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

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Abstract

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

Background

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

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

Methods

Patients

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

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

Anesthetic procedure

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

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

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

Blood sampling and analytical methods

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

Data analysis and internal validation

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

Pharmacokinetic model

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

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

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

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

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

Covariate analysis

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

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

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

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

Comparison with non-obese children and adolescents

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

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

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

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

Results

Patients and data collection

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

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

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

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

Pharmacokinetics analysis

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

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

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

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

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

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

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

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

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

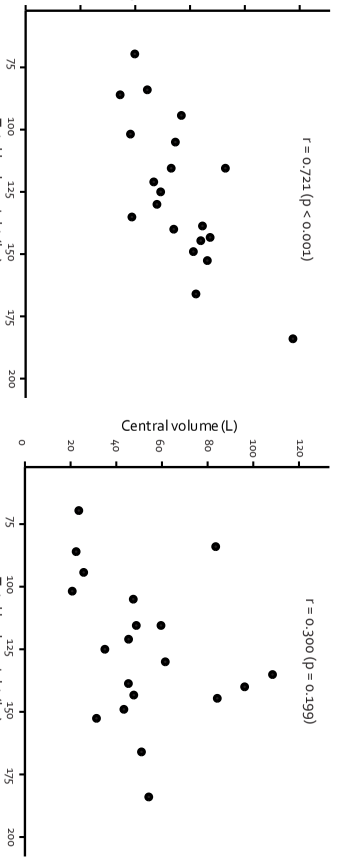

Figure 1 *Individual post hoc estimates for clearance (left) and central volume of distribution (right) of propofol versus total body weight in 20 obese and morbidly obese children and adolescents with Pearson's correlation coefficient (r).*

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

Comparison with non-obese children and adolescents

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

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

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

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

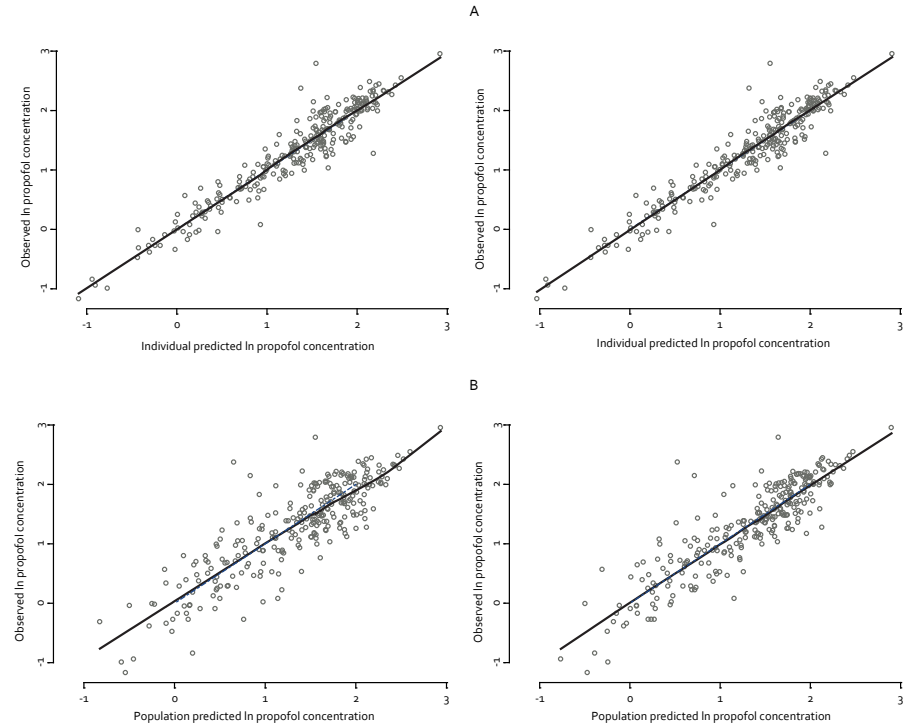

Figure 2 *Diagnostic plots for propofol pharmacokinetics in morbidly obese children and adolescents showing (A) individual log-normal propofol predictions versus observed logarithmic propofol concentrations and (B) population model log-normal propofol predictions versus observed log-normal propofol concentrations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

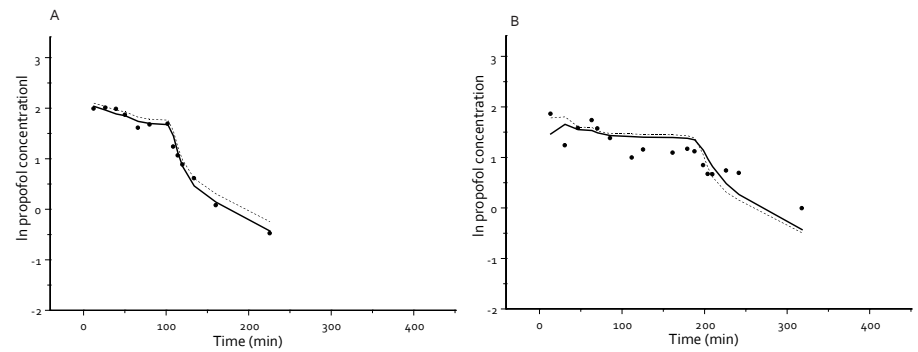

Figure 3 *Propofol concentration time relationships for the best (Age = 15 years old, TBW = 143 kg, BMI = 44 kg/m²) (A) and worst (Age = 15 years old, TBW = 145 kg, BMI = 54 kg/m²) (B) final TBW model predictions. The solid circles represent the measured propofol concentrations, the dotted lines represent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

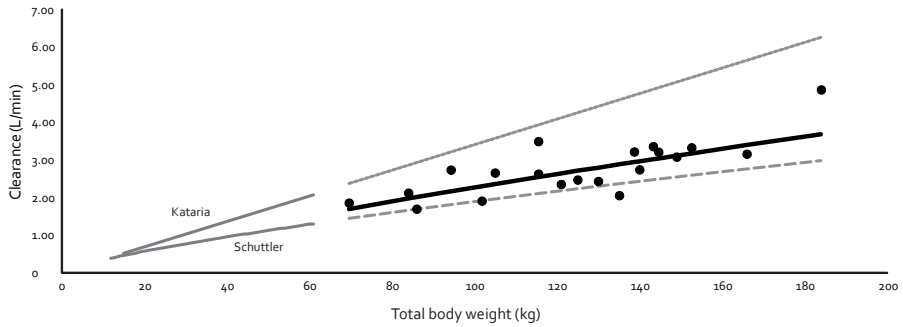

Figure 4 *Propofol clearance (CL) values versus TBW for morbidly obese children and adolescents of the present study (black line) and models of Kataria et al. (8) and Schuttler and Ihmsen (6) (grey lines). The black line indicates population clearance values for morbidly obese children and adolescents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

Discussion

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

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

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

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

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

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

Conclusion

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

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