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Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model

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Key points

- Obesity can alter the pharmacokinetics (PK) of drugs and make dosing difficult.
- Correction from total body weight (TBW) to lean body mass is often used but is not always appropriate.
- The kinetics of propofol target-controlled infusion were modelled in obese patients.
- An allometric model using TBW as the size descriptor performed best in obese patients.

Background. The objective of this study was to develop a pharmacokinetic (PK) model to characterize the influence of obesity on propofol PK parameters.

Methods. Nineteen obese ASA II patients undergoing bariatric surgery were studied. Patients received propofol 2 mg kg^{-1} bolus dose followed by a 5–20–40–120 min, 10–8–6–5 mg kg^{-1} h^{-1} infusion. Arterial blood samples were withdrawn at 1, 3, 5 min after induction, every 10–20 min during propofol infusion, and every 10–30 min for 2 h after stopping the propofol infusion. Arterial samples were processed by high-performance liquid chromatography. Time–concentration data profiles from this study were pooled with data from two other propofol PK studies available at http://www.opentci.org. Population PK modelling was performed using non-linear mixed effects model.

Results. The study involved 19 obese adults who contributed 163 observations. The pooled analysis involved 51 patients (weight 93 SD 24 kg, range 44–160 kg; age 46 SD 16 yr, range 25–81 yr; BMI 33 SD 9 kg m^{-2}, range 16–52 kg m^{-2}). A three-compartment model was used to investigate propofol PK. An allometric size model using total body weight (TBW) was superior to all other models investigated (linear TBW, free fat mass, lean body weight, normal fat mass) for all clearance parameters. Variability in V2 and Q2 was reduced by a function showing a decrease in both parameters with age.

Conclusions. We have derived a population PK model using obese and non-obese data to characterize propofol PK over a wide range of body weights. An allometric model using TBW as the size descriptor of volumes and clearances was superior to other size descriptors to characterize propofol PK in obese patients.

Keywords: anaesthetics i.v., propofol; obesity; pharmacokinetics

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The increasing number of obese patients worldwide has resulted in an increase in surgical procedures in this population.[1 2] The pharmacokinetic (PK) properties of some drugs are known to alter in obesity.[3 4] Although body fat has minimal metabolic activity, fat mass contributes to overall body size and may have an indirect influence on both metabolic and renal clearance. However, the volume of distribution of a drug depends on its physicochemical properties,[5] and there are drugs whose apparent volume of distribution is independent of fat mass (e.g. digoxin)[6] or is extensively determined by it (e.g. diazepam).[7 8] Consequently, changes in body composition in obesity require a strategy for dose adjustment.[2]

Propofol is commonly used for induction and maintenance of general anaesthesia in obese patients.[9–11] A controversial issue for propofol dose adjustment in this population has been the selection of an adequate size descriptor to scale PK parameters.[12 13] In normal-weight subjects, total body weight (TBW) is often used as a size descriptor.[12] However, in obese patients, adipose tissue and LBM do not increase proportionally and the percentage of lean body tissue per kg of TBW decreases.[4 13 14] A number of descriptors of body size have been proposed to scale doses in the obese,[13 15] but it is unclear which best describes the relationship between propofol dose and its plasma concentrations in this population.[13]

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Studies of propofol PK in obese are scarce and come from a small number of patients. A study in eight morbidly obese patients showed that compared with lean adults, the initial volume of distribution was not modified in obese patients.[16] It also found that total body clearance and volume of distribution at steady state correlated to TBW. The authors concluded that dose schemes based on TBW are the same as those in non-obese patients with no risk of accumulation. However, this scaling may result in the administration of largish doses of propofol with the inherent risk of haemodynamic adverse consequences.

We have investigated propofol PK in obese and non-obese subjects using a population-based approach to predict sources of the variability in propofol PK parameters. The objective of this study is to develop an integrated PK model to characterize the influence of obesity on propofol PK parameters.

Methods

Data from three sources were used for analysis.

Study 1

Schnider and colleagues[17] investigated 24 healthy volunteers aged 26–81 yr, weighing 44–122 kg given a bolus dose of propofol followed 1 h later by a 60 min infusion. Each volunteer was randomly assigned to an infusion rate of 1.5, 3, 6, and 12 mg kg^{-1} h^{-1}. Samples of 4–7 ml of arterial blood were obtained at 0, 1, 2, 4, 8, 16, 30, 60, 62, 64, 68, 76, 90, 120, 122, 124, 128, 136, 150, 180, 240, 300, and 600 min. The propofol plasma concentration was assayed using liquid–liquid extraction followed by reverse-phase high-performance liquid chromatography (HPLC) with fluorescence detection. The lower limit of quantification (LLOQ) was 0.02 μg ml^{-1}.

Study 2

Servin and colleagues[16] studied eight morbidly obese patients, aged 25–66 yr and weighing 97–169 kg, anaesthetized with a stepwise infusion regimen of propofol 21 mg kg^{-1} h^{-1} for 5 min, 12 mg kg^{-1} h^{-1} for 10 min, and 6 mg kg^{-1} h^{-1} for the remainder of the procedure. A corrected weight formula [corrected kg=ideal weight×(0.4×excess weight)] was used to adjust the dose. Samples of 2.5 ml of arterial blood were obtained at 0, 2, 5, 10, 15, 20, 25, 30, 45, 60, 75, 105, 120 and every 15 min until infusion was stopped. Thereafter, samples were obtained at 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, 420, and 480 min. Blood was assayed for propofol using HPLC. The LLOQ was 0.04 μg ml^{-1}. Blood concentration data were converted to a plasma concentration by assuming a blood/plasma ratio of 1.18.[18]

Study 3

These data were collected by our group for the purpose of this study. After Ethics Committee approval (Clínica Alemana, Santiago, Chile) and written informed consent, 19 obese patients undergoing elective bariatric surgery were studied prospectively. Patients of ASA >III, with a history of alcohol or drug abuse, were excluded. Patients fasted for at least 8 h before surgery. No premedication was given. Propofol was infused using the Anestfusor Serie II Pro* software (Facultad de Medicina, Universidad de Chile; http://www.smb.cl/en/anestfusor_serie2_proen.html) in a PC Compact Armada 7600. Anaesthetic induction was with a single propofol (10 mg ml^{-1}) bolus of 2 mg kg^{-1} at a rate of 20 ml min^{-1}. At the same time, remifentanil, using target-controlled infusion (TCI) (Minto PK model)[19] with an initial plasma target of 5 μg $litre^{-1}$, was started. Rocuronium 0.6 mg kg^{-1} was used to facilitate tracheal intubation. Five minutes after the propofol bolus dose, a decreasing infusion scheme of 10–8–6–5 mg kg^{-1} h^{-1} lasting 5–20–40–120 min, respectively, was given. All doses were based on TBW. Remifentanil was adjusted during surgery to maintain cardiac rate and arterial pressure within 20% of basal values.

Arterial blood samples (4 ml) were obtained at 1, 3, 5 min after the propofol bolus, every 10–20 min during propofol infusion, and every 10–30 min for 2 h after stopping propofol. Plasma was separated and stored at −20°C; HPLC was used for propofol assay from plasma samples.[20] The calibration curve was linear up to 50 μg ml^{-1} with coefficients of determination (r^2) 0.998. The LLOQ of propofol in plasma was 0.025 μg ml^{-1}. Inter- and intra-day assay precision (CV%) at 1, 12, and 30 μg ml^{-1} were 11.5%, 7.4%, 5.2% and 13.4%, 9.6%, 8.2%, respectively.

PK analysis

The analysis composed of two parts:

(i) Time–concentration data profiles from Study 3 (n=19, number of samples=163).
(ii) Time–concentration data profiles from this current study of adults administered propofol (Study 3) were pooled with data from Studies 1–2,[16 17] available at http://www.opentci.org. There were 51 subjects who contributed 1482 observations.

Population parameter estimations

A three-compartment mamillary model was used for the propofol PK. Population parameter estimates were obtained using a non-linear mixed effects model (NONMEM VI, Globomax LLC, Hanover, MD, USA).[21] The population mean parameters, between-subject variance, and residual variance were estimated using the first-order conditional estimation method using ADVAN 11 TRANS 4 of NONMEM VI. Convergence criterion was three significant digits.

The population parameter variability is modelled in terms of random effect (η) variables. Each of these variables is assumed to have a mean 0 and a variance denoted by ω^2, which is estimated. The between-subject

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variability in model parameters was modelled by exponentiating random effects (equivalent to assuming a log-normal distribution).

$$P_i = P_{TV} \times e^{\eta_i}$$

where P_i is the parameter value (e.g. CL and V) of the ith patient, P_{TV} the typical value of the parameter in the population, and η the random variable.

We report the estimate of ω for each variability component expressed as a percentage because these quantities are approximate coefficients of variation for a log-normal distribution.

The covariance between two elements of η (e.g. CL and V) is a measure of statistical association between these two variables. Their covariance is related to their correlation, that is,

$$R = \frac{\text{covariance}}{\sqrt{(\omega_{CL}^2 \times \omega_V^2)}}$$

The covariance of clearance and distribution volume variability was estimated.

Separate proportional terms were applied to each of the three studies to characterize the residual unknown variability (RUV).

Covariate analysis

Size

The parameter values were standardized for a body size of 70 kg using an allometric model.[22 23]

$$P_i = P_{std} \times \left(\frac{X_i}{W_{std}}\right)^{PWR}$$

where P_i is the parameter of the ith individual, X_i a measure of body size of the ith individual, and P_{std} the parameter in an individual with a standard size W_{std}. The PWR exponent is 1 for both clearance and distribution volumes when the linear model is used and 0.75 for clearance and 1 for distribution volumes with the allometric model.[24–26] Thus, total drug clearance may be expected to scale with a power of 3/4 with the allometric model:

$$CL_i = CL_{std} \times \left(\frac{X_i}{70}\right)^{3/4}$$

where CL_{std} is the population estimates for CL.

We investigated four measures of body size

(i) total body weight (TBW) (kg)
(ii) lean body weight (LBW)[27]

$$LBW_{(male)} = 1.10 \times TBW - 0.0128 \times BMI \times TBW$$

$$LBW_{(female)} = 1.07 \times TBW - 0.0148 \times BMI \times TBW$$

where BMI is expressed as

$$BMI = \frac{TBW}{H^2}$$

(iii) free fat mass (FFM)
FFM can be predicted from TBW and height (H, m).[28]

$$FFM = WHS_{max} \times H^2 \times \left[\frac{TBW}{WHS_{50} \times H^2 + TBW}\right]$$

For men, WHS_{max} is 42.92 kg m^{-2} and WHS_{50} is 30.93 kg m^{-2} and for women WHS_{max} is 37.99 kg m^{-2} and WHS_{50} is 35.98 kg m^{-2}.

(iv) normal fat mass (NFM)
NFM[23] is an extension of the concept of predicted normal weight[29] with a parameter (Ffat) which accounts for different contributions of fat mass (i.e. TBW minus FFM)

$$NFM(kg) = FFM + Ffat \times (TBW - FFM)$$

$$Fsize = \left(\frac{NFM}{W_{std}}\right)^{PWR}$$

Instead of assuming a fixed value of Ffat in all cases, the idea of NFM is to estimate the value of Ffat that is most appropriate for the parameter being predicted. If Ffat is estimated to be zero, then FFM alone is required to predict size, but if Ffat is 1, then size is predicted by TBW. Other estimates of Ffat reflect different weighting of body composition components.

The weight model used by Servin and colleagues[16] to determine propofol infusion rate [corrected kg=ideal weight+(0.4×excess weight)] is consistent with this NFM equation where Ffat=0.4.

Age

Covariate analysis included a model investigating age of the pooled data

$$FAGE_p = EXP(SL_p \times [AGE - 50])$$

$FAGE_p$ was estimated separately for each clearance parameter (p refers to CL1, Q2, or Q3) and volume parameter (p refers to V1, V2, or V3).

Quality of fit

The quality of fit of the PK model to the data was judged by NONMEM's objective function. Models were nested and an improvement in the objective function was referred to the χ^2 distribution to assess significance, for example, an objective function change (OBJ) of 3.84 is significant at α=0.05. The phenomenon of shrinkage may occur where uninformative data lead to individual parameter predictions that shrink towards the population mean. Use of these shrinkage

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estimates can both miss important covariates and suggest spurious relationships.[30]

Bootstrap methods, incorporated within the Wings for NONMEM program, provided a means to evaluate parameter uncertainty.[31] A total of 1000 replications were used to estimate parameter confidence intervals. A visual predictive check (VPC),[32] a modelling tool that estimates the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardized dose, was used to evaluate how well the model predicted the distribution of observed propofol concentrations. Simulation was performed using 1000 subjects with characteristics taken from studied patients. This is an advanced internal method of evaluation[33 34] and is considered better than the commonly used plots of observed *vs* predicted values.[33 34] For data such as these where covariates such as dose, weight, height, and sex are different for each patient, we used a prediction corrected VPC (PC-VPC).[35] Observations and simulations are multiplied by the population baseline value divided by the individual-estimated baseline.

Simulated TCI scenario

Computer simulations based on the PK described by Marsh and colleagues,[36] Schnider and colleagues,[17] and the current pooled PK model are performed to visually compare the PK profile of propofol predicted by these three models in obese patients. The simulation used a 30-yr-old female with TBW 140 kg, height 160 cm, and BMI 54.7 kg m^{-2}. First, the predicted infusion rates needed to reach and maintain a target plasma propofol concentration of 3.0 μg ml^{-1} over 180 min are calculated. Then, the recovery profiles predicted by these three models are compared by means of the estimated context-sensitive half-time and 80% decrement time.[37 38] Computer simulations were performed with the Anestfusor™ TCI program.

Results

The obesity study involved 19 adults who contributed 163 observations (Table 1). Parameters scaled with the linear model using TBW, without any other size model applied to any parameter was the best model (OBJ 178.098). The use of NFM parameters for clearance and volume did not improve the objective function (OBJ 177.969). The use of allometric 3/4 power scaling to clearance did not improve the objective function (OBJ 181.640) and the substitution of NFM instead of TBW for clearance made no improvement (ΔOBJ 2.828) (Supplementary Table S1). Parameter estimates for the allometric model scaled to a 70 kg person are shown in Table 2. The PC-VPC plot (Fig. 1) shows that in general model predictions encompass the observed data.

The pooled analysis involved 51 patients (weight 93 SD 24 kg, range 44–160 kg; age 46 SD 16 yr, range 25–81 yr; BMI 33 SD 9 kg m^{-2}, range 16–52 kg m^{-2}). Data from 1482 assay samples in these subjects were available for study. The best linear model was that using TBW (OBJ −3214.91).

Table 1 Characteristics of the obese patients. Values are mean, SD (range)

	(*n*=19)
Age (yr)	40, SD 8.7 (28–56)
ASA (I/II/III)	0/19/0
Female/male ratio (*n*)	11/7
Weight (kg)	106, SD 18 (82–134)
Height (cm)	163, SD 13 (139–185)
BMI (kg m^{-2})	39.7, SD 4.1 (33–50)
Duration of infusion (min)	131, SD 42 (72–215)

Table 2 Propofol population PK parameter estimates for a 70 kg 50-year-old person for index study [BSV, between-subject variability; %SE, relative standard error of the estimate; 95% CI, 95% confidence interval of the structural parameter obtained from a non-parametric bootstrap procedure (1000 replications)].

Parameter	Estimate	95% CI	%BSV	%SE
V1 (litre 70 kg^{-1})	4.47	2.58, 5.99	53.4	14.2
V2 (litre 70 kg^{-1})	26.6	4.75, 38.53	71.9	20.6
V3 (litre 70 kg^{-1})	53.8	31.1, 566	80.9	42.2
CL1 (litre min^{-1} 70 kg^{-1})	2.25	1.55, 2.63	36.9	9.0
Q2 (litre min^{-1} 70 kg^{-1})	3.20	0.97, 5.14	95.3	22.2
Q3 (litre min^{-1} 70 kg^{-1})	0.52	0.45, 1.77	0 FIX	13.5
Proportional residual error	31%	26.2, 35.1	—	14.2

The allometric 3/4 power exponent on TBW for clearance was superior to the linear TBW model (ΔOBJ 7.389). This allometric model using TBW was not improved by the use of other size descriptor (FFM, LBW, NFM).

The addition of age functions to both V2 and Q2 decreased the OBJ (ΔOBJ 43.484) and showed both parameters decreased with age. V2 decreased by 1.6% and Q2 by 1.5% per year (Supplementary Table S1). This final allometric model was better than that using a linear TBW model (ΔOBJ 15.371).

PK parameters were estimated with reasonable precision, and with an alternative parameterization based on the typical values showed for volumes and clearances (Supplementary Table S2A and B). The correlation of between-subject variability for structural parameters showed the residual errors for the three studies were similar—the proportional errors were 31% in the index study and 30%, 22% for the other two studies (Supplementary Table S3). The final model used common proportional error to explain residual unexplained variability (RUV) without any change in structural parameter estimates (RUV 24.4%, CV 19.2%). The PC-VPC plot (Fig. 2) confirms the adequacy of model predictions, showing no apparent deviations between model and data. The 90% confidence interval and median for

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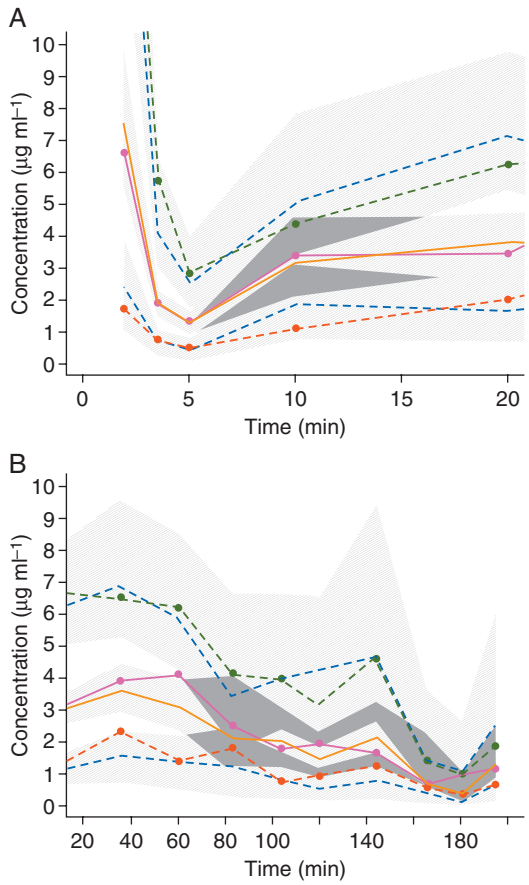

Fig 1 PC-VPC for the index study. The dashed blue lines present the 5th and 95th percentiles and the solid orange line depicts the model predicted median. The shaded grey area is the 90% confidence interval for the prediction percentiles. The 90% prediction interval and median for prediction corrected observed data are shown as lines with closed circles. (A) The first 20 min and (B) from 20 to 200 min.

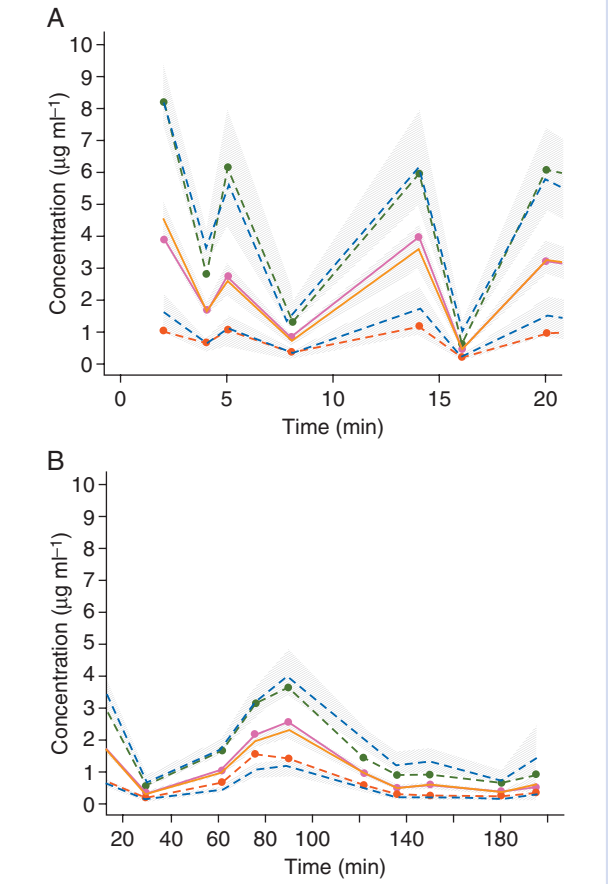

Fig 2 PC-VPC for the pooled analysis. See Fig. 1 for legend.

observed data lies within the predicted intervals obtained by simulation.

Parameter estimates from the pooled study were suitable for prediction of time–concentration profiles from the index study despite parameter estimate differences between the two studies (Fig. 3). Simulated subjects of similar age and weight (n=1000) to those in the pooled study were given propofol 2 mg kg^{-1} at 200 mg min^{-1}. An infusion of 10 mg kg^{-1} h^{-1} was started at 5 min and ran for 5 min. This was then decreased to 8 mg kg^{-1} h^{-1} for 20 min. The infusion was further decreased to 6 mg kg^{-1} h^{-1} for the next 30 min before slowing to 4.8 mg kg^{-1} h^{-1} for 120 min. The figure shows the 90% prediction interval obtained using parameters from the pooled analysis. Time–concentration profiles for the 19 index subjects estimated using individual Bayesian parameters obtained from the index analysis comply with the 90% prediction interval.

The simulation showed that the infusion rates decreased from 10.9 to 8.8 mg kg^{-1} h^{-1} with the Schnider model, followed by the Marsh model (11.1 to 5.8 mg kg^{-1} h^{-1}) and the current pooled model (10.5 to 5.1 mg kg^{-1} h^{-1}) to maintain the 3 μg ml^{-1} target concentration (Figs 4 and 5). Infusion rates were consistently lower (7.1 to 3.7 mg kg^{-1} h^{-1}) when the Marsh model was used with a weight-corrected formula[16] (Fig. 4). In addition, this simulation shows that after 3 h of infusion, the predicted context-sensitive half-times were shorter with the Schnider model (0.7 min) compared with the current pooled model (3.6 min) and longer with the Marsh model (8.8 min). The predicted 80% context-sensitive decrement-times were also shorter with the Schnider model (8.2 min) but very close with the pooled model (51 min) and the Marsh model (55 min) (Fig. 5). To further validate the anestfusor device used to administer propofol to study patients and to perform the simulation analysis, we compared its performance with Rugloop©, a Windows-based TCI infusion and general data management programme. For this, we used the time and the cumulative infusion (in ml) that anestfusor administered in the TCI simulated scenarios and calculated the differences in the predicted concentrations between both devices. The difference was negligible with a mean of 0.0006 SD 0.007 μg ml^{-1}.

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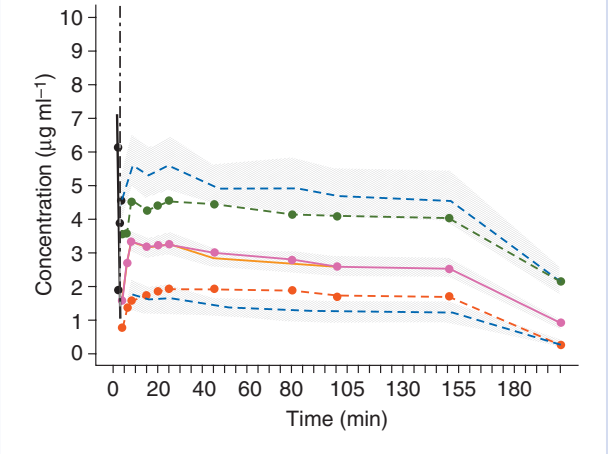

Fig 3 Population prediction corrected visual predictive checks. See Fig. 1 for legend. The 90% prediction interval from the pooled analysis encompasses time–concentration profiles from the index study. Dosing comprised propofol 2 mg kg^{-1} at 200 mg min^{-1}. An infusion of 10 mg kg^{-1} h^{-1} was started at 5 min and ran for 5 min. This was then decreased to 8 mg kg^{-1} h^{-1} for 20 min. The infusion was further decreased to 6 mg kg^{-1} h^{-1} for the next 30 min before slowing to 4.8 mg kg^{-1} h^{-1} for 120 min.

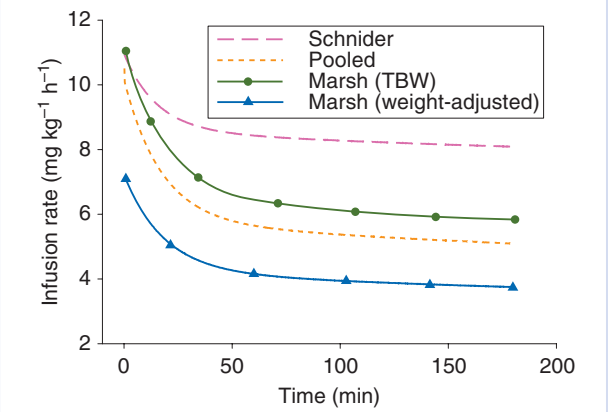

Fig 4 Simulated propofol infusion rates of different PK models to reach and maintain a plasma concentration of 3.0 μg ml^{-1}. The simulated case is a 30 yr woman with a TBW of 140 kg and a height of 160 cm (BMI 54.7 kg m^{-2}).

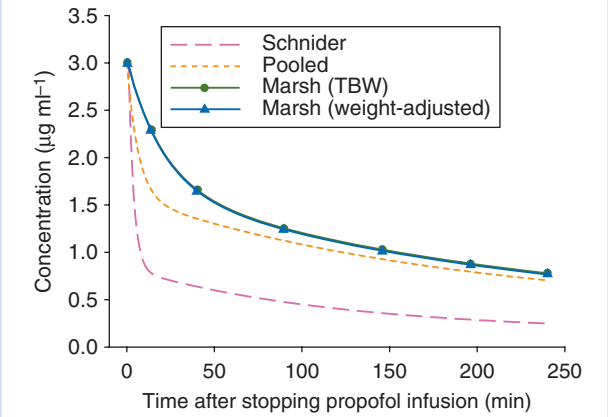

Fig 5 Simulated propofol time–concentration profiles predicted by three different PK models after a 3 h infusion with a plasma target of 3.0 μg ml^{-1} The simulated case is a 30 yr woman with a TBW of 140 kg and a height of 160 cm (BMI 54.7 kg m^{-2}). Marsh (TBW) and Marsh (weight-adjusted) are indistinguishable since rate constants in Marsh PK parameters are not influenced by weight.

Discussion

This study has shown that an allometric model using TBW as the size descriptor for volumes and clearances in obese patients is superior to other size descriptors. Age also appeared to be an important covariate for the distributional components of propofol PK, which is consistent with the effect on distribution rates described by Schnider and colleagues[17] who showed selective effects on Q2 and V2. The pooled analysis showed that the peripheral volume and its distribution clearance were smaller in older subjects. In our modelling strategy, we first used different size descriptors to explain individual variability. Once size was standardized, the effects of other covariates were tested. In general, our results showed that using TBW was superior to LBM,[27] fat free mass,[28] and no worse than NFM.[29] Although the index study analysis, judged by NONMEM objective function, suggested that the best model was the one where all parameters were scaled linearly per kilogram to TBW (with the exception of elimination clearance which was better using NFM), the larger pooled analysis revealed that allometric scaling using TBW was superior for all parameters. The index study involved only obese patients and therefore body composition was relatively similar, allowing the use of a simple linear scale to normalize the parameters to TBW.

Propofol is largely metabolized by the liver, although the kidneys may contribute 27% of total body clearance.[39 40] It has been postulated that long-term changes induced by obesity might cause fatty degeneration of the liver,[14] glomerular injury of the kidneys, or both with a consequent reduction in drug elimination.[4] However, these clearances, unscaled for body size, are usually increased in the obese patient.[41] In obese subjects, clearance does not increase linearly with TBW.[13] Consequently, scaling clearance to LBM instead of TBW has been suggested as a more logical approach.[4 12 13 15] However, the justification for a linear rather than allometric relationship using FFM has not been supported.[42] The use of dosing linear to LBW, where LBW had a non-linear relationship with TBW, has been proposed, but the relationship between LBW and CL for propofol was not estimated from real data.[15] LBW was simply substituted for TBW in the TBW relationship derived from data collected and analysed by others.[43] We have demonstrated that using

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an allometric relationship between TBW and clearance provides a better description in obese patients. Allometric scaling of clearances using TBW is consistent with other studies[9–11] and simplifies dosage regimes over a wide range of body weights. A recent study of anticancer drugs found that the values of CL when normalized to BSA, calculated using TBW, were not significantly different between obese and lean patients.[44] These results further support the allometric model used in our study because BSA in humans is approximated with a TBW exponent of 2/3. The allometric 3/4 power model is a non-linear model that has been described as a means of predicting physiological function from body size. Interestingly, a more mechanistic size descriptor, NFM, showed that TBW (Ffat=1) rather than using another fraction of fat mass gave the best description. It seems that each kilogram of fat mass is equivalent to FFM for describing the size-dependent differences in clearance in obese subjects. The current allometric 3/4 power (non-linear) model for clearance and linear model (exponent of 1) for volume is supported by fractal geometric concepts and observations from diverse areas in biology.[22] Quarter-power scaling laws are widespread in biology with, for example, most organisms having scaling exponents very close to 3/4 for metabolic rate.[26]

The pooled data set has patients from 25 to 81 yr, so, in theory, this pooled model should be applicable within this age range, but the data in the elderly are limited. A larger data set over a bigger age range may give a better model. The current model agrees with Schnider PK parameters,[45] the pooled model predicts that younger patients will have faster Q2 and bigger V2 compared with elderly patients. This means that slower initial infusion rates will be predicted by this model in the elderly. Similarities between Schnider[45] and the pooled model with respect to age adjustments are not surprising since most data from elderly patients come from their study.[45]

We did not find any influence of gender on propofol PK. These results are in contrast to an earlier study[46] in which younger female patients were found to have higher elimination clearances (per kilogram). These findings could be explained by not accounting for the non-linear relationship of TBW with clearance. However, comparisons between these two studies are difficult as, in that study,[46] formal covariate analysis was not performed, and only the effect of age and gender on V1 and CL1 was explored.

One limitation of the index study is the relatively short infusion period (Table 1) and post-infusion sampling times (2 h) that were constrained by clinical limitations. This index study was performed in routinely scheduled patients and as such, ethical and clinical limitations were present. These relatively short observation periods affected the precision of some estimates in our model (V3, V2, and Q2) (Table 2). In general, the longer the infusion duration, the more time there is to distribute to V3 and the better the estimate of V3. When the data of the three studies were pooled, the precision of all estimates was improved and this pooled model adequately characterized the time–concentration profiles (Fig. 3). A further limitation of our conclusions regarding covariate models is the rather small number of patients (n=51). It has been pointed out that covariate model conclusion will often be subject to selection bias when the number of subjects is <100.[47] Nevertheless, we cannot find any support for using anything other than TBW as a size predictor for between-patient differences in propofol PK.

Current propofol PK models, used in TCI devices, were derived from studies that did not include morbidly obese patients.[17 36] The current recommendation is that TCI should be used with caution in the obese.[48] The results of our TCI simulated scenario show that the infusion rates predicted by the current pooled model are very similar to those predicted by the Marsh TCI model using TBW as the input function (Fig. 4). A study of 20 obese patients (ASA physical status II–III, age 32–64 yr) undergoing bariatric surgery,[9] delivering anaesthesia with the Marsh TCI model and the Servin and colleagues[16] corrected weight dosing formula, showed, in agreement with our predictions, that observed propofol concentrations were consistently lower than the target concentration (under dosing) with a median (range) bias of −32.6% (−53.4% to −2.5%).

Our model based on three pooled studies eliminates the need for the James equation[49] used in the Schnider model to calculate LBM. This equation is inappropriate for morbidly obese patients[4 12 28] and results in an overestimation of metabolic clearance in this population. An overestimation of clearance explains the higher infusion rates required to maintain a set concentration and the faster recovery times predicted by this model when compared with Marsh (TBW) and the currently derived pooled model. Shorter recovery times predicted by the Schnider model[17] have also been described in a previous study assessing the predictive performance of different PK models in non-obese healthy subjects.[50] In that study, the Schnider model tended to under-predict propofol concentrations during recovery, with median bias of −15%. This small underestimation during recovery is likely to be magnified in very obese patients from the overestimation of metabolic clearance caused by the James equation.[49] In contrast, Glen and Servin[50] demonstrated that the Marsh model showed an overprediction tendency during the recovery phase with median bias of +10.5%.[50] This is also in agreement with our simulation scenario in an obese patient.

We have derived a population PK model using data from obese and non-obese patients to characterize propofol PK over a wide range of body weights. An allometric model using TBW as the size descriptor of volumes and clearances was superior to other size descriptors to characterize propofol PK in the obese. Inclusion of this model into TCI pumps circumvents the need for LBM equations that contribute to inaccurate dosing of the obese.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Conflict of interest

None declared.

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