2024-03-13

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Braathen, MR

10.1111/aas.14407
ACTA ANAESTHESIOLOGICA SCANDINAVICA
Wiley

Received: 27 June 2023 | Revised: 23 February 2024 | Accepted: 26 February 2024

DOI: 10.1111/aas.14407

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Pharmacokinetics of propofol in severely obese surgical patients

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Abstract

Background: Existing PK models of propofol include sparse data from very obese patients. The aim of this study was to develop a PK model based on standardised surgical conditions and spanning from normal-weight up to, and including, a high number of very obese patients.

Methods: Adult patients scheduled for laparoscopic cholecystectomy or bariatric surgery were studied. Anaesthesia was induced with propofol 2 mg/kg adjusted body weight over 2 min followed by 6 mg/kg/h adjusted body weight over 30 min. For the remainder of the operation anaesthesia was maintained with sevoflurane. Remifentanil was dosed according to clinical need. Eight arterial samples were drawn in a randomised block sampling regimen over a span of 24 h. Time-concentration data were analysed by population PK modelling using non-linear mixed-effects modelling.

Results: Four hundred and seventy four serum propofol concentrations were collected from 69 patients aged 19–60 years with a BMI 21.6–67.3 kg/m^2. Twenty one patients had a BMI above 50 kg/m^2. A 3-compartment PK model was produced wherein three different body weight descriptors and sex were included as covariates in the final model. Total body weight was found to be a covariate for clearance and Q3; lean body weight for V1, V2 and Q2; predicted normal weight for V3 and sex for V1. The fixed allometric exponent of 0.75 applied to all clearance parameters improved the performance of the model. Accuracy and precision were 1.4% and 21.7% respectively in post-hoc performance evaluation.

Conclusion: We have developed a new PK model of propofol that is suitable for all adult weight classes. Specifically, it is based on data from an unprecedented number of individuals with very high BMI.

KEYWORDS
Anaesthetics i.v. propofol, bariatric surgery, obesity, pharmacokinetics, target-controlled infusion

Editorial Comment

This article presents a pharmacokinetic model of propofol which is suitable for normal-weight and obese adult surgical patients. The model is based on 474 blood samples collected from 69 patients aged 19–60 years undergoing laparoscopic cholecystectomy for bariatric procedures. The analysis included performance evaluation and simulations.

1 | INTRODUCTION

Obese patients presenting for general anaesthesia is no longer a rare occurrence as the prevalence of morbid obesity is increasing worldwide. By 2025 it is estimated that 6% of men and 9% of women will be severely obese—with a body mass index (BMI) > 35 kg/m^2.[1] While a patient with a BMI slightly higher than 35 kg/m^2 is not uncommon and may not be associated with anaesthetic dosing challenges, one may expect increasing problems as patients present with BMI of 50 kg/m^2 and higher.[2]

While investigators have studied the pharmacokinetics (PK) of propofol in obesity, most data sets are comprised of a small number of obese patients.[3,4] Van Kralingen et al. published a PK/PD model based on 20 patients with obesity as well as 40 lean patients from another study and found that clearance, predicted with total body weight as covariate and an allometric exponent of 0.72, was nearly the same in both populations.[5] No other covariates were identified. As with previous published models, it had a short period of sampling after the infusion has been stopped, which may have limited its utility. The models resulting from these studies have not been routinely incorporated into commercially available Target Controlled Infusion (TCI) pumps.

The widely used Marsh and Schnider pharmacokinetic models for propofol—based on data primarily from normal-weight subjects—are not inherently suitable for use in obese patients.[6,7] Therefore, clinicians may be forced to utilise weight scalars such as lean body weight (LBW) and adjusted body weight (ABW) when anaesthetising high-BMI patients with propofol TCI.[3,8]

However, TCI pumps are increasingly being programmed with the latest iteration of the Eleveld model, which is expected to gradually replace Marsh and Schnider as the model of choice in TCI pumps.[9] This model, drawing on 30 studies of patients with widely differing ages and body sizes, may eliminate the need to use different models in clinical practice. In the clinical validation study by Vellinga et al., it performed adequately and better than other models when tested in the obese population, with an imprecision of 18.3%.[10]

Still, a major limitation of the Eleveld data set is that despite comprising 1033 patients it only includes three patients with a body mass index (BMI) above 50 kg/m^2. At our centre, approximately a quarter of patients undergoing bariatric surgery over a 10-year period had a BMI > 50 kg/m^2.[11] No model exists that is built upon representative data for this population.

In the present study we aimed to build a propofol PK model based on a single, comprehensive data set spanning from normal-weight to severely obese adults.

2 | METHODS

2.1 | Patient recruitment

This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REC South East ref 1.2007.366) and registered with Clinical Trials. (identifier: NCT01536002). Patients scheduled for elective laparoscopic surgery, either cholecystectomy or bariatric procedures, were recruited after written informed consent. Male and female patients, aged 18–60 years with a BMI > 20 kg/m^2 were eligible for inclusion. Patients considered not to tolerate induction with propofol, with known hypersensitivity to propofol as well as pregnant patients were excluded.

2.2 | Anaesthesia

Patients were monitored with 5-lead ECG, pulse oximetry, capnography and bispectral index monitoring (BIS). A radial arterial line was placed, before induction of anaesthesia, for blood sampling and blood pressure monitoring.

Glycopyrronium bromide 0.2 mg iv and esomeprazole 40 mg iv were given prior to the start of general anaesthesia, which was induced with propofol 2 mg/kg adjusted body weight (ABW) administered over 2 min. ABW was calculated as follows: ABW = IBW + 0,4(TBW–IBW), where total body weight (TBW) was measured in the morning of surgery; ideal body weight (IBW) equals height in cm minus 100 for men and minus 105 for women.[3] Remifentanil effect-site TCI (Minto model) was simultaneously started at a target of 5 ng/mL dosed to TBW or as high as the pump algorithm would allow, with infusion adjustments done at the discretion of the attending anaesthesiologist throughout anaesthesia, with a BIS target of 40–60.[12] Vecuronium 0.1 mg/kg TBW was given to facilitate intubation. Immediately following the bolus infusion of propofol an infusion was maintained at a rate of 6 mg/kg/h (ABW) for 30 min before the infusion was stopped. Anaesthesia was maintained for the remainder of the operation with sevoflurane, dosed by the

attending anaesthesiologist and 100 µg fentanyl iv was administered at the end of surgery.

Eight arterial blood samples were collected from each patient according to a randomised block sampling regimen from a set of 25 time points ranging 0–1440 min from the start of anaesthesia, such that the number of total samples at every time point was the same. Blood samples were centrifuged 30–60 min after sampling. Serum samples were then stored at −82°C until analysis.

2.3 | Analysis of propofol in serum

Serum concentrations of propofol were analysed by an ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) method specifically developed for this study.

Reference standards of propofol and the internal standard propofol-d_{17} were purchased from Merck (Darmstadt, Germany) and Toronto Research Chemicals (Toronto, Canada), respectively. For the preparation of spiked standards and quality controls, blank human serum was collected from healthy medication-free blood donors. After thawing, automatic sample preparation was performed on Tecan pipetting robot (Tecan, Männerdorf, Switzerland). Aliquots of 200 µL of patient, internal standard or quality control serum and 25 µL of the internal standard propofol-d_{17} (50 µg/mL) were pipetted onto a 96-well plate (Ostro protein precipitation & phospholipid removal plate, 25 mg, Waters, Milford, MA, USA). Ice-cold acetonitrile with formic acid (1% v/v, 350 µL) was added and mixed with the sample for protein precipitation. A positive pressure unit (Positive pressure processor-96, Waters) was used to facilitate the filtration of the samples in order to reduce the content of phospholipids in the eluates. The eluates were collected in a 1-mL sample collecting well plate (Captiva 96-well collection plate, Waters) and sealed with a Captiva collection plate cover (Waters).

Separation was performed on an Acquity UHPLC I-Class FTN system (Waters) at 30°C with a Poroshell 120 C18 column (2.0 × 100 mm, 2.7 µm) (Agilent, Santa Clara, CA, USA) and an Agilent Fast Guard SB-C18 pre-column (Waters). The mobile phase consisted of 10% of a mix of 0.025% (w/v) ammonium hydroxide in water and 90% of pure methanol. The injection volume was 5 µL and total run time was 5 min. Detection was performed on a Xevo TQ-S tandem-quadrupole MS (Waters Manchester, UK). The capillary voltage was set to −4.5 kV and the desolvation gas was heated to 350°C and delivered with a flow rate of 7 L/min. Mass transitions were *m/z* 177.2 > 177.2 and 177.2 > 161.2 for propofol and *m/z* 194.4 > 174.2 for the internal standard propofol-d_{17}.

The method was validated according to the US Food and Drug Administration guidelines.[13] The limit of quantification was 5 ng/mL, and the method was linear at least up to 1000 ng/mL ($r^2 = 0.9991$ using six standards). Concentrations above 1000 ng/mL were diluted and thereafter reanalysed. Recoveries were 89%–103% at concentrations of 12.5 and 300 ng/mL. Within-day and between-day coefficients of variations were in the range of 1.5%–3.5% at concentrations of 12.5, 75 and 300 ng/mL.

2.4 | Development of the basic pharmacokinetic model

Propofol arterial serum concentration versus time data were pooled and the data used to construct a mixed-effects population pharmacokinetic model using NONMEM software (version 7.1.0; ICON Development Solutions, Ellicott City, MD, USA). A licenced version of PLT Tools (PLTSoft, San Francisco, CA, USA) was used to provide graphics, to set up and run a batch model and provide relevant statistical analyses. An Intel Visual Fortran compiler was used (Professional edition, version 11.1.048) with a Dual Xeon Quad Core E5620 2.4GHZ CPU (Intel, Santa Clara, CA) under Windows 7 Professional 64-bit. The mixed-effects approach defines a single basic model of typical values (population means) for the pharmacokinetic parameters. Variations in each individual from the basic model were defined by the use of a variable number of additional, user-defined 'inter-individual variability parameters', or Etas, each defining a degree of variability in one or more of the basic parameters. The basic parameters of the models used here were: volume of the central compartment (V1), volume of the peripheral compartments (V2 and V3), clearance (CL, elimination clearance equal to $V1 \cdot k_{10}$) and distribution clearances (Q2 equal to $V1 \cdot k_{12}$ and Q3, equal to $V1 \cdot k_{13}$). Volume of distribution at steady state (Vss) was equal to V1 plus V2 plus V3.

Models were fitted using NONMEM's first-order conditional estimation method with interaction allowed. The interaction option requests that NONMEM preserve the dependence of the model for intra-individual random error on the Etas during the computation of the objective function. Intra-individual variability was described using a log error model.

A sequential model building approach was used. The appropriateness of the structural base model and the requirement for Etas was assessed, using the likelihood ratio test (for nested models) and by consideration of the Akaike Information Criterion (non-nested models) and the precision of the final parameter estimates (all models). For nested models, the justification for each additional effect (additional parameter) was for it to improve the goodness-of-fit statistic (−2 log likelihood) by more than 3.84, evaluated against the chi-square distribution, considered equivalent to significance at the 0.05 concentration. The improvement, or lack thereof, in model goodness-of-fit was also assessed visually by the examination of diagnostic plots.

2.5 | Covariate model build

The covariate model build focused on the following body size metrics: (1) those considered by us to be more informative of the relationship between dose and concentration in the obese, (2) those reported in the literature as being significant covariates for pharmacokinetics model parameters of propofol in the obese and (3) those revealed to significantly reduce the NONMEM objective function value when evaluated using an automated covariate search (PLT Tools, version 6.0.0, D. Fisher, PLessThan, San Francisco, CA).[4,5,14] Hence, the covariate model build considered various mathematical relationships

(e.g., additive, linear, power, allometric) between the structural model parameters and: sex, age, total body weight, predicted normal weight, lean body weight, normal fat mass and three different derivations of adjusted body weight.[3,8,15–18] The equations for the aforementioned body size descriptors are as follows:

Total Body Weight: $\mathrm{TBW(kg)}$,

Body Mass Index: $\mathrm{BMI} = \frac{\mathrm{TBW}}{\mathrm{Height}^2(\mathrm{meters})}$,

Predicted Normal Weight: $\mathrm{PNWT(male)} = 1.57 * \mathrm{TBW} - 0.0183 * \mathrm{BMI} * \mathrm{TBW} - 10.5$,

$$\mathrm{PNWT(female)} = 1.75 * \mathrm{TBW} - 0.0242 * \mathrm{BMI} * \mathrm{TBW} - 12.6,$$

Lean Body Weight:

$$\mathrm{LBW(male)} = \frac{9.27 * 10^3 * \mathrm{TBW}}{6.68 * 10^3 + 216 * \mathrm{BMI}},$$

$$\mathrm{LBW(female)} = \frac{9.27 * 10^3 * \mathrm{TBW}}{8.78 * 10^3 + 244 * \mathrm{BMI}},$$

Normal Fat Mass (with fixed *Ffat* of 0.21): $\mathrm{NFM} = \mathrm{LBW} + 0.21 * (\mathrm{TBW} - \mathrm{LBW})$,

For three derivations of Adjusted Body Weight: $\mathrm{ABW} = \mathrm{TBW} + 0.4 * (\mathrm{TBW} - \mathrm{IBW})$, we evaluated using the following formulas for Ideal Body Weight:

$$\mathrm{IBW_{Devine}(male)} = \mathrm{Height(cm)} - 152.4 * 0.9055 + 50,$$

$$\mathrm{IBW_{Devine}(female)} = \mathrm{Height(cm)} - 152.4 * 0.9055 + 45.5,$$

$$\mathrm{IBW_{Lemmens}} = 22 * \mathrm{Height(cm)}^2,$$

$$\mathrm{IBW_{Broca}(Male)} = \mathrm{Height} - 100,$$

$$\mathrm{IBW_{Broca}(Female)} = \mathrm{Height} - 105.$$

2.6 | Evaluation of final pharmacokinetic model

Likelihood profiling and bootstrap simulations were used to generate 95% confidence intervals for the final pharmacokinetic model parameters. Jackknife analyses were performed to evaluate whether any one particular subject's data unduly influenced the final parameter estimates. A licenced version of PLT Tools software was used to facilitate the jackknife, bootstrap, and likelihood profile analyses, which were performed as follows:

2.6.1 | Jackknife

Multiple datasets ($n = 69$) were produced, each of which excluded one patient from the analysis, a different patient being excluded from each dataset. The final population models were applied to each dataset and the parameter estimates compared with the estimates resulting from the analysis of the entire dataset to identify any individuals who may have exerted a large influence on the final parameter values.

2.6.2 | Log-likelihood Profiling

Log-likelihood profiling is a method of estimating parameter confidence intervals that makes no assumptions regarding the symmetry of the resulted intervals. The relationship between the model parameter estimates and the NONMEM objection function value was explored by individually fixing each parameter estimate to values close to the final estimate, and then refitting the model, allowing all other parameter values to vary. The 95% confidence interval was estimated from the log-likelihood profile at 3.84 units from the minimum objective function value. When a single parameter of the full model is fixed, a decrease of 3.84 in the minimum value of the objective function is significant at $p < .05$.

2.6.3 | Bootstrap

One thousand bootstrap datasets were created by sampling the data, with replacement, from the original dataset. The final pharmacokinetic models were then fitted to each of the resulting datasets. The mean parameter values and the 2.5 and 97.5 percentiles for all were determined, and 95% confidence intervals for the parameter estimates were obtained. A prediction-corrected visual predictive check (PC-VPC) was used to evaluate model performance.[19]

2.7 | Comparative performance evaluation

The median prediction error (MdPE), median absolute prediction error (MdAPE), divergence MdPE, divergence MdAPE and wobble % were calculated for the final population pharmacokinetic model, the Marsh model, the Schnider model and the Eleveld model, as described by Varvel et al.[20]

2.8 | Simulations

Simulations were conducted using Marsh, Schnider and Eleveld 2 pharmacokinetic models applying their respective published parameters as well as those of our own model to the lowest, median and maximum weights from our study, that is, (1) Female, 30 years, 158 cm, 55 kg, (2) male, 30 years, 175 cm, 126 kg and (3) male, 30 years, 191 cm, 241 kg. Serum concentrations at an infusion rate of 6 mg/kg/h over 20 min were calculated.

3 | RESULTS

3.1 | Patient Characteristics

During a three-year period, 69 patients were included in the study, according to the inclusion criteria. There were five patients classed as normal weight (BMI 18.5–24.9 kg/m^2), six as overweight (BMI 25–29.9 kg/m^2), seven in the obesity 1 category (BMI 30–34.9 kg/m^2), nine in the obesity 2 category (BMI 35–39.9 kg/m^2) and 42 patients in the obesity 3 category (BMI ≥40 kg/m^2).[21] (Table 1) Twenty one patients had a BMI above 50 kg/m^2; 23 patients had a body weight of more than 150 kg.

3.2 | Model

The data set comprises 69 patients and 474 propofol serum concentration versus time observations. All samples were arterial, except for the last sample, taken at 24 h, from six of the patients which were drawn by venous puncture, due to failure of the arterial cannula.

We first tested models with two and three compartments. The 3-compartment model was superior as evidenced by the significant reduction in the objective function and the markedly improved diagnostic plots. Inter-individual variability parameters were added to all of the structural model parameters but could not be supported on V3.

Parameters for the final PK model are shown in Table 2. Table 3 shows model parameter estimates for two sample patients of different body weights. The prediction-corrected visual predictive check plot is shown in Figure 1 and only few observed data points are seen outside of model predictions. Diagnostic plots and the NONMEM control stream of the final model are available as supplementary digital content.

The allometric exponent of 0.75 improved the objective function for all clearances. Sex influenced the estimate of the volume of the central compartment (V1 parameter). Lean body weight (LBW) improved the objective function of V1, V2 and Q2; predicted normal weight was a covariate for V3 and total body weight for CL and Q3. Age was not found to be a significant covariate. Over a thousand candidate models were evaluated, Table 4 describes the NONMEM objective function value, and the Akaike Information Criteria for the major stages of the model, that is, each time a covariate was selected and added to the model.

TABLE 1 Patients' characteristics. Values are mean, SD (range).

	(*n* = 69)
Age (years)	40.4 SD 10 (19–60)
Sex (male/female) (*n*)	30/39
Weight (kg)	131.5 SD 40.6 (55–241)
Height (cm)	173.3 SD 10.1 (152–195)
BMI (kg/m^2)	43.4 SD 11.7 (21.6–67.3)
Bolus dose propofol (mg)	197 SD 46 (106–323)
Total dose propofol (mg)	475 SD 105 (266–774)

TABLE 3 Propofol population pharmacokinetic parameter estimates for 2 women of 170 cm.

	70 kg		160 kg	
Parameter	Estimate	95% CI	Estimate	95% CI
V1 (L)	4.21	2.78–6.97	6.34	4.19–10.49
V2 (L)	44.5	39.6–50.2	67.0	59.6–75.6
V3 (L)	672	251–1201	611	250–1095
CL (L/min)	1.24	1.18–1.31	2.31	2.20–2.43
Q2 (L/min)	0.92	0.80–1.03	1.25	1.09–1.40
Q3 (L/min)	0.39	0.35–0.42	0.72	0.66–0.79

TABLE 2 Parameter estimates for the final pharmacokinetic model.

Theta	Parameter	Typical Value	CV %	Bootstrap mean	Bootstrap 95% CI		Jackknife mean	Likelihood Profiling 95% CI	
1	CL L/min	1.964*(WGT/129)**0.75	16.6	1.961	1.868	2.071	1.964	1.874	2.061
2	V1 L (Male)	3.863*(LBW/65.1)**1	49.7	3.970	2.968	5.191	3.882	2.926	5.297
3	Q2 L/min	1.230*(LBW/65.1)**0.75)	28.2	1.222	1.068	1.381	1.228	1.098	1.376
4	V2 L	65.585*(LBW/65.1)	23.1	66.279	58.330	73.976	65.765	59.299	73.802
5	Q3 L/min	0.611*(WGT/129)**0.75	16.4	0.615	0.561	0.672	0.611	0.565	0.659
6	V3 L	305.111*(PNWT/78.5) + THETA(8)	.-	302.891	3.454	526.531	304.150	56.208	531.702
7	V1 L (Female)	6.200*(LBW/65.1)**1	49.7	6.682	4.103	10.267	6.244	4.633	9.239
8	. + V3 L	404.821	.-	429.069	247.470	739.005	408.329		
Intraindividual error %									
Sigma	0.0402291	20.1							

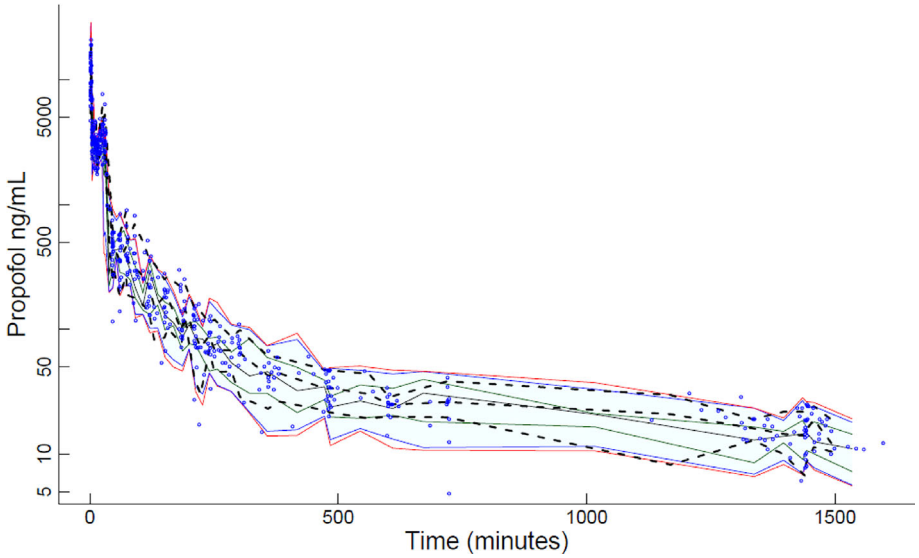

FIGURE 1 Prediction-corrected visual predictive check (PC-VPC) plot of the new model, all groups. The shaded area indicates 90% confidence interval; Solid lines indicate percentiles: 2.5, 97.5 (red); 5, 95 (blue); 25, 75 (green); 50 (black). Dashed lines indicate percentiles 5, 50 and 95 of observations.

TABLE 4 Goodness of fit criteria at the major stages of the PK model build.

		Objective function value	Akaike information criterion
Model 1	Base model (3 compartments, no covariates)	4767.21	4791.21
Model 2	As model 1 plus weight on clearance, allometric	4727.78	4751.78
Model 3	As model 2 plus weight on Q3, allometric	4688.85	4712.85
Model 4	As model 3 plus LBW on V1, allometric	4676.43	4700.43
Model 5	As model 4 plus LBW on V2	4664.71	4688.71
Model 6	As model 5 plus LBW on Q2, allometric	4649.68	4673.68
Model 7	As model 6 PNWT on V3, linear	4645.49	4671.49
Model 8	As model 7 plus SEX on V1	4640.79	4668.79

3.3 | Evaluation of final pharmacokinetic model

Figure 2 demonstrates population and individualised model fits for the best fit, a typical individual, and the worst fit. Eta versus weight plots are shown in Figure 3 and goodness of fit plots in Figures 4 and 5. All individual plots, diagnostic plots and likelihood profiles are available as Supplementary digital files 2 and 3. The prediction of propofol serum concentrations, based on the typical pharmacokinetic parameter values of the new model, demonstrated a median prediction error (reflecting model bias) of 1.4% and a median absolute prediction error (a measure of model precision) of 21.7%. The PK models of Marsh, Schnider and Eleveld were also validated on our data set and the results of the Varvel analysis are presented in Table 5. The Eleveld model showed the second-best performance metrics with both bias and precision of 26.73%.

3.4 | Simulations

Figure 6 shows simulated propofol concentration profiles predicted by four pharmacokinetic models in three different patients from our data set during an infusion of propofol, at a rate of 6 mg/kg/h for 20 min. For the heaviest patient of 241 kg the peak propofol concentration (at 20 min infusion time) was 4.43 μg/mL for our (Braathen) model, 3.15 μg/mL for the Eleveld model, 2.20 μg/mL for the Schnider model and 1.97 μg/mL for the Marsh model. Forty minutes after stopping the infusion the predicted propofol concentration was 0.36 ng/mL for Eleveld, 0.25 μg/mL for Braathen, 0.22 μg/mL for Marsh and 0.04 μg/mL for Schnider.

4 | DISCUSSION

Under highly standardised surgical conditions we have derived a PK model to predict serum concentrations of propofol based on a single, comprehensive data set spanning from normal-weight to severely obese adult surgical patients. Crucially, the data set—which was collected from 69 patients—includes a large number of patients of very high BMI. The covariate analysis showed that our new model requires three different body size descriptors in order to best predict compartment volumes and clearances. Employing allometric exponents of 0.75 for clearances further improved the model fit. The final model exhibited less bias and better precision than currently used models, when tested in a post-hoc evaluation

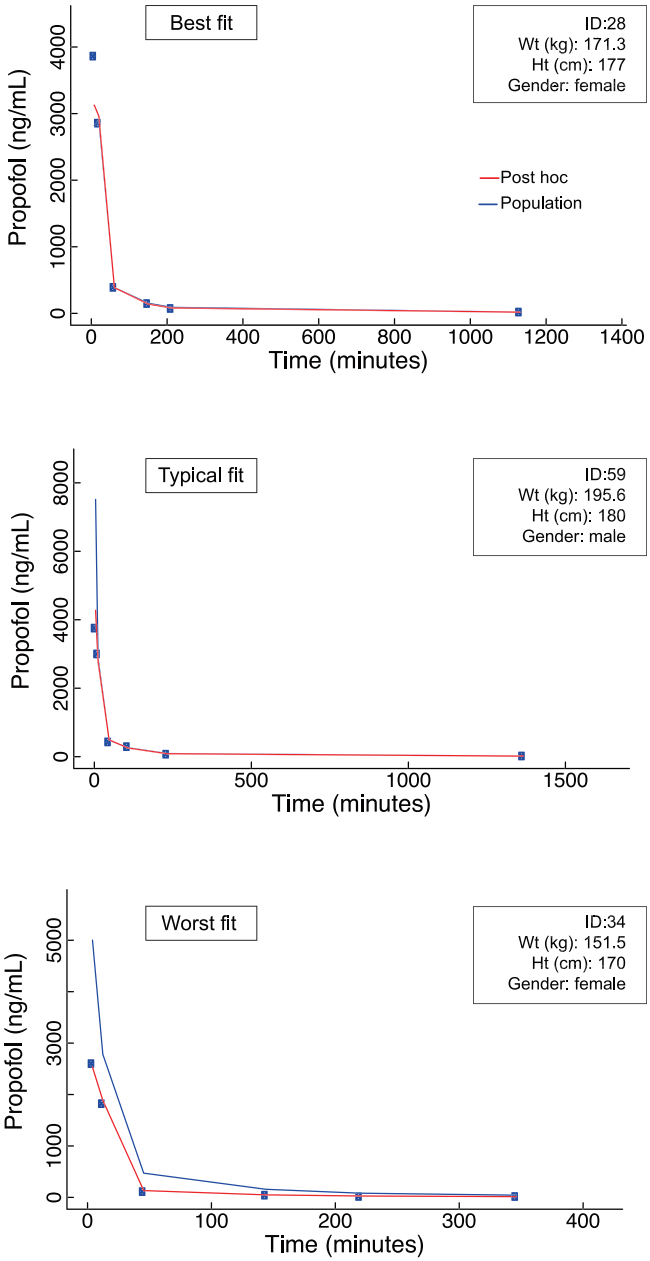

FIGURE 2 Population and individualised model fits for the best fit, a typical individual and the worst fit.

on the same data set. A bias of up to 20% and an imprecision of 20%–40% are considered acceptable for clinical use.[22] Our new model fulfils these criteria, as the median prediction error (reflecting model bias) was 1.4% and the median absolute prediction error (a measure of model precision) was 21.7%. However, it is acknowledged that an appropriately built kinetic model will always describe the data that it is derived from well and that applying the model to an external data set is the true test.

Propofol is one of the drugs having underwent the highest number of population analyses.[23] However, in the case of obese patients there is much uncertainty and we still—after 30 years of commercially available TCI algorithms—mostly use weight scalars to modify PK models derived from predominantly normal-weight patients.[24] There have been published studies on the PK of propofol in obese subjects, but no single work has collected materials from more than 20 patients, and few subjects were severely obese.[3–5] Van Kralingen et al. did include 20 patients in their study with a mean body mass index of 43 kg/m^2 but did not take arterial concentration samples later than 150 min after the end of the propofol infusion, which may result in lower predicted distribution volume and shorter elimination half-life.[25] Cortinez et al. published a PK/PD model based on previous propofol studies that was prospectively tested against other models.[26] This model cannot be used in lean patients and did not perform as well as the Eleveld model in the performance evaluation on obese patients. Eleveld et al have attempted to solve the issue of scarce data in certain patient categories by pooling several data sets into a general-purpose PK/PD model for propofol.[9] This model was nevertheless developed with sparse numbers of very obese patients, despite incorporating data sets from Servin's and Cortinez's studies. Examination of the data set sent to us by prof. Eleveld reveals three patients with a BMI > 50 kg/m^2, compared to 21 patients in our data set. In terms of TBW, the Eleveld data set has only a single patient >150 kg, whereas we have included 23 such patients in our study. The aim of making a general-purpose model for all populations is based on a hypothesis that we may limit practitioner mistakes in choosing the correct TCI model for each patient. This potential advantage may, however, be negated if the if the patient demographics which originated the model is not representative of the patient we wish to anaesthetise. While using NONMEM, sparse data from various studies with different populations and different sampling regimens may enhance covariate identification, but this technique may also potentially introduce unknown confounders in the model building. Therefore, we believe the optimal way of constructing a PK model is to collect samples from a large number of patients with a wide range of body sizes from normal-weight to BMI > 60 kg/m^2 in the same study.[26,27] This becomes apparent in the present study where our model has a better fit compared to the one of Eleveld, when tested post hoc on the same data set. A comparison of patient body size characteristics in the Eleveld data set and the current study is presented in Table 6.

In our study nearly all samples were arterial samples, drawn according to a randomised block sampling regimen from as little as 1 min after start of induction and up to 24 h after induction, in order to properly characterise the early and late kinetics.

As seen in Table 2, three different body size metrics were included as covariates in the model and the current most widely accepted derivation of lean body mass was used to modify V1, V2 and Q2.[8] Predicted normal weight was the best predictor of V3, whereas total body weight was the best predictor for CL and Q3. Fat free mass and derivations of adjusted body weight were not supported as model covariates. Allometric scaling using exponents of 0.75 for clearance parameters, and 1 for volumes was supported. Notably, these fixed parameter exponents resulted in a better model fit than when the power exponents were unfixed, that is, when estimated as part of the modelling building process. The matter of applying an allometric exponent to extrapolate metabolic processes with increasing body size has

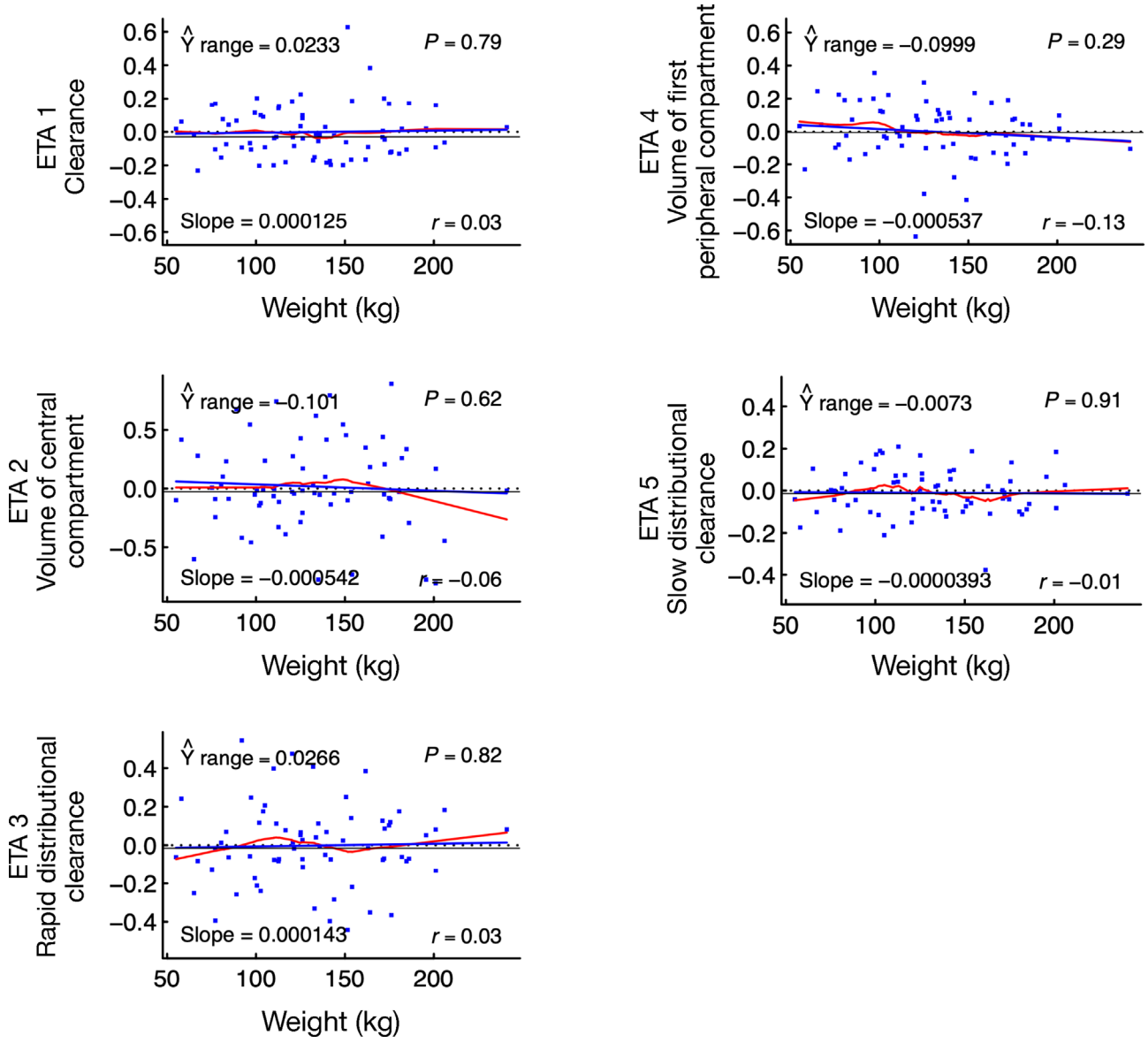

FIGURE 3 Post-hoc Etas versus weight. Blue lines indicate linear regression; red lines indicate supersmoother; black lines are median. *r* and *p* values are derived by linear regression.

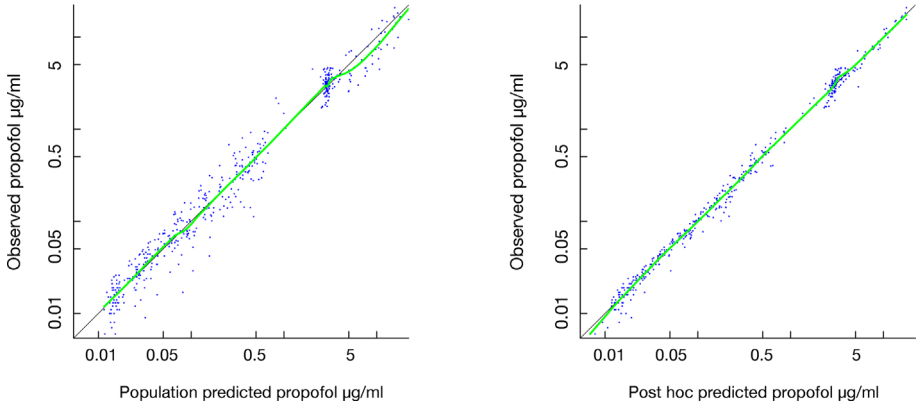

FIGURE 4 Goodness of fit plots showing population predictions and post hoc predictions of the final model versus observed propofol serum concentrations. Black is the line of unity; green indicates supersmoother.

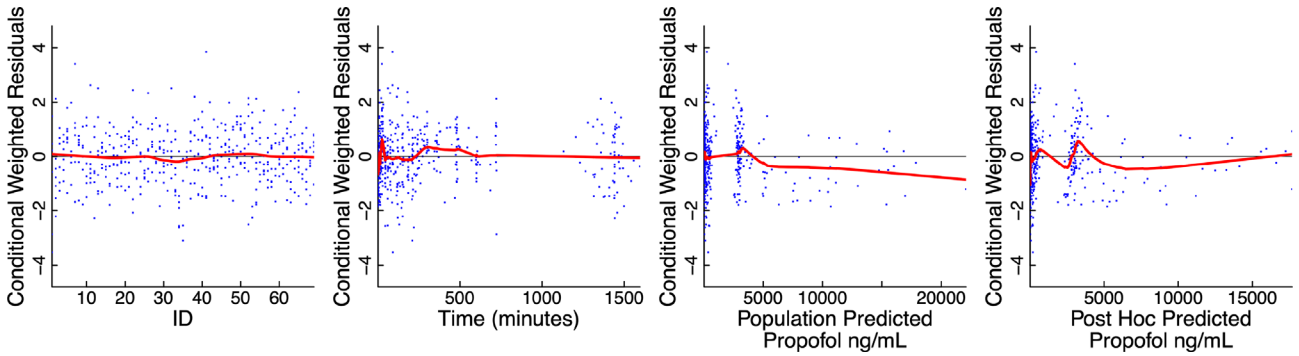

FIGURE 5 Goodness of fit plots of conditional weighted residuals versus study subjects, time and population and post hoc predictions. The red line is a supersmoother.

TABLE 5 Performance evaluation: Applying four pharmacokinetic models to our data set.

Model	MDPE	MDAPE	Divergence PE%/h (95% CI)	Divergence APE%/h (95% CI)	Wobble % (25th to 75th percentile)
Braathen	1.42	21.73	0.0067 (−0.0128–0.0262)	−0.0049 (−0.0354–0.0246)	13.2 (9.14–20.18)
Marsh	52.91	54.11	0.0353 (0.0320–0.0387)	0.0374 (0.0339–0.0408)	34.2 (22.6–54.7)
Schnider	111.19	111.19	0.0055 (0.048–0.0061)	0.0055 (0.0048–0.0061)	69.7 (31.7–145.4)
Eleveld	26.73	26.73	51.99 (47.04–56.16)	50.99 (46.46–55.52)	25.5 (16.8–35.9)

been extensively discussed over time, in recent years in conjunction with PK models for anaesthetic agents.[28–31] It has been argued by some to be an unscientific approach to describe pharmacokinetic parameters or an unnecessarily cumbersome calculation. Still, as a multi-compartment model may not be practically used unless incorporated into a computerised TCI pump, this should not be a problem.

The predicted V3 values in the new model are higher than those determined in earlier studies—that is, 672 litres in a 70 kg woman of 170 cm. This may be due to serum being sampled as late as 24 h in every study subject. Campbell et al have previously demonstrated the influence and importance of extended sampling times in order to prevent bias in calculation of pharmacokinetic parameters.[25] In particular, shorter sampling times such as the 10- and 8-h final sampling times of the Schnider and Gepts data sets (which the Marsh model was based on), are prone to negatively biased elimination half-times and distribution volumes.[32] Clearance will tend to be higher in studies with shorter sampling times.

One methodological limitation of our study may be that some arterial serum samples were drawn during the initial rapid propofol bolus infusion, over the first 2 min. As demonstrated by Major et al., sampling within 60 s after a bolus dose can result in artefactually high measured concentrations.[33] This may account for why the clearance predicted by our model is lower than those found in, that is, Schnider, Marsh and Eleveld models. This is a plausible explanation for the high propofol concentrations displayed by our model in the infusion simulation and this new model may thus be expected to administer comparatively lower doses during the induction phase of a plasma-controlled TCI. Additionally, the predicted clearance which is lower than published in several previous studies may be due to the extended serum sampling times, as discussed above.

The relatively short duration of 30 min fixed infusion in our study is likely too short in order to achieve steady-state concentrations of propofol and, moreover, is not in accordance with the practical clinical TCI dosing. This may have affected calculation of certain pharmacokinetic parameters, in particular those describing late distribution and elimination. However, for the purpose of modelling we considered a 30 min fixed infusion to be adequate and more consistent to handle. Serum concentration sampling was done up to 24 h in order to improve modelling accuracy and better describe the terminal kinetics.

We refrained from pharmacodynamic modelling in this study, for several reasons. First, it is well known that remifentanil influences BIS levels in the presence of propofol; dynamic endpoints may also be hard to define exactly.[34,35] In the present study we were unable to address these issues in any meaningful way, because our patients were due for surgery within a short time after induction of anaesthesia and in addition might need adjustable opioid supplements. The attending anaesthesiologist was therefore allowed to administer remifentanil at his or her discretion. Second, previous studies have shown that the effect of obesity on the k_e0 or on the relationship of propofol concentration to BIS is not likely to be clinically relevant.[36] Finally, PK models have previously been successfully adapted retrospectively to effect-site TCI models. That is, for the so-called modified Marsh model, the k_e0 was adapted and published 9 years after the original PK model was published.[37] Integration of dynamic parameters into our plasma model may be a subject for further investigations.

We reiterate that the performance evaluation and simulations were performed on the same data which generated the model and should thus be interpreted with caution.

Prospective evaluation on an independent data set together with other relevant PK models should be done prior to employing the

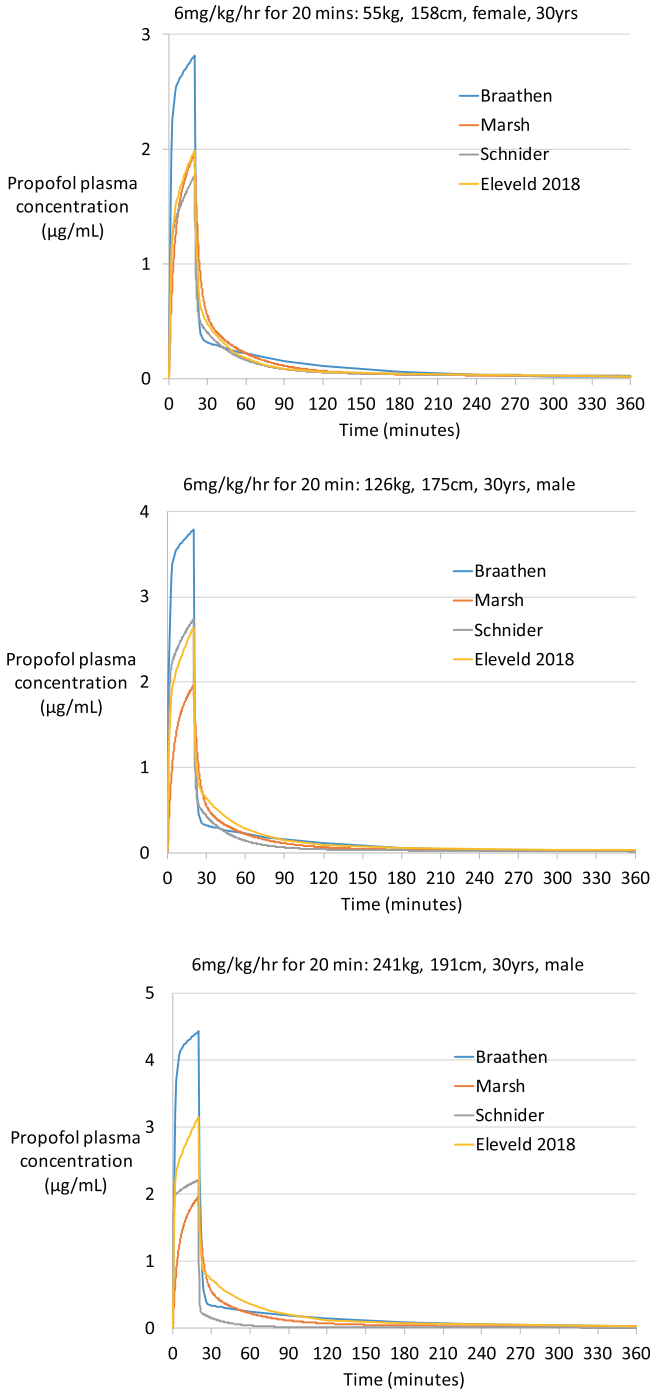

FIGURE 6 Simulated propofol concentration profiles predicted by 4 PK models, including the new model, in three different patients.

TABLE 6 Numbers of patients, within various weight categories, contributing data to the Braathen and Eleveld data sets.

	Eleveld	Braathen
Weight > 130 kg	4	34
Weight > 150 kg	1	23
Weight > 170 kg	0	16
BMI > 40 kg/m^2	25	42
BMI > 50 kg/m^2	3	21
BMI > 60 kg/m^2	0	5

model in clinical use. The performance statistics do, however, suggest that that the model is appropriate for propofol concentration predictions in both normal-weight and obese adult surgical patients.

AUTHOR CONTRIBUTIONS

TH designed the study. ARJ did statistics and NONMEM. OS did mass spectrometry. MB carried out the clinical part of the study, collected serum samples and wrote the first draft of the manuscript. JR collected serum samples and edited the manuscript. All contributed in the writing of the manuscript.

ACKNOWLEDGEMENTS

We are grateful to professor Robert Sneyd for valuable discussions and support throughout the analytical and writing phases of this project. We extend sincere thanks to professor Douglas Eleveld for assistance with simulations of the Eleveld pharmacokinetic model. We are indebted to the anaesthetic nursing staff, including Ragnhild Heltberg, Gerd Norunn Sveen and Ingrid von Zernichow as well as PACU nurses and fellow anaesthesiologists at Aker Hospital for their enthusiasm. Special thanks to Drs. Ingrid Schage Førde, Amund Formo, Theresa Mariero Olasveengen and Lene Fries for assisting with serum sampling. We acknowledge director Jon Kristinsson and the Dept. of Morbid Obesity and Bariatric Surgery for facilitating our work. We thank head of the department of anaesthesiology Dr. Anne Bøen for her patience and unwavering support.

FUNDING INFORMATION

Support was provided entirely by departmental sources.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Study data are available for review upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Braathen MR, Rigby-Jones AE, Ræder J, Spigset O, Heier T. Pharmacokinetics of propofol in severely obese surgical patients. *Acta Anaesthesiol Scand*. 2024;1-11. doi:10.1111/aas.14407