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Research Paper

Encouraging the Move Towards Predictive Population Models for the Obese Using Propofol as a Motivating Example

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Purpose. To develop a predictive pharmacokinetic model for propofol that could inform development of a dosing strategy for the obese population.
Methods. A prior model that included a nonlinear relationship between clearance (CL) and Total Body Weight (TBW) was re-parameterized with a linear relationship between CL and Lean Body Weight (LBW). The predictive performance of both models was compared and the LBW model used to explore propofol exposure from normal to obese patients. A dosing strategy was evaluated that normalized awakening time across a range of patient weights.
Results. The predictive performance of the LBW model was similar to the nonlinear TBW model for normal weighted subjects. Simulations in 70–160 kg subjects indicated that dosing linearly on TBW (label recommendation), in contrast to LBW, resulted in increased plasma concentrations in the larger weight groups. This result might explain why obese subjects take longer to awaken from anesthesia compared to normal weighted subjects. Dosing by LBW normalized patient awakening times across this weight range.
Conclusions. LBW as a covariate provides a plausible mechanistic explanation for an observed nonlinear increase in drug CL with TBW and may be suitable for developing dosing strategies that are appropriate for use in the obese population.

KEY WORDS: lean body weight; mechanistic covariates; obesity; population pharmacokinetics; propofol.

INTRODUCTION

When building population pharmacokinetic/pharmacodynamic (PKPD) models, identification of covariates that can explain some of the variability in the PKPD parameters is often a primary goal. These models can help define optimal dosing schedules and explore if covariate specific dosing regimens are necessary to normalize exposure across a range of varying population demographics. During development of such models, both objective and subjective measures can be employed by the modeler to aid identification and subsequent retention of covariates in the model. These measures include a combination of statistical tests, assessment of the biological, mechanistic and clinical relevance of the covariate together with prior knowledge of the modeled system.

The final model's predictive performance is not only dependent on the choice of methods used to select covariates, but also the incorporation of covariates that underlie biological behaviour. Mechanistic covariates are those which are expected to describe the parameter of interest as a function of some known biological or physiological phenomena, *e.g.* renal function on clearance (CL) for a drug which is renally cleared, whereas empirical covariates are descriptive explanations of variability that have no clear physiological basis, *e.g.* hair colour. A covariate model can therefore function as either a descriptive model, which might include empirical covariates, or a predictive model, which, by including mechanistic covariates, can be used for simulation purposes outside of the population used to build the model. The utility of descriptive models is somewhat limited, serving to primarily explain the observations, whereas predictive models can be used to inform decision making during a drug development program (1,2).

Total Body Weight (TBW) is commonly used as a covariate to describe changes in pharmacokinetic parameters in relation to subject size. We propose that TBW is suitable as a covariate on CL for subjects of normal body composition as it closely correlates with underlying physiological mechanisms, but that it loses its predictive properties when transported to the obese population. The consequence of using TBW as a body size metric to describe CL in the obese population has been recently discussed by Han *et al.* (3). Briefly, TBW ignores differences in body composition across a range of weights and inherently assumes that structural and functional aspects remain similar in the lean and obese population. However, obese patients in comparison to their lean counterparts have a much larger ratio of fat to lean tissues, with Lean Body Weight (LBW) increasing non-linearly with TBW. As lean tissues are responsible for the

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majority of metabolic processes in the body (4), CL can be overestimated for this patient group if scaled by TBW from the normal weight population. Therefore, it has been hypothesized that LBW is a more suitable descriptor for CL due to its mechanistic ability to describe changes in body composition with patient size, especially in studies that include obese subjects (5).

Indeed, various PK studies in adults have identified a nonlinear relationship between drug CL and TBW for both hepatic and renally eliminated drugs, supporting the LBW hypothesis (6–12). In studies where LBW was not considered as a covariate, the curvilinear relationship has often been accounted for by the inclusion of covariates such as body surface area (BSA), TBW with an allometric coefficient (either fixed to ¾ or estimated), or inclusion of empirically derived body composition metrics such as 'PK mass' (12). However, as with TBW, these metrics are only appropriate for describing PK within the study population demographics and are unlikely to predict CL outside the 'normal' weight range. Furthermore, it is pertinent to mention that despite any advantages gained by incorporating these metrics into a PK model, dose strategies are rarely developed based on these nonlinear relationships and instead, with the exception of chemotherapeutic agents for which BSA is often used, most drug labels recommend dosing linearly according to TBW. LBW as described by Janmahasatian *et al.* (13) provides a plausible mechanistic explanation for such observations and may be a suitable metric to extrapolate into the obese population (3).

The material presented in this paper seeks to demonstrate that LBW can be chosen as a mechanistic covariate on CL for propofol in preference to covariates chosen on statistical grounds, with minimal loss in the model's performance. This approach was necessary to develop a model that could be used to propose a suitable dosing strategy for propofol in the obese.

Propofol is a commonly used intravenous anesthetic for induction and maintenance of general anesthesia (14). It exhibits high systemic clearance (CL) by extensive liver and kidney metabolism which respectively constitute approximately 70% and 30% of total CL (15,16). The approved label for propofol indicates that dosing should be determined on a mg/kg total body weight (TBW) basis for all patients (17). However, caution is advised when dosing obese patients by this method as it may lead to higher than expected plasma concentrations and an increased risk of deleterious haemodynamic side effects (18–24). Additionally, anecdotal evidence from anesthetists suggests the current dosing label is unsuitable for the obese population as it results in deeper anesthesia and increased time to awakening (personal communication). Thus, our aim was to develop an improved dosing schedule to normalize responses in the obese population.

MATERIALS AND METHODS

Previously published models for propofol had been developed in predominantly non-obese populations (25–29) *i.e.* body mass index (BMI)<30 kg m^{-2} or TBW<100 kg and included either a linear relationship with TBW or empirically derived covariate relationships on CL *e.g.* $CL=1.89+((TBW-77)\times0.0456)+((LBW_{James}-59)\times-0.0681)+((HT-177)\times0.0264)$ L min^{-1} (27). Although these models would have been suitable for simulating and developing dosing strategies within the weight range in which they were developed, *i.e.* in patients of normal body composition, it was anticipated that they would be unsuitable to simulate concentration time profiles in the obese due to the lack of a mechanistic covariate relationship to predict CL in the obese population. Therefore, a previously published model that had potential to be re-parameterized was identified from the literature. This model included a three-compartment disposition model and described a nonlinear relationship between CL and TBW by means of an estimated exponent (θ) of 0.75, where clearance $(CL)=86.4\ L\ h^{-1}\times(TBW/70)^{\theta}$ (28). We hypothesized that the empirical nonlinear covariate relationship between CL and TBW could be replaced by a linear covariate relationship with LBW, allowing the model to predict more accurately into the obese population and explain why dosing on TBW is unsuitable for obese patients. Thus, the specific objectives of this study were to (1) evaluate if a linear LBW covariate model could replace a nonlinear TBW covariate model for propofol clearance, and (2) explore how awakening time might vary following different propofol dosing regimens in the obese population.

Overview

PK datasets were simulated from the posterior distribution using a population PK model reported by Schuttler and Ihmsen (28) that included multiple covariates (henceforth referred to as the 'Full' model). Individual PK parameters were estimated using both (1) the Full model and (2) a 'LBW' model, which was the same as the Full model except that we removed the nonlinear TBW covariate relationship on CL and replaced it with a linear function of LBW on CL. For both models the covariate relationships for volumes of distribution and initial typical parameter estimates were the same as the Full model. The predictive performance of the LBW model was compared to that of the Full model. The LBW model was then used to explore propofol exposure across the normal to obese patient range in order to determine an optimal dosing metric that helps normalize awakening time between obese and normal weighted patients.

Simulation of Datasets

Study Populations

One-hundred datasets, each containing 198 subjects, were simulated for the study. Patient covariates were simulated from a covariate distribution model determined from a population of general medical patients at Christchurch Hospital, Christchurch, New Zealand (30). For each sex, the model consisted of a vector of population means of weight, height and age, and a variance–covariance matrix of log-normal weight, height and age covariate distributions (Table I). Datasets were simulated with the following demographics: 52% male/48% female with age constrained to 17–60 years, height 130–195 cm and weight 40–100 kg. Weight was stratified into three groups of 66 subjects each of 40–60 kg, 60–80 kg and 80–100 kg (*i.e.* 198 subjects total per dataset) to maximize the likelihood of identifying the relationship between weight/body composition and clearance in the estimation procedure. As our aim was to explore

Table I. Parameter Values for the Population Simulation Covariate Distribution Model

Parameter		Males		Females	
Mean [variance]	Age (years)	55	[0.159]	54	[0.172]
	Weight (kg)	77.5	[0.0327]	67.7	[0.056]
	Height (m)	1.75	[0.0016]	1.63	[0.00192]
Covariance	Age–weight	−0.004		−0.014	
	Age–height	−0.001		−0.003	
	Weight–height	0.003		0.004	

variability in CL as a function of body size and composition only, age was limited to 60 years to exclude any confounding effects of age on CL above 60 years as reported in the original PK model (Table II) (28). Simulated populations were validated by assessment of population covariate means, ranges, and frequency histograms.

Simulation of PK Data: The Input–Output Model

Pharmacokinetic data were simulated for each individual from the Full model (Table II) with between-subject variability (BSV) log-normally distributed as shown in Equation 1:

$$\theta_i = \theta_{\text{pop}} \cdot e^{\eta i} \tag{1}$$

where θ_i is the parameter value for the ith individual, θ_{pop} is the population parameter value, and η_i is normally distributed with a mean of zero and variance of Ω. Residual unexplained variability (RUV) was defined as heteroscedastic with a coefficient of variation (CV) of 17.6% (28).

For the simulation-estimation experiments, subjects were administered a 2 mg/kg bolus dose of propofol over 60 s, which represents a typical induction dose for propofol anesthesia (17). Seven sampling time points for the simulations were defined using D-optimality in WinPOPT© (version 1.1.1 beta (31)) using the final pharmacokinetic parameter values from the Full model (28). The seven sampling times were at the end of the infusion, then 4 s, 4.9 min, 16.4 min, 1.2, 4.3 and 17.9 h after infusion, resulting in 1,386 observations in total for each dataset.

Visual Predictive Check of Simulated Data

In order to assess the ability of the simulation platform to generate adult CL data representative of the original Full model data, we performed a visual predictive check (VPC) in which simulated CL data from the Full model was compared to the original data reported in Fig. 1 of the manuscript by Schuttler and Ihmsen (28). For this purpose, we defined adult data in the original figure as TBW >40 kg (n=174). We simulated 174,000 subjects (*i.e.* 1,000 datasets of 174 subjects each) of weight 40–100 kg and determined the 10th, 50th and 90th percentiles of CL for each 5 kg weight range. These were overlaid with the original CL data which were obtained from the original manuscript (28) using the data extraction tool TechDig version 2.0© (R.B. Jones 1998). Approximately 10% of original data was expected to fall below, and 10% above, the 10th and 90th prediction intervals, respectively.

Estimation Procedure

Two models were fitted to the simulated datasets: the Full model (*i.e.* the same model used for simulation of data, Table II) and a LBW model (Table III). The LBW model differed from the Full model in that the nonlinear TBW covariate relationship on CL was replaced with a linear LBW relationship, where LBW (13) was determined as:

$$\text{LBW(kg)} = \frac{9{,}270 \cdot \text{TBW(kg)}}{6{,}680 + 216 \cdot \text{BMI}\left(\text{kg} \cdot \text{m}^{-2}\right)} \text{ for males} \tag{2}$$

$$\text{LBW(kg)} = \frac{9{,}270 \cdot \text{TBW(kg)}}{8{,}780 + 244 \cdot \text{BMI}\left(\text{kg} \cdot \text{m}^{-2}\right)} \text{ for females} \tag{3}$$

In all estimations, the covariate relationships for volume and initial typical parameter estimates were unchanged from the Full model.

Table II. The Full Model that Was Used for Simulating the 'True' Data

Reference	Drug, model, n, M:F	Parameter value	%CV
Schuttler and Ihmsen (28)	Propofol, 3-cpt, 270 patients, 150:120	CL=86.4 L h^{-1}·(TBW/70)$^{0.75}$ if age <60	37.4
		CL=86.4 L h^{-1}· (TBW/70) $^{0.75}$−(age−60) ·2.7 if age >60	
		CL_2=135 L h^{-1}· (TBW/70)$^{0.62}$·(1+ven·−0.4)·(1+bol·2.02)	51.9
		CL_3=55.2 L h^{-1}· (TBW/70)$^{0.55}$· (1+bol·−0.48)	50.9
		V_1=9.3 L· (TBW/70)$^{0.71}$· (age/30)$^{-0.39}$· (1+bol·1.61)	40.0
		V_2=44.2 L· (TBW/70)$^{0.61}$· (1+bol·0.73)	54.8
		V_3=266 L	46.9

The same model was fit to the 'true' data in the estimation procedure to allow comparison of predictive ability with the competing LBW model, in which the nonlinear TBW relationship on CL was replaced by a linear LBW relationship on CL
CL elimination clearance (L h^{-1}), CL_2, CL_3 inter-compartmental clearances (L h^{-1}), V_1 volume of central compartment (L), V_2, V_3 volumes of compartments two and three (L), *TBW* total body weight, *ven* 1 for venous sampling all subjects, *bol* 1 for bolus dosing all subjects, *3-cpt* three compartment model, *%CV* between subject variability expressed as percentage of coefficient of variation

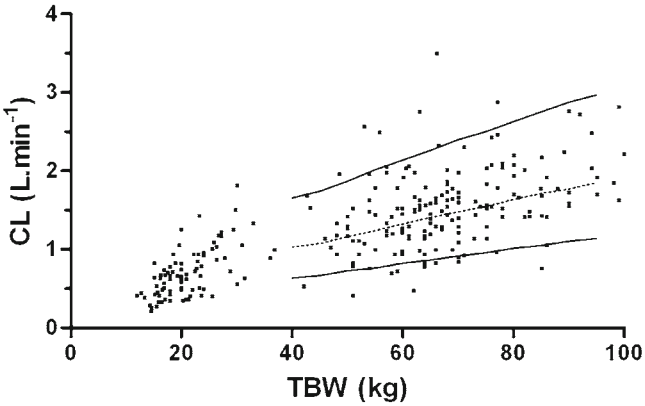

Fig. 1. Visual predictive check of simulated CL data. The *solid lines* represent the 10th and 90th percentiles of the simulated adult data and the *dashed line* the median. Original CL data as reported by Schuttler and Ihmsen (28) is overlaid.

Model Evaluation

Parameter Bias and Precision

The predictive performance of the LBW model was compared to the Full model by assessment of model bias and precision. Bias was evaluated by computing the mean error (ME) between the observed and individual predicted parameter values:

$$\mathrm{ME} = \left(\sum \left(P_t - P_p\right)\right)/n \tag{4}$$

where P_t is the simulated (true) parameter value, P_p is the predicted value, and n is the number of subjects in the dataset. Precision was evaluated by computing the root mean squared error (RMSE) between the true parameter values and the individual predictions in each dataset where:

$$\mathrm{RMSE} = \sqrt{\left(\sum \left(P_t - P_p\right)^2\right)/n} \tag{5}$$

Estimates of Parameter Variability

To evaluate the ability of the LBW model to correctly estimate random effects, median CV% values from the one-hundred estimations were compared between models.

Numerical Predictive Check

A numerical predictive check (NPC) was performed as follows: a dataset of 198 subjects was simulated from the Full model and considered as the 'true' data. The LBW model was fitted to the 'true' data and final population parameter estimates were used to simulate new data (n=1,000 datasets) for the same 198 subjects and seven time points. The 10th to 90th prediction intervals from the 1,000 simulated datasets were determined for each time point and the percent of 'true' data outside this range was calculated. This process was repeated for ten 'true' datasets. Analogous to the VPC evaluation process, approximately 10% of true data should be expected to fall below and 10% above, the 10th and 90th prediction intervals generated by an acceptable model.

To allow the predictive performance of the LBW model to be compared to that of the Full model, the same process was also performed for the Full model using the same ten 'true' datasets.

Simulation Dose–Response Study

Pharmacokinetics

The LBW model was used to simulate PK profiles for 4,000 male subjects (180 cm, 30 years) in four weight categories of 70, 100, 130 and 160 kg, given a dosing regimen of (a) a 2 mg/kg bolus dose followed by a 1 h, 6 mg/kg per hour infusion based linearly on TBW (according to label recommendations), and (b) a 2.5 mg/kg bolus dose followed by a 1 h, 7.6 mg/kg per hour infusion based linearly on LBW (equivalent to the recommended dose per kg of TBW for a 70 kg subject). Concentration data were simulated based on a dense sampling scheme of 22 concentrations over 0–3 h post-infusion.

Pharmacodynamics

To consider the effects that each dosing strategy might have on expected patient awakening times, 1,000 patients were generated by stochastic simulation for each weight group and the percentage of patients still asleep over time, post-infusion, was calculated based on a reported awakening concentration of 1.07 μg/ml (32).

Computer System

The nonlinear mixed effects modeling program NONMEM version V (GloboMax, LLC, Hanover, MD) was used for all simulations and estimations in this study, using the Wings for NONMEM (version 408, http://wfn.sourceforge.net/) interface. Estimations were performed using first order conditional estimation with interaction (FOCE-I). Results were analysed using R version 2.6.1 for Windows (The R

Table III. The Competing LBW Model Used for Re-estimation

Model	Parameter value
LBW model	CL=86.4 L h^{-1}·(**LBW/55**[a])
	CL_2=135 L h^{-1}·(TBW/70)$^{0.62}$·(1+ven·−0.4)·(1+bol·2.02)
	CL_3=55.2 L h^{-1}·(TBW/70)$^{0.55}$·(1+bol·−0.48)
	V_1=9.3 L·(TBW/70)$^{0.71}$·(age/30)$^{-0.39}$·(1+bol·1.61)
	V_2=44.2 L·(TBW/70)$^{0.61}$·(1+bol·0.73)
	V_3=266 L

This model was the same as the Full model except the nonlinear TBW relationship on CL was replaced by a linear LBW relationship on CL (highlighted in bold)

CL elimination clearance (L h^{-1}), CL_2, CL_3 inter-compartmental clearances (L h^{-1}), V_1 volume of central compartment (L), V_2, V_3 volumes of compartments two and three (L), *TBW* total body weight, *LBW* lean body weight as determined by the LBW_{2005} equation (13), *ven* 1 for venous sampling all subjects, *bol* 1 for bolus dosing all subjects, *3-cpt* three compartment model

[a] Approximate median LBW of population

Foundation for Statistical Computing) and Prism 5 for Windows v5.01 (GraphPad Software, Inc.). All runs were completed on an Intel® Xeon™ 2.4 GHz processor with a G77 compiler.

RESULTS

Simulation of Datasets

Demographics of Simulated Populations

Histograms of population demographics showed correct distributions around the population mean (results not shown) with values correctly constrained, indicating that the simulated populations were representative of the true population from which the simulation platform was developed.

Verification of Simulation Platform

Figure 1 shows the 10th, 50th and 90th percentiles of simulated CL values from the Full model overlaid with the original CL data reported by Schuttler and Ihmsen (28). Results show that the simulated data displayed a similar relationship between CL and TBW to that of the original data, suggesting that the simulation platform was able to generate CL data representative of the original data from which the Full model was developed.

Model Evaluation

Parameter Bias and Precision

The predictive performance of the LBW model was compared to the Full model by assessment of model bias and precision, determined as the ME and RMSE of individual parameter estimates from simulated (true) parameter values. Estimation of individual CL values using the Full model and the LBW model showed that both models performed similarly, with median errors of −3.85 and −3.97 L h^{-1}, respectively (Fig. 2a). As would be expected due to model simplification, the estimates of CL from the LBW model were more biased than the Full model. However, given that the mean value of CL in the population was 91 L h^{-1}, the median bias of the LBW model was less than 5% and was therefore considered comparable to the Full model. The precision of CL estimates was similar between models, with median RMSE values of 8.16 and 8.31 L h^{-1} for the Full and LBW model, respectively (Fig. 2b).

The bias and precision of other individual PK parameter estimates were also comparable between models. Table IV presents the ME and RMSE results from the inter-compartmental clearances CL_2 and CL_3 and volume parameters V_{1-3}. The LBW model underestimated CL_2 by only 0.7% (determined as the median percent bias from mean parameter values) and overestimated CL_3 by 0.6% (determined as the median percent bias from mean parameter values), displaying similar precision for CL_2 and CL_3 to that of the Full model. For volume parameters, estimates were again similar between the models, with the median bias of V_1, V_2 and V_3 within 0.6%, 0.7% and 16.2% of the mean individual parameter values, respectively.

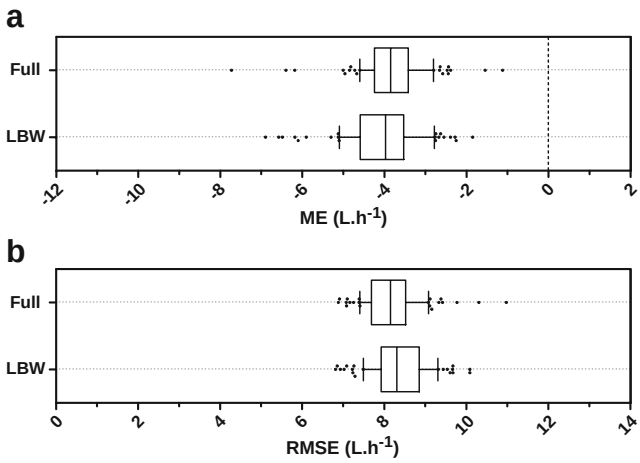

Fig. 2. The **a** ME (bias) and **b** RMSE (precision) between the simulated individual CL values and predicted CL values obtained with the Full and LBW model (n=100 runs). The mean individual value of CL was 91 L h^{-1}. Note: different scales. The *centre line* is the median. The *length* of each *box* represents the 25–75% range and the *whiskers* represent the 10–90% range.

To assess whether random effects were inflated for the LBW model in order to better fit to the data, median %CV estimates were compared to the simulation values. Estimates were comparable between models (Table V), with all estimates of BSV (as %CV) within 9% of simulation values and RUV within 0.2%. All estimated values of BSV were lower than simulation values.

Numerical Predictive Check

The total percentage of 'true' data falling below and above the 10th and 90th prediction interval (presented as median % [25th, 75th percentile] of 10 VPCs) of the LBW model was 6.4% [5.6, 7.2] and 10.3% [9.8, 10.5], respectively. As these values were close to 10%, this confirmed that the LBW model was able to adequately describe the 'true' data generated from the Full model. Furthermore, the LBW model showed a similar predictive ability to that of the Full model, which had 9.1% [8.1, 9.5] of 'true' data falling below and 12.0% [11.4, 13.1] above its 10th to 90th prediction interval, respectively. Results from one NPC that are representative of all ten NPCs are presented in Table VI.

Simulation Dosing Study

Under the assumptions of the simulation study, it was concluded that the LBW model appeared to have similar predictive properties to the empirically derived Full model across the normal weight range. Therefore, the LBW model was used to explore the effects of dosing propofol on TBW *vs*. dosing on LBW across a large range of body weights. The typical predicted concentration–time profiles for a weight of 70, 100, 130 and 160 kg are given in Fig. 3. As expected, dosing linearly on TBW results in increasing plasma concentrations as patient weight increases (Fig. 3a), whereas dosing on LBW results in similar profiles across all TBW (Fig. 3b).

To investigate the pharmacodynamic effects of dosing on TBW *vs*. dosing on LBW, an awakening concentration of

Table IV. The ME (bias) and RMSE (precision) Between the Simulated Individual Parameter Values (Inter-Compartmental Clearances CL_2 and CL_3 and Volumes V_{1-3}) and Predicted Parameter Values Obtained with the Full and LBW Model (n=100 Runs)

		ME		RMSE	
Parameter	Mean individual value	Full model	LBW model	Full model	LBW model
CL_2 (L h^{-1})	269.5	1.36 [−6.63, 9.31]	1.95 [−8.19, 8.81]	78.90 [71.38, 86.45]	79.01 [71.72, 87.71]
CL_3 (L h^{-1})	31.6	−0.43 [−3.38, 2.66]	−0.18 [−3.35, 2.92]	11.68 [10.42, 13.88]	11.61 [10.35, 13.09]
V_1 (L)	22.9	−0.07 [−0.52, 0.25]	−0.13 [−0.63, 0.26]	3.23 [2.98, 3.55]	3.24 [2.98, 3.58]
V_2 (L)	86.0	0.58 [−5.51, 5.02]	−0.10 [−6.59, 4.03]	23.30 [20.82, 25.48]	23.25 [20.52, 26.12]
V_3 (L)	289.1	46.89 [26.86, 59.96]	44.99 [29.12, 62.38]	114.2 [100.9, 125.9]	114.6 [101.1, 126.0]

Data is presented as median [10th, 90th percentile]

1.07 μg/ml (32) was used to determine the percentage of subjects still asleep over time, post-infusion, for each weight group based on each individual's concentration-time profile. Results are presented in Fig. 4. Dosing on TBW suggested an increased time to awakening in the larger weight groups (Fig. 4a), with 77% of 160 kg subjects *vs*. 42% of 70 kg subjects still asleep at 30 min, whereas dosing on LBW resulted in only slight differences between groups (Fig. 4b).

DISCUSSION

In this study we investigated the difference in a model's bias and precision following substitution of an empirically derived nonlinear covariate relationship between TBW and CL with a presumed linear mechanistic relationship between LBW and CL. The covariate substitution was performed to specifically enhance the model's predictive ability beyond the demographic range in which it was developed, allowing extrapolation of the model into the obese population. To the best of our knowledge, this is the first study that has attempted covariate substitution in a prior model for such a purpose.

For the study, we selected a model in which a nonlinear relationship between TBW and CL had been identified by the authors and described by means of an empirical estimated power function on TBW (28). We loosely use the term 'empirical' in this context as we recognize that TBW, especially scaled allometrically, has been used to explain variability in CL across individuals of differing size and normal body composition, including children. We contest however that it has limited value when used to scale between normal and obese subjects. Thus, LBW provided a plausible mechanistic basis for this observation and a possible means to allow prediction of PK response in obese subjects, supported by a recent review of pharmacokinetic studies that showed LBW had the greatest success in describing CL across a range of patient weights that specifically included the obese (5).

Results indicated that the LBW model had similar predictive properties to the Full model across a normal weight range. Furthermore, NPC results confirmed that the LBW model was able to adequately describe the 'true' data generated by the Full model. Therefore, we deemed the LBW model acceptable to be used to simulate propofol concentrations across a wider weight range that specifically included the obese in order to potentially explain observed differences in obese compared to normal weight patients when dosing propofol on TBW as per label recommendations. Simulations showed that dosing on TBW, in contrast to dosing on LBW, resulted in increased plasma concentrations in the larger weight groups. This was not unexpected as maintenance dosing is dependent on CL; however, it provides a plausible explanation as to why dose individualization using TBW is unsuitable for obese patients.

Both the Full and LBW models displayed some parameter bias under the study design, despite the WinPOPT reported standard errors for the selected time points being less than 4% for fixed effects and 10.6% for random effects. Unlike D-optimality, however, NONMEM linearizes the model when using a maximum likelihood approach. The bias may have therefore been due to this linearization process in NONMEM and may have been reduced in the simulation-

Table V. Median %CV as Estimated by the Full and LBW Models from 100 Simulation-Estimation Experiments

Parameter	Simulated value	Full model	LBW model
CL	37.4	32.4	35.5
CL_2	51.9	44.9	45.4
CL_3	50.9	42.5	42.1
V_1	40.0	35.1	35.4
V_2	54.8	49.4	49.7
V_3	46.9	41.4	42.0
RUV	17.0	17.0	17.2

Table VI. NPC Results from One Example Dataset, Showing the Percentage of 'True' Data Generated from the Full Model Falling Outside the 10th to 90th Prediction Interval (PI) Simulated by Each Model at Each Time Point

		Full model		LBW model	
Time point	Time	<10%	>90%	<10%	>90%
1	End of infusion	8.6	14.6	5.1	12.1
2	4 s	7.1	12.6	4.5	9.6
3	4.9 min	7.6	16.7	8.1	15.2
4	16.4 min	5.1	10.1	6.1	8.1
5	1.2 h	8.1	13.6	6.6	10.1
6	4.3 h	10.6	10.1	8.1	8.6
7	17.9 h	9.1	13.1	7.6	9.1
	Mean %	8.0	13.0	6.6	10.4
	Total % outside PI	21.0		17.0	

An acceptable model should have ~10% true data falling below, and ~10% above, the 10th to 90th PI across all time points

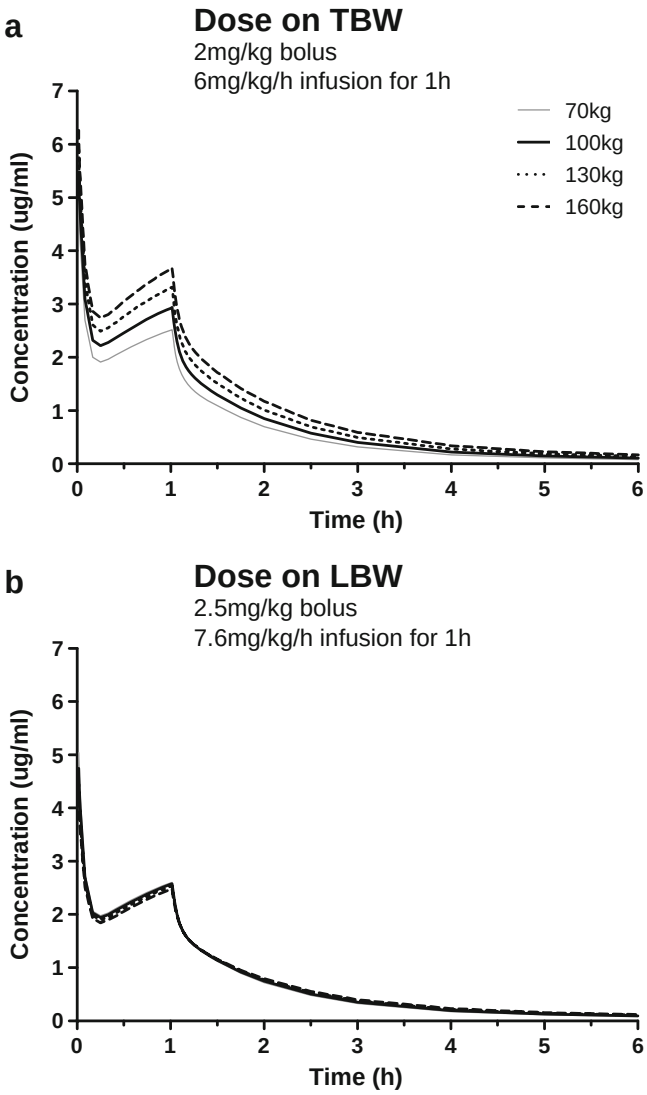

Fig. 3. Deterministic simulation showing differences in typical plasma concentrations across a range of patient weights when dosed linearly according to **a** TBW *versus* **b** LBW.

estimation experiments by increasing the number of sampling times and/or by using an estimation method that does not make the same linearization assumptions. Due to the computational intensiveness of the experiments, however, we chose to use seven time points rather than a fully saturated design which in itself is not 'sparse'. Furthermore, the version of NONMEM we used for the study (version V) does not allow use of the Laplacian method with the INTERACTION option which again could have helped minimize the bias. Nonetheless, the observed bias in both models does not detract from our finding that there was minimal loss in model performance when the original nonlinear TBW relationship on CL was substituted with a linear LBW relationship.

Under the assumption that LBW describes propofol CL, we further explored how dose individualization according to LBW could normalize patient PD responses across the weight range of 70–160 kg. The LBW dosing regimen was selected based on a 70 kg healthy weight subject (BMI of 21.6 kg m^{-2}) receiving the same dose as recommended by the label. As expected, dosing by this method decreased awakening times of the heavier weight groups to that observed in the 70 kg weight group, normalizing patient awakening times.

In clinical practice, a randomized controlled trial showed that dosing on LBW compared to conventional dosing (dosing linearly per kg TBW) for enoxaparin reduced adverse events with no apparent reduction in treatment effectiveness (33). Interestingly, this particular study also demonstrated the uncertainty physicians have when dosing their obese patients on TBW due to concerns of potential overdose, with all patients >100 kg in the conventional arm being under-dosed according to label recommendations (33). Indeed, further evidence will be required to confirm the simulation findings of our study and a prospective population PKPD study to further investigate the LBW hypothesis for propofol CL and dosing is currently underway.

The present study highlights the need for, and encourages the development of predictive models for learning. Again, we iterate that for a model to be predictive outside of the demographics from which it was derived, mechanistic covariates must be used (2). However, poor study design,

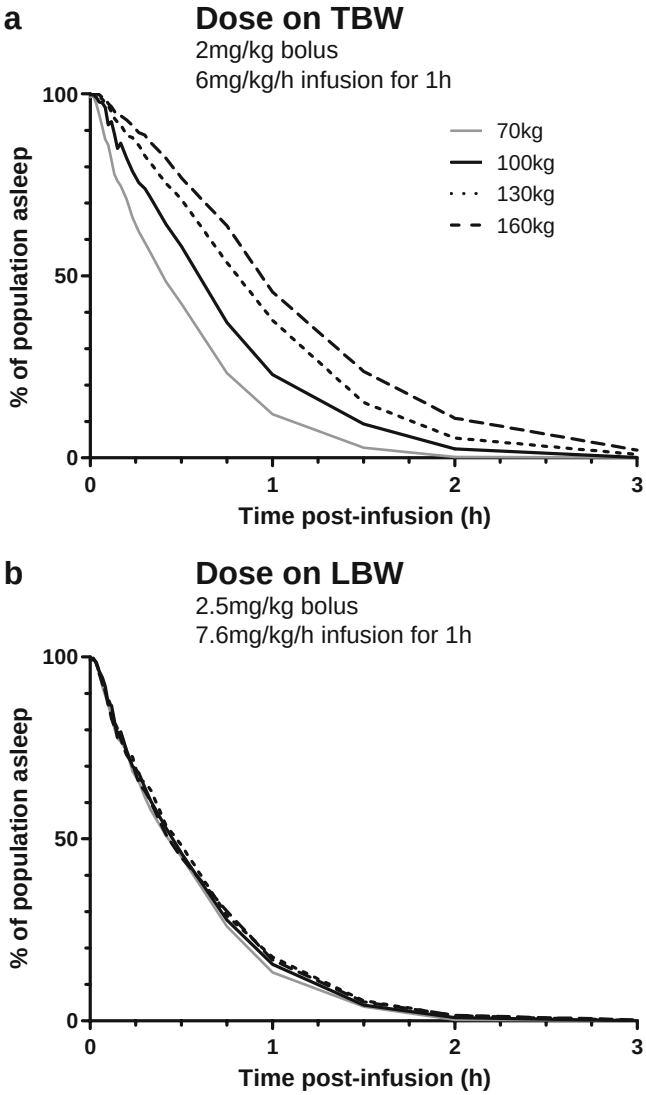

Fig. 4. Percent of population asleep, post-infusion, when dosed linearly according to **a** TBW *versus* **b** LBW.

limitations in current knowledge of biological processes, a limited record of physiological covariates in study data and homogeneous population groups can result in an inability to identify mechanistic covariates. So too can force-fitting desired covariates to PKPD data because of incorrect prior assumptions about parameter–covariate relationships or regulatory requirements *e.g.* TBW as a covariate on CL for the specific purpose of developing a TBW dosing strategy. Additionally, the statistical significance of covariates can be overstated, resulting in selection of empirical covariates, *i.e.* those which are statistically significant yet only descriptive.

The effect of the study population demographic range on the ability to discriminate between size scalars on drug CL must also be considered. Across the normal weight range (defined here as BMI of 20–25 kg m^{-2}), all common size descriptors *e.g.* TBW, LBW, BSA, TBW allometrically scaled, are in close agreement when used to scale the typical population mean value (Fig. 5a), which explains why LBW was able to sufficiently replace the original relationship between TBW and CL in the Full model.

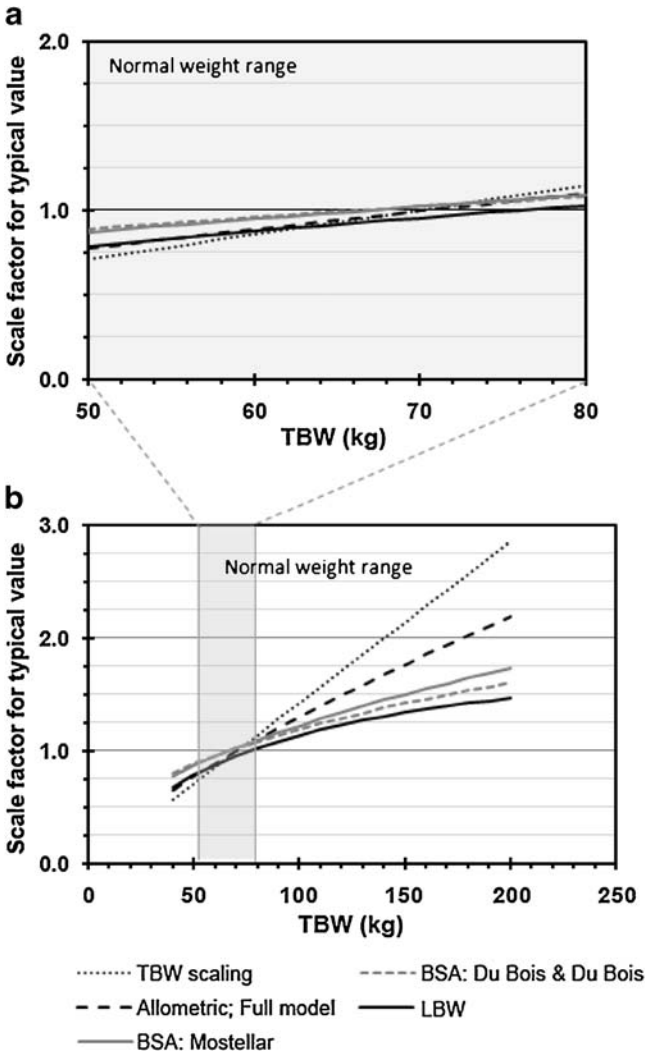

Fig. 5. Size descriptors used to scale CL in population PK models. Scaling factors determined based on a median population TBW of 70 kg and height of 180 cm. **a** Within the normal weight range (BMI 20–25 kg m^{-2}), all scale factors result in similarly scaled values of CL. **b** Beyond this range, however, they become increasingly disparate. As such, a nonlinear relationship is more easily identifiable in studies which include a wider range of subject weights. *BSA* = body surface area.

Thus, any body size metric may be found to be statistically significant for model inclusion during the covariate selection process, despite another perhaps being the 'true' covariate, *i.e.* one which might mechanistically explain variability across the whole demographic range, such as LBW. Although the resulting model will sufficiently predict within the range in which it was developed, size scalars become increasingly disparate beyond this range (Fig. 5b) and the model may not be useful for prediction outside the study population demographics *e.g.* TBW has long been thought to be a predictive covariate which can be used in a simulation setting. This concept is not disputed for subjects of normal weight. However, weight as a covariate loses its predictive ability when extrapolated into the obese population.

This has two main implications for predictive model development. Firstly, the preferential selection of a mechanistic covariate over an empirical covariate should be encouraged even at the expense of a slightly worse statistical model fit (*e.g.* higher objective function). Secondly, the ability to discriminate between covariates and hence identify a 'true' relationship may improve as the demographic range of the study group is widened, especially if a stratification strategy is employed (Han *et al.*, in press).

Due to the assumptions required for such simulation experiments, there are several limitations to this study. In clinical practice, a patient's propofol concentration on awakening may vary depending on the type of surgery, concomitant medications and age, which would increase variability in patient response. Additionally, we discounted the reported decline in CL with age >60 years in the Full model (28) by constraining the simulated study population to below 60 years. Other factors have also been suggested to affect propofol PK such as cardiac output (34) and hepatic blood flow (35,36) on distribution and CL, respectively. Nevertheless, as the aim of this study only focused on exploring variability in CL as a function of body size and composition, our results still demonstrate a possible explanation for observed increased time to awakening when obese patients are dosed on TBW. Furthermore, drug doses are most commonly scaled according to some measurement of body size and therefore our proposal to dose propofol on LBW is of practical use. We note also that many obese surgical patients can weigh significantly more than the largest weight we investigated (160 kg) and so greater differences in patient outcomes might be accounted for with LBW despite other contributing factors to PK variability.

CONCLUSION

In conclusion, we substituted a mechanistic covariate relationship for an empirically derived relationship in an attempt to enhance the predictive ability of a prior model beyond the demographic range in which it was developed. In this case, a nonlinear TBW relationship on CL in a propofol model was replaced with a hypothesized mechanistic linear LBW relationship in order to predict PK response in the obese population. Dosing simulations using this LBW model suggest that a relationship between LBW and CL may be a possible explanation as to why dosing on a TBW basis is unsuitable in the obese population. We encourage the use of

mechanistic covariates in order to enhance the future usefulness of PK models.

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