Universiteit
Leiden
The Netherlands

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

Kralingen, S. van

Citation
Kralingen, S. van. (2011, June 23). *Pharmacokinetics and/or pharmacodynamics of propofol, atracurium and cefazolin in morbidly obese patients*. Retrieved from https://hdl.handle.net/1887/17732

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/17732

Note: To cite this publication please use the final published version (if applicable).

Section V

Conclusions and Perspectives

Chapter 8

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

General introduction

The overall goal of the research in this thesis was to evaluate the pharmacokinetics and/or pharmacodynamics of commonly used peri-operative drugs during anaesthesia of morbidly obese patients undergoing bariatric surgery.

In chapter 1 the pathophysiological changes associated with morbid obesity and their potential effects on a drugs' pharmacokinetics are described, while from this perspective a review of the available literature on the commonly used drugs propofol, atracurium and cefazolin in morbidly obese patients is presented. Numerous physiological changes are 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 [1, 2]. Blood volume and cardiac output are increased [3, 4] and systemic hypertension, as well as pulmonary hypertension, are 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 [5] which, altogether, makes this population prone to desaturation. Furthermore, an increase in glomerular filtration as well as perfusion in the kidneys in the early stages of obesity is described, while in the later stages of obesity, glomerular filtration rate is found to normalize and subsequently decrease [6, 7]. Non-alcoholic steatohepatitis is very common in morbidly obese patients [8] even though hepatic clearance is not necessarily reduced in obesity [9]. Obesity exacerbates the diabetic state [10] and recent investigations suggest that bariatric surgery improves or even effectuates resolution of type II diabetes mellitus [11]. The excess of adipose tissue is potentially poorly perfused, making it difficult for medication to penetrate into this tissue [12, 13]. Together with the altered immune system associated with obesity [14] this can lead to a higher risk of infection. Increased concentrations of triglycerides, lipoproteins, cholesterol, free fatty acids [15], and acute phase proteins as α_1 acid glycoprotein [16] have been reported, which may result in altered plasma protein binding of some drugs.

Propofol is a commonly used anaesthetic in non-obese and obese patients, because of its rapid onset of action and early recovery. It has suitable pharmacological

properties to prevent desaturation in morbidly obese patients. Another advantage is the lack of accumulation [17] and the low incidence of post-operative nausea and vomiting. Propofol distributes over a relatively small central volume of distribution which is reported to be similar in obese and non-obese patients [18]. As the apparent and peripheral volumes of distribution are more dependent on fat and muscle tissue [19-21], these volumes may subsequently be larger in obese patients compared to non-obese patients. However, as these volumes are also very large in non-obese patients the potential increase may not be of clinical relevance. Plasma clearance of propofol in non-obese patients is estimated to range from 1.4 to 2.2 L min^{-1} [22-26], exceeding hepatic blood flow suggesting extra-hepatic elimination of propofol. The commonly reported non-alcoholic steatohepatitis in morbidly obese patients is not expected to influence propofol clearance, as propofol clearance is mainly determined by hepatic flow, which is not expected to be reduced in obesity and may even be increased in obesity, e.g. due to the increased blood volume.

Atracurium is a non-depolarizing muscle relaxant of which the elimination is independent of hepatic and kidney function, making it a suitable drug for muscle relaxation in morbidly obese patients undergoing bariatric surgery. As it is a hydrophilic drug, it is distributed poorly into excess adipose tissue. Conflicting literature exists on the weight-input to be used in morbidly obese patients when atracurium is used during induction of anaesthesia. Doses based on total body weight (TBW) [27] and total body weight with a dose reduction have been proposed [28]. A prolonged duration of action was shown by Kirkegaard-Nielsen *et al.* when an induction dose of atracurium 0.5 mg kg^{-1} was based on total body weight in obese patients, that is why they proposed a dose reduction by 2.3 mg for each 10 kg TBW more than 70 kg when using total body weight as weight input [28]. Although their study showed a prolonged duration of action when a dose of 0.5 mg per kg total body weight was administered, Weinstein [29] 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.

Cefazolin is the standard prophylactic antibiotic drug for surgery in the Netherlands. While it has been reported that a larger dose of cefazolin (2 gram *versus* 1 gram) in morbidly obese patients reduces the incidence of post-operative wound infections, others state that that even cefazolin two gram might not be enough for patients with a body mass index higher than 50 kg m^{-2} [30, 31]. As cefazolin is mainly eliminated by glomerular filtration which is reported to be increased in the early stages of obesity [32], it seems of relevance to study total and unbound concentrations of cefazolin over time in morbidly obese patients.
In chapter 2 the scope and intent of the investigations of this thesis were outlined. Based on both the available evidence on pathophysiological changes associated with obesity and specific reports on commonly used drugs in obese patients, it can be concluded that limited information is available on routinely used peri-operative drugs in morbidly obese patients. Beside this paucity of information in this special group, the available studies included most of the times patients with lower body mass indices than the body mass indices of the patients that are currently undergoing bariatric surgery. The lack of information is of particular relevance because morbidly obese patients undergoing surgery have an increased risk for peri-operative complications compared to non-obese patients. Namely, morbidly obese patients are often difficult to intubate, are prone to desaturation due to altered pulmonary physiology and are known to have an altered cardiac state (e.g. cardiomyopathy or an increased cardiac output and/or blood volume). In addition, they are at increased risk of developing thrombo-embolism, postoperative apnoea and wound infections. As a result, knowledge of optimal dosing schemes of anaesthetics, analgesics, neuromuscular blocking agents, antibiotics and all other drugs administered peri-operatively to morbidly obese patients is a prerequisite, which is of specific relevance for the anaesthesiologist taking care of these patients during bariatric surgery. In summary, the aim of this thesis was to evaluate the pharmacokinetics and/or pharmacodynamics of commonly used peri-operative drugs. These studies will provide the basis for adjustment of dosages of routinely used drugs in morbidly obese patients and ultimately generate information on the physiological changes that are associated with (morbid) obesity. The studied drugs were propofol, atracurium and cefazolin.

Propofol for induction of anaesthesia in morbidly obese patients

In chapter 3 a randomized double-blind pilot study is described in which two different induction doses of propofol were evaluated in twenty unpremedicated morbidly obese patients (body weight 98-167 kg, BMI 39-60 kg m^{-2}); one group received propofol 350 mg and the other group propofol 200 mg, both in combination with fentanyl 250 μg. Endpoints were the Bispectral Index (BIS), which is a measure of the level of consciousness by algorithmic analysis of a patient's electroencephalogram, haemodynamic monitoring and quality of anaesthesia according to the attending anaesthesiologist during induction of anaesthesia and intubation. The results showed that 200 mg of propofol in combination with fentanyl 250 μg is an inadequate induction dose in morbidly obese patients in terms of efficacy of induction of anaesthesia measured using Bispectral Index values, haemodynamic parameters and clinical observations. In this small patient group the 350 mg induction dose proved adequate and safe, provided the maintenance dose of propofol was not started within five minutes after induction, thereby preventing temporary cardiovascular instability. While these results show that it is necessary to give a larger induction dose in morbidly obese patients compared to non-obese patients, the results indicate that propofol dosing for induction of anaesthesia should not be based on ideal body weight. Propofol 350 mg, though, seems an adequate induction dose in morbidly obese patients, indicating that dosing of propofol for induction should be based on total body weight (TBW) or lean body mass (LBM).

Propofol for maintenance of anaesthesia in morbidly obese patients receiving remifentanil or epidural analgesia

In chapter 4 maintenance of anaesthesia is described using propofol with continuous Bispectral Index monitoring in ten morbidly obese patients receiving propofol-remifentanil (body weight 98-167 kg, BMI 39-60 kg m^{-2}) and six morbidly obese patients receiving propofol-epidural anaesthesia (body weight 103-164 kg, BMI 38-58 kg m^{-2}).

In the first group in ten morbidly obese patients receiving remifentanil analgesia, a propofol infusion was started at 10 mg $kg^{-1}hr^{-1}$, which was subsequently modified

by aiming at Bispectral Index values between 40-60 together with predefined haemodynamic parameters. In the second group, the propofol dose resulting from the first group (5 mg $kg^{-1}hr^{-1}$) was prospectively evaluated in a matched cohort of six morbidly obese patients receiving propofol-epidural analgesia aiming for the same Bispectral Index values and haemodynamic parameters. In both cohorts, propofol concentrations, infusion rates, Bispectral Index values and haemodynamic values were collected.

In the propofol-remifentanil group the mean propofol infusion rate that corresponded to the predefined Bispectral Index values and haemodynamic parameters was 4.8 mg $kg^{-1}hr^{-1}$ (SD 1.5). In the propofol-epidural group the mean propofol infusion rate that corresponded to predefined Bispectral Index values and haemodynamic parameters was 5.0 mg $kg^{-1}hr^{-1}$ (SD 0.6), which did not differ from the initial infusion rate of 5 mg $kg^{-1}hr^{-1}$ based on the results of the first study. In the two studies, there was no difference in the propofol concentration-Bispectral Index relation.

In conclusion, in morbidly obese patients receiving propofol-remifentanil or propofol-epidural anaesthesia, based on both Bispectral Index values and haemodynamic parameters, a maintenance dose of propofol of 4-6 mg $kg^{-1}hr^{-1}$ on the basis of total body weight was observed. As there was no difference in propofol concentration-Bispectral Index relation between morbidly obese patients receiving propofol-remifentanil anaesthesia and those receiving propofol-epidural anaesthesia, we conclude that BIS values are influenced to the same extend by adding remifentanil compared to epidural analgesia to propofol anaesthesia.

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

In chapter 5 a study is described evaluating the influence of excess body weight on the pharmacokinetics and pharmacodynamics of propofol using Bispectral Index values as pharmacodynamic endpoint (body weight 98-167 kg, BMI 39-60 kg m^{-2}). For both the pharmacokinetics and pharmacodynamics a systematic covariate analysis was performed using body weight (BW), body mass index (BMI), ideal body weight (IBW) and lean body weight (LBW) as weight covariates. For the

pharmacokinetic analysis, data of lean patients were available from previously published studies [33, 34].

In a three-compartment pharmacokinetic model, body weight (BW) proved to be the most predictive covariate for clearance (CL) of propofol in twenty morbidly obese patients ($CL = 2.33\ L/min \bullet (BW/70)^{0.72}$). Similar results were obtained when morbidly obese patients and forty lean patients were analyzed together ($CL = 2.22\ L/min \bullet (BW/70)^{0.67}$). No covariates were identified for other pharmacokinetic parameters. Depth of anaesthesia in morbidly obese patients was adequately described by a two-compartment biophase distribution model with a sigmoid E_{max} pharmacodynamic model (EC_{50} 2.12 mg/l) without covariates. In conclusion, a pharmacokinetic and pharmacodynamic model for propofol in morbidly obese patients has been derived with body weight as the major determinant for clearance using an allometric function with an exponent of 0.72.

Atracurium for muscle relaxation during induction of anaesthesia in morbidly obese patients

In chapter 6 a randomized double-blind study is described evaluating two different doses of atracurium when used as muscle relaxant at the time of induction of anaesthesia in morbidly obese patients (body weight 112-260 kg, BMI 38-79 kg m^{-2}). The aim of this study was to evaluate the time course of atracurium effect when atracurium 0.5 mg per kg was dosed on ideal body weight *versus* total body weight in twenty morbidly obese patients. Effects of these two doses were primary evaluated by use of the neuromuscular train-of-four (TOF) monitor and secondary by intubation conditions and need for antagonism with neostigmin. In the ideal body weight group, times to recovery of train-of-four-ratio from zero to 5%, 50% and 75% were significantly shorter (train-of-four-ratio from zero to 5%: mean difference 30 min (95% CI 23-39 min)) and with lower variability compared to the total body weight group. In the total body weight group there was a significant correlation between atracurium dose and time to a train-of-four-ratio of 5% ($r=0.82$, $p<0.001$), which was absent in the ideal body weight group ($r=0.24$, $p=0.566$). In both groups, intubation conditions were good while 70% of the patients in the total body weight group needed neostigmin at the end of

surgery compared to 0% in the ideal body weight group (p=0.003). Based on the findings in this study in morbidly obese patients (112-260 kg), atracurium 0.5 mg per kg ideal body weight results in a predictable profile of muscle relaxation allowing for adequate intubation conditions and recovery of muscle strength to a train-of-four-ratio>90% within 60 minutes with lack of need for antagonism. An unanticipated, dose-dependent prolongation of action is shown when dosing is based on total body weight.

Cefazolin used as antibiotic prophylaxis during bariatric surgery in morbidly obese patients

Chapter 7 describes the evaluation of pharmacokinetics and protein binding of cefazolin in morbidly obese patients undergoing bariatric surgery, the influence of bodyweight measures and age on pharmacokinetic parameters and unbound cefazolin concentrations over time in this population (BMI 38-79 kg m^{-2}).

Cefazolin clearance was 4.2 (1.0) L hr-1 (mean (SD)) and showed a negative correlation with age (p=0.003) but not with bodyweight measures (p>0.05). Volume of distribution was 13.0 (3.1) L (mean (SD)) and correlated positively with bodyweight measures (p≤0.001). Saturable protein binding was observed with a median protein binding of 79% (interquartile range 74-82), which proved similar to reported protein binding in non-obese patients. In all patients, unbound cefazolin concentrations remained above 1 mg L-1 (minimal inhibitory concentration for 90% (MIC_{90}) of methicillin sensitive isolates of *S. aureus* in Europe) until four hours after dosing.

In conclusion, instead of bodyweight, younger age was significantly associated with higher cefazolin clearance. However, as in all patients with bodyweights up to 260 kg unbound plasma cefazolin concentrations remained above 1 mg L-1 until four hours after a dose of two gram intravenously, re-dosing within four hours or another antibiotic class should only be considered in case of higher MIC_{90} of the local isolates.

Perspectives

In this thesis we initiated pharmacokinetic and/or pharmacodynamic studies in morbidly obese patients undergoing bariatric surgery in order to study propofol, atracurium and cefazolin in this population. The studies in this thesis show that these types of investigation in morbidly obese patients can most adequately be performed in a large teaching hospital by a multidisciplinary team working closely with a university centre. In the bariatric centre in the St. Antonius Hospital in Nieuwegein a large number of bariatric procedures (300 yearly) are carried out and all patients remain in a life-long follow-up program within a multidisciplinary team of medical specialists and nurses. While this program also allows for long-term studies, we have shown in this thesis the suitability of the infrastructure for pharmacokinetic and/or pharmacodynamic studies for different kind of drugs.
The pilot study (chapter 3) on propofol for induction of anaesthesia shows that a dose based on ideal body weight (i.e. 200 mg) is an inadequate induction dose for morbidly obese patients in terms of efficacy of induction of anaesthesia measured using Bispectral Index values, haemodynamic parameters and clinical observations. While propofol 200 mg typically is an adequate dose for induction of anaesthesia in non-obese patients, it seems that the higher induction dose in morbidly obese patients (i.e. 350 mg) may be explained by the increased blood volume and cardiac output [3, 4] that can be expected in morbidly obese patients. Upton and co workers [35] also showed in sheep that a higher cardiac output resulted in lower initial arterial concentrations of propofol, as upon a dose of 100 mg over two minutes, arterial concentrations of propofol were found to be inversely related to cardiac output. This implies that cardiac output may be a determinant of the induction of anaesthesia with propofol [35]. In our pilot study, an induction dose of 350 mg seemed adequate, although temporary cardiovascular instability was observed in one patient, which was attributed to the start of the propofol maintenance infusion of 10 mg kg^{-1} $hour^{-1}$ within five minutes after induction of anaesthesia. On the basis of these results, it was concluded that for future studies, a dose based on total body weight with or without a dose cap at 350 mg or a dose based on lean body mass in a larger sample of morbidly obese patients seems

appropriate. More recently, the study of Ingrande *et al*. [36] showed that lean body mass is a more appropriate weight based scalar for propofol infusion for induction of anaesthesia in morbidly obese patients compared to total body weight. These recent findings seem consistent with a report on the correlation of cardiac output with lean body mass [37].

In the study evaluating propofol for maintenance of anaesthesia in morbidly obese patients (chapter 4), a dosing regimen of 4-6 mg $kg^{-1}hr^{-1}$ was proposed for both the combination of propofol with remifentanil and the combination of propofol with epidural analgesia because no difference was observed in the propofol concentration – Bispectral Index relation between the two groups. Although in this study Bispectral Index values are influenced to the same extend by adding remifentanil compared to epidural analgesia to propofol anaesthesia, the current opinion is that opioids such as remifentanil do exert a propofol-sparing effect when given in combination with propofol. Some studies did show reductions in Bispectral Index values when an opioid was given during anaesthesia with propofol [38-40], which may potentially be explained by a decrease in blood pressure, heart rate or cerebral blood flow and thus a decrease in Bispectral Index values [40]. Guignard *et al.* on the other hand 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 [41]. Other studies did demonstrate a deeper level of anaesthesia when an opioid was co-administered with propofol which was not reflected by lower Bispectral Index values [42, 43, 44]. As the use of the Bispectral Index can be questioned as an endpoint to evaluate propofol dosing in co-administration with remifentanil, we also used haemodynamic parameters as an endpoint for propofol dosing. The predefined range of the haemodynamic parameters, however, was easier to aim for compared to the predefined range of Bispectral Index values. It seems therefore that a propofol-sparing effect by remifentanil co-administration can not be excluded and that potentially other pharmacodynamic measures are required to answer this question.

From the study evaluating the population pharmacokinetics and pharmacodynamics of propofol when used in combination with remifentanil

in morbidly obese patients (chapter 5) it can be concluded that body weight is the major determinant for clearance of propofol using an allometric function with an exponent of 0.72. This conclusion indicates that propofol in morbidly obese patients should be dosed in mg $kg^{-0.72}$ instead of mg kg^{-1} as was reported in chapter 4. In our opinion, this different conclusion can be explained by the difference in analysis techniques. In the study described in chapter 4 dosing of propofol was based on clinical practice and dosing was thus performed in mg kg^{-1} hr^{-1} (linear). As a result, a dosing advice in mg kg^{-1} hr^{-1} was given for maintenance of anaesthesia with propofol. In chapter 5, though, a population pharmacokinetic and pharmacodynamic analysis was performed using NONMEM allowing for a systematic covariate analysis in which the influence of different measures of body weight on pharmacokinetic and pharmacodynamic parameters can be studied. Although Lemmens *et al.* [37] concluded that dosing of propofol in morbidly obese patients should be based on lean body mass, this is not confirmed by our analysis. In our study total body weight was the major determinant for clearance of propofol in morbidly obese patients, with body mass index as a good alternative, while there was no basis for the use of lean body mass. This was confirmed by repeating the analysis with the inclusion of non-obese patients. As propofol clearance is mainly influenced by hepatic blood flow, it may be speculated that in morbidly obese patients hepatic blood flow is correlated to total body weight in an allometric function with an exponent of 0.72 instead of lean body mass.

Using these techniques it was also found that there was no significant influence of body weight on any of the other pharmacokinetic and pharmacodynamic parameters. A non-significant trend was identified towards an increased central volume of distribution in morbidly obese patients. This result may be explained by an increased blood volume in morbidly obese patients and thereby explain part of the results of the pilot study described in chapter 3, in which a larger dose of propofol was reported for induction of anaesthesia in morbidly obese patients compared to non-obese patients. However, another explanation for the larger dose of propofol necessary for induction in morbidly obese patients described in chapter 3 may be an increase in cardiac output in morbidly obese patients.

In the pharmacokinetic and pharmacodynamic analysis of propofol described in chapter 5 patients with body weights up to 167 kg were included. The non-linear dosing regimen that is derived from this pharmacokinetic and pharmacodynamic model should therefore primarily be used in patients up to this body weight. However, it also seems of interest to evaluate the extrapolation possibilities of the model and its dosing regimen by applying this dosing regimen in patients with larger body weights. A prospective study, in this respect, is of importance to show the predictive, clinical and practical value of the model in addition to its descriptive properties in morbidly obese patients.

The study of atracurium (chapter 6) showed that dosing of this muscle relaxant when used at the time of induction of anaesthesia should be based on ideal body weight, as this results in a predictable profile of muscle relaxation allowing for adequate intubation conditions and recovery of muscle strength to a train-of-four-ratio > 90% within 60 minutes with lack of need for antagonism. A dose-dependent prolongation of action is shown when dosing is based on total body weight. The relative decrease in the percentage of lean body mass and total body water together with the hydrophilic characteristics of atracurium may lead to the hypothesis that less atracurium is needed per kilogram of body weight in obese patients compared to non-obese patients. This is in accordance with the findings described in chapter 6. Whether this is applicable to other muscle relaxants as rocuronium remains uncertain, as the clearance of this agent is more dependent on liver and kidney function [45]. For rocuronium, an antagonist (sugammadex) is on the market, and it would be of interest to study the dose requirements of both drugs in morbidly obese patients. As for atracurium, in the European drug information for rocuronium a dosing advice is given in mg kg^{-1}. In our study, this proved to be incorrect for atracurium, and provokes speculations on this advice for rocuronium and sugammadex, providing a basis for future research on this topic in morbidly obese patients.

The study on cefazolin in this thesis (chapter 7) shows unbound plasma cefazolin concentrations above 1 mg L^{-1} (minimal inhibitory concentration for 90% (MIC_{90}) of methicillin sensitive isolates of *S. Aureus* in Europe) during four hours after a dose of two gram intravenously in morbidly obese patients. Whether these unbound

plasma cefazolin concentrations are adequate in specific hospitals or countries depends on the minimal inhibitory concentration for 90% of the isolates in the local setting. As discussed in the introduction of this thesis, cefazolin is mainly albumin-bound and it is not expected that obesity influences the plasma protein binding of cefazolin. This is in accordance to our study described in chapter 7, where we conclude that plasma protein binding of cefazolin in morbidly obese patients is 79%, which is the same as in non-obese patients.

The negative correlation between peak cefazolin concentration and body weight described in our study may potentially be explained by the increased volume of distribution due to the increased blood volume described in morbidly obese patients. In addition, the positive correlation between age and trough plasma cefazolin concentrations described in our study may be explained by the increase in glomerular filtration and perfusion of the kidneys described in the early stages of obesity, while in the later stages of obesity these tend to normalize and subsequently decrease [6, 7].

As described in the introduction of this thesis, 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 [12, 13]. As cefazolin is excreted via the kidneys, an increase of glomerular filtration as well as perfusion as described in obesity [6, 7] may result in increased cefazolin clearance, necessitating a higher dose of cefazolin in morbidly obese patients. As was shown in our study, this particularly occurred in younger individuals, even though in all cases cefazolin concentrations remained above 1 mg L^{-1}. However, it is unknown if cefazolin can penetrate into the target organ, i.e. the subcutaneous tissue. Altogether, this may explain the wound infections that occurred despite adequate plasma cefazolin concentrations in two patients in our study, even though the statistical importance of the high infection rate in our study remains uncertain due to the small patient group (n=20). A future study evaluating plasma cefazolin concentrations together with tissue concentrations of cefazolin using a microdialysis catheter is in progress.

In conclusion, we initiated pharmacokinetic and/or pharmacodynamic studies in morbidly obese patients undergoing bariatric surgery by investigating propofol, atracurium and cefazolin in this population. To allow for this type of research a large (teaching) hospital with a multidisciplinary team of medical specialists and nurses is essential. Pharmacokinetic and/or pharmacodynamics studies provide the basis for dosing regimen of medication used in morbidly obese patients and give insight into the pathophysiological changes in this special population. A large amount of future research in morbidly obese patients is yet to be performed and is essential as the body weights and body mass indices in this population are still increasing.

References

1. Cheymol, G., *Clinical pharmacokinetics of drugs in obesity. An update.* Clin Pharmacokinet, 1993. **25**(2): p. 103-14.
2. Cheymol, G., *Effects of obesity on pharmacokinetics implications for drug therapy.* Clin Pharmacokinet, 2000. **39**(3): p. 215-31.
3. Alexander JK, D.E., Smith WG., *Blood volume, cardiac output and distribution of systemic blood flow in extreme obesity.* Cardiovasc Res Cent Bull, 1962-1963. **1**: p. 39-44.
4. Licata, G., et al., *Effect of obesity on left ventricular function studied by radionuclide angiocardiography.* Int J Obes, 1991. **15**(4): p. 295-302.
5. Yao, A., *Anesthesiology.* 2008: p. 1260.
6. Kasiske, B.L., et al., *Effects of genetic obesity on renal structure and function in the Zucker rat.* J Lab Clin Med, 1985. **106**(5): p. 598-604.
7. Schmitz, P.G., et al., *Renal injury in obese Zucker rats: glomerular hemodynamic alterations and effects of enalapril.* Am J Physiol, 1992. **263**(3 Pt 2): p. F496-502.
8. Guzzaloni, G., 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. **24**(6): p. 772-6.
9. Casati, A. and M. Putzu, *Anesthesia in the obese patient: pharmacokinetic considerations.* J Clin Anesth, 2005. **17**(2): p. 134-45.
10. Yao, A., *Anesthesiology.* 2008: p. 1264-1265.
11. Spector, D. and S. Shikora, *Neuro-modulation and bariatric surgery for type 2 diabetes mellitus.* Int J Clin Pract Suppl, (166): p. 53-8.
12. Choban, P.S., et al., *Increased incidence of nosocomial infections in obese surgical patients.* Am Surg, 1995. **61**(11): p. 1001-5.
13. Lesser, G.T. and S. Deutsch, *Measurement of adipose tissue blood flow and perfusion in man by uptake of 85Kr.* J Appl Physiol, 1967. **23**(5): p. 621-30.
14. Wolf, A.M., et al., *Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes.* Biochem Biophys Res Commun, 2004. **323**(2): p. 630-5.
15. Wasan, K.M. and G. Lopez-Berestein, *The influence of serum lipoproteins on the pharmacokinetics and pharmacodynamics of lipophilic drugs and drug carriers.* Arch Med Res, 1993. **24**(4): p. 395-401.

16. Derry, C.L., et al., *Pharmacokinetics and pharmacodynamics of triazolam after two intermittent doses in obese and normal-weight men.* J Clin Psychopharmacol, 1995. **15**(3): p. 197-205.
17. de Baerdemaeker LEC, M.E., Struys MMRF., *Pharmacokinetics in obese patients. Continuing education in anaesthesia, critical care and pain.* 2004. **4**(5).
18. Kanto, J. and E. Gepts, *Pharmacokinetic implications for the clinical use of propofol.* Clin Pharmacokinet, 1989. **17**(5): p. 308-26.
19. Abernethy, D.R. and D.J. Greenblatt, *Drug disposition in obese humans. An update.* Clin Pharmacokinet, 1986. **11**(3): p. 199-213.
20. Blouin, R.A., J.H. Kolpek, and H.J. Mann, *Influence of obesity on drug disposition.* Clin Pharm, 1987. **6**(9): p. 706-14.
21. Jung, D., et al., *Thiopental disposition in lean and obese patients undergoing surgery.* Anesthesiology, 1982. **56**(4): p. 269-74.
22. Cockshott, I.D., et al., *Pharmacokinetics of propofol in female patients. Studies using single bolus injections.* Br J Anaesth, 1987. **59**(9): p. 1103-10.
23. Gin, T., et al., *Pharmacokinetics of propofol in women undergoing elective caesarean section.* Br J Anaesth, 1990. **64**(2): p. 148-53.
24. Kay, N.H., et al., *Disposition of propofol in patients undergoing surgery. A comparison in men and women.* Br J Anaesth, 1986. **58**(10): p. 1075-9.
25. Schuttler, J. and H. Ihmsen, *Population pharmacokinetics of propofol: a multicenter study.* Anesthesiology, 2000. **92**(3): p. 727-38.
26. Schnider, T.W., et al., *The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers.* Anesthesiology, 1998. **88**(5): p. 1170-82.
27. Varin, F., et al., *Influence of extreme obesity on the body disposition and neuromuscular blocking effect of atracurium.* Clin Pharmacol Ther, 1990. **48**(1): p. 18-25.
28. Kirkegaard-Nielsen, H., et al., *Anthropometric variables as predictors for duration of action of atracurium-induced neuromuscular block.* Anesth Analg, 1996. **83**(5): p. 1076-80.
29. Weinstein, J.A., et al., *Pharmacodynamics of vecuronium and atracurium in the obese surgical patient.* Anesth Analg, 1988. **67**(12): p. 1149-53.
30. Edmiston, C.E., et al., *Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels?* Surgery, 2004. **136**(4): p. 738-47.

31. Falagas, M.E. and D.E. Karageorgopoulos, *Adjustment of dosing of antimicrobial agents for bodyweight in adults.* Lancet. **375**(9710): p. 248-51.
32. Ribstein, J., G. du Cailar, and A. Mimran, *Combined renal effects of overweight and hypertension.* Hypertension, 1995. **26**(4): p. 610-5.
33. Knibbe, C.A., 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): p. 653-60.
34. Knibbe, C.A., 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. **72**(6): p. 670-84.
35. Upton, R.N., et al., *Cardiac output is a determinant of the initial concentrations of propofol after short-infusion administration.* Anesth Analg, 1999. **89**(3): p. 545-52.
36. Ingrande, J., J.B. Brodsky, and H.J. Lemmens, *Lean Body Weight Scalar for the Anesthetic Induction Dose of Propofol in Morbidly Obese Subjects.* Anesth Analg. 2010 Sep 22. [Epub ahead of print]
37. Lemmens, H.J., *Perioperative pharmacology in morbid obesity.* Curr Opin Anaesthesiol. **23**(4): p. 485-91.
38. Strachan, A.N. and N.D. Edwards, *Randomized placebo-controlled trial to assess the effect of remifentanil and propofol on bispectral index and sedation.* Br J Anaesth, 2000. **84**(4): p. 489-90.
39. Koitabashi, T., J.W. Johansen, and P.S. Sebel, *Remifentanil dose/electroencephalogram bispectral response during combined propofol/regional anesthesia.* Anesth Analg, 2002. **94**(6): p. 1530-3.
40. Ferreira, D.A., 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): p. 305-10.
41. Bouillon, T.W., et al., *Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy.* Anesthesiology, 2004. **100**(6): p. 1353-72.
42. Guignard, B., et al., *The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation.* Anesth Analg, 2000. **90**(1): p. 161-7.

43. Wang, L.P., 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. **104**(2): p. 325-31.

44. Lysakowski, C., et al., *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): p. 523-7.

45. Proost, J.H., et al., *Urinary, biliary and faecal excretion of rocuronium in humans.* Br J Anaesth, 2000. **85**(5): p. 717-23.