The influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs in adolescents and adults : focus on propofol and nadroparin.

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

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Abstract

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

Background

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

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

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

Methods

Patients

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

Morbidly obese adults (6)

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

Non-obese adults (11, 12)

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

Morbidly obese children and adolescents (7)

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

Non-obese children and adolescents (13)

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

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

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

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

Data analysis and internal validation

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

Pharmacokinetic model

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

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

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

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

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

Covariate analysis

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

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

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

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

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

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

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

Results

Subjects

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

Pharmacokinetics

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

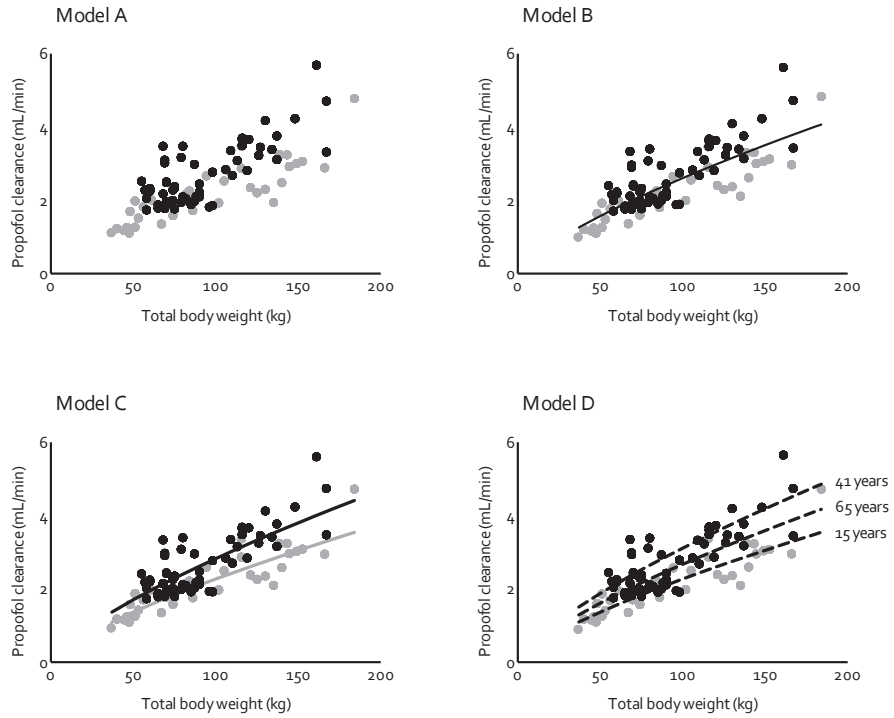

Figure 1 *Individual post hoc propofol clearance estimates (symbol) versus total body weight for the simple model (model A) and three covariate pharmacokinetic models (B, C and D) for morbidly obese adults (black circles), adolescents and children (grey circles) and their non-obese controls (n=94). In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

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

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

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

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

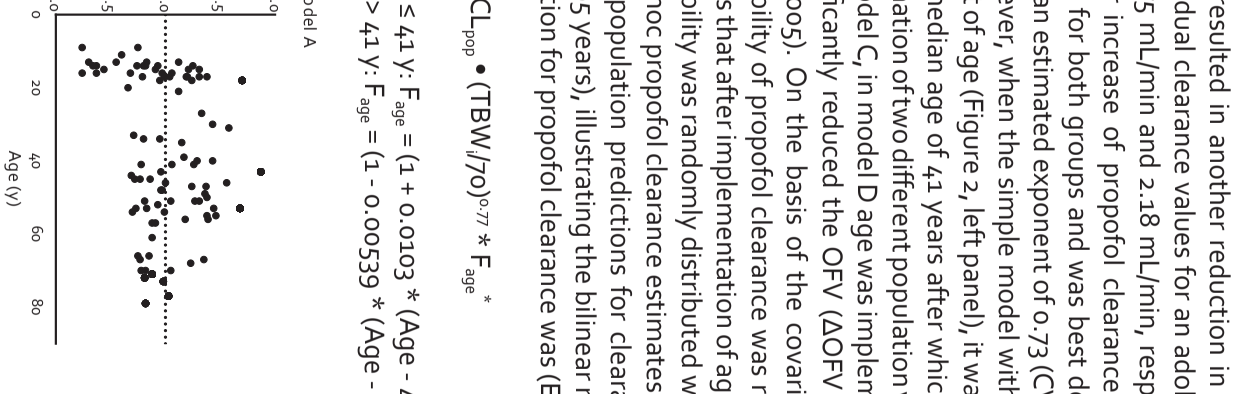

Figure 2 *Interindividual variability of propofol clearance versus age for the simple model without covariates (Model A) and the final covariate model including age and total body weight on propofol clearance (Model E).*

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

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

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

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

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

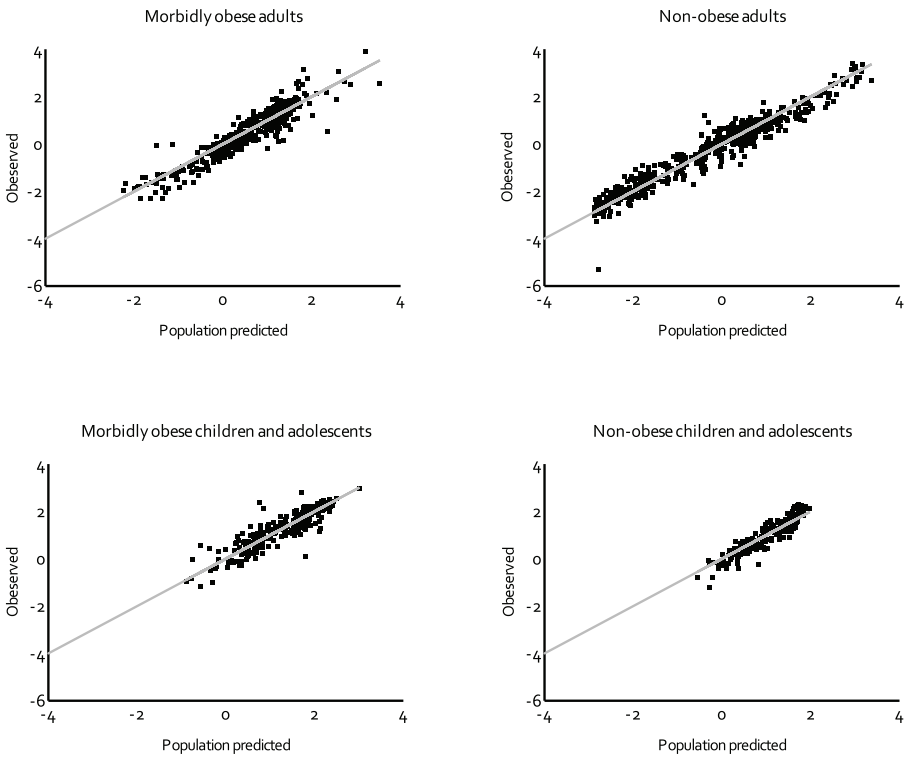

Figure 3 *Observed versus population predicted ln propofol concentrations of the final model (Model E). Panels represent data of morbidly obese adults, non-obese adults, morbidly obese children and adolescents and non-obese children and adolescents. The solid grey line represents the line of identity,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

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

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

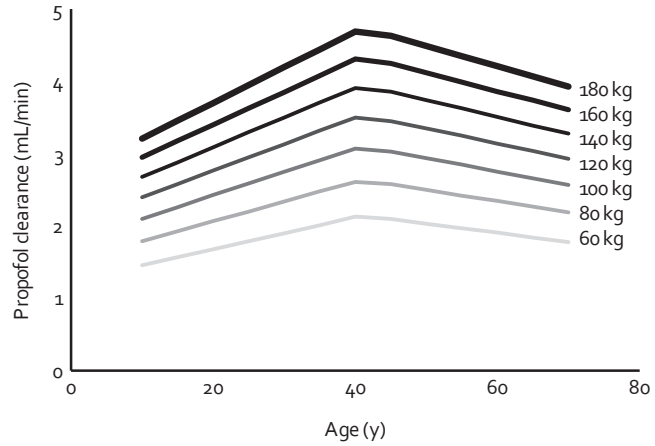

Figure 4 *Model based predictions of population clearance estimates of propofol versus age for patients with different total body weights.*

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

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

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

Discussion

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

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

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

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

Conclusion

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

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

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