaneously at physiological temperature and pH through Hofmann's elimination and non-specific esterase hydrolyses, breaking atracurium down to produce a tertiary amine, laudanosine and a mono-acrylate compound which are eliminated by the kidneys [93]. Protein binding (mainly α_1 acid glycoprotein) is reported to be 82% [94]. Atracurium can cause histamine release and hypotension, but when given in doses $< 0.5 \text{ mg kg}^{-1}$ or when larger doses are given slowly this is rarely elicited [95].

In non-obese patients a dose of $0.4\text{--}0.5 \text{ mg kg}^{-1}$ is recommended by the RxList, the internet drug index and leads to muscle relaxation in 2 to 2.5 minutes, with a maximum neuromuscular block in 3 to 5 minutes after injection. Clinically, in non-obese patients the neuromuscular block typically lasts 20 to 35 minutes while recovery is usually 95% complete approximately 60 minutes after injection.

3.b.ii Atracurium in morbidly obese patients

Atracurium is a hydrophilic drug that is distributed poorly to excess adipose tissue. Its elimination is independent of hepatic and kidney function, which makes atracurium a suitable drug for muscle relaxation in morbidly obese patients undergoing bariatric surgery. When considering the physiological changes associated with morbid obesity together with the pharmacological properties of atracurium, some interpretations can be made. The increase in

both fat and lean masses, with a relative decrease in the percentage of lean body mass and total body water, may influence the pharmacokinetics of atracurium, because atracurium is hydrophilic and distributes poorly to adipose tissue. The hydrophilic characteristics of atracurium together with the decrease in total body water could lead to the hypothesis that less atracurium is needed per kilogram of body weight in obese patients compared to non-obese patients. In contrast, the increase in blood volume in obesity may lead to an increase in the initial volume of distribution. No influence is expected from the increase in glomerular filtration as well as perfusion in the kidneys and non-alcoholic steatohepatitis reported in obesity due to its organ-independent elimination. Plasma protein binding of atracurium may be altered in obesity due to increased concentrations of acute phase proteins as α_1 acid glycoprotein [51], which is the protein atracurium binds to. This may indicate that plasma protein-binding of atracurium can be increased in morbidly obese patients.

Based on the existing literature, it can be concluded that drugs with weak or moderate lipophilicity should be dosed on the basis of lean body mass (LBM) [96]. Adding 20% to the estimated ideal body weight (IBW) dose of hydrophilic medications is reported to be sufficient to include the extra lean mass. While it can be assumed that non-depolarizing muscle relaxants can be dosed in this manner [96, 97], for atracurium doses based on total body weight (TBW) [98] and total body weight with a dose reduction for every 10 kg more than 70 kg have been proposed [99]. However, a prolonged duration of action when an induction dose of atracurium 0.5 mg kg^{-1} was based on total body weight in obese patients was shown in a study by Kirkegaard-Nielsen *et al.* [99], reason why they proposed a dose reduction of atracurium by 2.3 mg for each 10 kg TBW more than 70 kg when using total body weight as weight input [99]. Although this study showed a prolonged duration of action when an induction dose of 0.5 mg kg^{-1} was administered, Weinstein [100] studied recovery times from neuromuscular blocks induced by atracurium (dose 0.5 mg kg^{-1} of total body weight) in obese (mean weight 80 kg, range 61-95) and non-obese patients (mean weight 60 kg, range 48-77) and found no difference in recovery times.

As for propofol, current available literature of atracurium is conflicting when describing its use in (morbidly) obese patients.

3.c Cefazolin

3.c.i General characteristics of cefazolin

Cefazolin, a first generation cephalosporin, is a commonly used peri-operative antibiotic to prevent post-operative wound infections. Cefazolin is sensitive for β -lactamases while infection with gram-positive and gram-negative micro-organisms can be treated with cefazolin [101]. Plasma protein binding of cefazolin is 70-86% (mainly albumin), its elimination is by glomerular filtration and cefazolin is excreted in its biologically active form in urine. Plasma concentrations of cefazolin after a bolus dose of one gram in non-obese patients are 188.4 $\mu\text{g ml}^{-1}$ after 5 minutes, 135.8 $\mu\text{g ml}^{-1}$ after 15 minutes, 106.8 $\mu\text{g ml}^{-1}$ after 30 minutes, 73.7 $\mu\text{g ml}^{-1}$ after 1 hour, 45.6 after 2 hours and 16.5 after 4 hours [94].

For a prophylactic effect of an antibiotic drug given peri-operatively, time above the minimal inhibitory concentration (MIC) of the unbound cefazolin concentration for the most common pathogens is crucial. The MIC for 90% (MIC_{90}) of methicillin sensitive *S. aureus* isolates may differ between countries and hospitals but is usually around 1 mg L^{-1} in Europe [102].

3.c.ii Cefazolin in morbidly obese patients

When considering the physiological changes associated with morbid obesity together with the pharmacological properties of cefazolin, some interpretations can be made. Morbidly obese patients are exposed to an increased risk of developing post-operative wound infections compared to non-obese patients due to poorly perfused excess of adipose tissue [32, 33]. Furthermore, it is unknown if cefazolin can penetrate into the target organ, e.g. the subcutaneous tissue. The altered immune system associated with obesity may explain higher infection risks [38]. The increase in blood volume may alter the initial volume of distribution of cefazolin. As cefazolin is excreted through the kidneys, an increase of glomerular filtration as well as perfusion as described in obesity may result in increased cefazolin clearance, necessitating a higher dose in morbidly obese patients. As cefazolin is mainly albumin-bound it is not expected that obesity influences

the plasma protein binding of cefazolin, although no studies have previously evaluated plasma protein binding of cefazolin.

In order to prevent postoperative wound infection prophylactic use of antibiotics peri-operatively is recommended. It has previously been shown that prophylactic use of cefazolin one gram significantly reduced the incidence of post-operative wound infections after bariatric surgery from 21.7% to 3.7% [103]. According to the latest literature, two gram of cefazolin should be administered in morbidly obese patients as, compared to cefazolin one gram, cefazolin two gram increased serum tissue levels of cefazolin and decreased the wound infection rate from 16.5% to 5.6% in morbidly obese patients [104]. More recently, however, Edmiston *et al.* concluded that cefazolin two gram may not even be sufficient for patients with a body mass index over 50 kg m⁻² [105].

This was also highlighted by Falagas *et al.* [106], who suggested the importance of body weight adjusted dosing of antimicrobial agents due to unknown consequences of individual body weight on distribution, binding and elimination of antibiotics in morbidly obese patients. Raising the dose in morbidly obese patients seems rational, as elimination of cefazolin is mainly by glomerular filtration which may be increased in overweight subjects compared to lean subjects [18]. Additionally, a higher dose seems necessary in obese patients due to presumed poor perfusion of adipose tissue. A study evaluating soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing concluded that the penetration process into the interstitial space fluid is impaired in obese subjects, as plasma concentrations of ciprofloxacin were higher in obese subjects, but interstitial tissue concentrations were not significantly different [107]. In this respect, plasma protein binding of an antibiotic is of importance for tissue concentrations, with the degree of penetration increasing with decreasing protein binding [108]. Protein binding of cefuroxime is 33% [109], for ciprofloxacin protein binding is 20-40% [110], while for cefazolin protein binding is 89.2% [111], indicating better penetration of extravascular tissue for the first two antibiotics.

As body weights of patients are still increasing and studies of cefazolin in a population with higher body mass indices than 50 kg m⁻² are limited it seems prudent to study cefazolin in this higher body mass index group.

4. Conclusions

In this chapter the pathophysiological changes in morbidly obese patients are described relative to the pharmacokinetics and pharmacodynamics of specific drugs used for anaesthesia in this population. In the existing pharmacological literature there is still much debate on the specific impact of obesity on the pharmacokinetics and pharmacodynamics of peri-operative administered medication. As not only the absolute number of (morbidly) obese patients but also the body weight and body mass indices in this population are increasing and the existing literature on this topic is scarce, with studies including patients with lower body mass indices than patients currently undergoing bariatric surgery, more studies are needed to gain more knowledge about the influence of obesity on the pharmacokinetics and pharmacodynamics of drugs. This is of special importance because morbidly obese patients are at increased risk of developing thrombo-embolism, postoperative apnoea and wound infections, which makes the development of knowledge of optimal dosing schemes of anaesthetics, analgesics, neuromuscular blocking agents, antibiotics and all other drugs administered peri-operatively a prerequisite.

The aim of this thesis is to describe the results of a series of clinical studies in morbidly obese patients in order to derive dosing regimens for peri-operative medication used in this specific population. In chapters 3-5 we evaluate the dosage of propofol for induction and maintenance of anaesthesia when co-administered with remifentanyl or with epidural analgesia, in chapter 6 we evaluate the dosing of atracurium when given at induction of anaesthesia and in chapter 7 we evaluate cefazolin as prophylaxis for surgical wound infection in morbidly obese patients undergoing bariatric surgery.

