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Effect-Site Target-Controlled Infusion in the Obese: Model Derivation and Performance Assessment

Luis I. Cortínez, MD,* Pablo Sepúlveda, MD,† Augusto Rolle, MD,* Pauline Cottin, PharmD,‡ Alexandre Guerrini, PhD,‡ and Brian J. Anderson, PhD, FANZCA§

BACKGROUND: The aim of this study is to derive a propofol pharmacokinetic (PK) pharmacodynamic (PD) model to perform effect-site target-controlled infusion (TCI) in obese patients, and to analyze its performance along with that of other available PK models.
METHODS: In the first step of the study, a 3-compartment PK model linked to a sigmoidal inhibitory E_{max} PD model by a first-order rate constant (keo) was used to fit propofol concentration–bispectral index (BIS) data. Population modeling analysis was performed by nonlinear mixed effects regression in NONMEM (ICON, Dublin, Ireland). PK data from 3 previous studies in obese adult patients (n = 47), including PD (BIS) data from 1 of these studies (n = 20), were pooled and simultaneously analyzed. A decrease in NONMEM objective function (ΔOBJ) of 3.84 points, for an added parameter, was considered significant at the 0.05 level. In the second step of the study, we analyzed the predictive performance (median predictive errors [MDPE] and median absolute predictive errors [MDAPE]) of the current model and of other available models using an independent data set (n = 14).
RESULTS: Step 1: The selected PKPD model produced an adequate fit of the data. Total body weight resulted in the best size scalar for volumes and clearances (ΔOBJ, −18.173). Empirical allometric total body weight relationships did not improve model fit (ΔOBJ, 0.309). A lag time parameter for BIS response improved the fit (ΔOBJ, 89.593). No effect of age or gender was observed. Step 2: Current model MDPE and MDAPE were 11.5% (3.7–25.0) and 26.8% (20.7–32.6) in the PK part and 0.4% (−10.39 to 3.85) and 11.9% (20.7–32.6) in the PD part. The PK model developed by Eleveld et al resulted in the lowest PK predictive errors (MDPE = <10% and MDAPE = <25%).
CONCLUSIONS: We derived and validated a propofol PKPD model to perform effect-site TCI in obese patients. This model, derived exclusively from obese patient's data, is not recommended for TCI in lean patients because it carries the risk of underdosing. (Anesth Analg 2018;127:865–72)

KEY POINTS

- **Question:** Can we derive a dedicated propofol model to improve effect-site target-controlled infusion in obese patients?
- **Findings:** A weight proportional effect-site model was derived and validated in an independent data set.
- **Meaning:** The new model is a good alternative to perform effect-site target-controlled infusion in obese patients (body mass index >35 kg/m^2).

The application of propofol target-controlled infusion (TCI) in morbidly obese patients poses several problems.[1] The most important one for clinicians is the absence of a validated model for obese patients in currently available TCI pumps. Traditional pharmacokinetic (PK) or pharmacokinetic pharmacodynamic (PKPD) models used in TCI were not derived from obese patients[2,3] and observations in obese patients revealed that these models had poor predictive ability and a tendency to overdose.[1,4,5] Dose corrections based on adjusted body weight (ideal weight +40% of excess weight) have been proposed to improve the performance of these models in obese patients.[5]

Newer propofol PK parameter sets have been derived with data from obese patients.[6–8] Those models, however, were derived using data that also included nonobese subjects[6,8] or included children.[7] The inclusion of disparate patients improves the characterization of covariate effects and therefore should be able to allow propofol dose prediction in differing populations. It is also possible, however, that confounders coming from a more variable population or clinical scenarios may limit their predictive performance within certain patient groups. When prospectively tested in obese patients, these models had a marked tendency to under estimate propofol concentrations.[5] The parameter set estimated by Eleveld et al[7] ("the Eleveld model" study in which we collaborated with data and coauthorship) was the

From the *Department of Anaesthesiology, Pontificia Universidad Católica de Chile, Santiago, Chile; †Servicio de Anestesia, Clínica Alemana Universidad del Desarrollo, Santiago, Chile; ‡BU Application Devices, Fresenius Kabi, Brézins, France; and §Department of Anaesthesiology, University of Auckland, Auckland, New Zealand.

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Address correspondence to Luis I. Cortínez, MD, Department of Anaesthesiology, Pontificia Universidad Catolica de Chile, Marcoleta 377, 4th Floor, Santiago, Chile. Address e-mail to licorti@med.puc.cl.

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only 1 with predictive errors within acceptable limits for plasma-targeted TCI.[5]

General purpose models may be too complex for commonly used TCI pumps and a simplified model for obese patients derived exclusively from data taken from obese patients only may be better suited. Whether a dedicated model might show better predictive performance in the obese than currently available general purpose models is not known. A dedicated model, however, has the advantage of a simpler structure, since characterizing the effect of multiple covariates becomes unnecessary, and therefore may favor its understanding and implementation in the clinical scenario.[9] In addition, if a dedicated model is also derived with propofol effect data, it will allow its use in effect-site TCI mode which is a more rational approach than plasma target and allows a more precise control of the effect[4]: a limitation of some models that characterize PK only rather than integrate PK with PD (ie, PK only rather than PKPD).

Because there are no dedicated PKPD models available for TCI in obese patients, the development of such a model would be of great interest for clinical practice. The aim of this study is to derive a dedicated propofol PKPD model to perform TCI in obese patients and to assess its performance along with that of 3 other currently available PK parameters sets (models).

METHODS

Step 1: Derivation of a PKPD Model

Data from 3 sources were used in the analysis.

Study 1 (PK Only)

Servin et al[10] studied 8 morbidly obese patients, aged 25–66 years, and weighing 97–169 kg, anesthetized with a stepwise infusion regimen of propofol 21 mg·kg^{-1}·hour^{-1} for 5 minutes, 12 mg·kg^{-1}·hour^{-1} for 10 minutes, and 6 mg·kg^{-1}·hour^{-1} for the remainder of the procedure. A corrected weight formula was used to adjust the dose. Adjusted body weight = ideal weight or lean body mass + (0.4 × excess weight). Excess weight is total body weight (TBW) − ideal weight or lean body mass. Samples of 2.5 mL of arterial blood were taken at 0, 2, 5, 10, 15, 20, 25, 30, 45, 60, 75, 105, 120 and every 15 minutes until infusion was stopped. Thereafter samples were taken at 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, 420, and 480 minutes. Blood was assayed for propofol using high-performance liquid chromatography (HPLC). The lower limit of quantification (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.[11]

Study 2 (PK Only)

We previously studied 19 American Society of Anesthesiologists physical status II–III obese patients, aged 28–56 years and weighing 82–134 kg, scheduled for elective bariatric surgery.[6] Anesthetic induction was with a single propofol (1%) bolus of 2 mg·kg^{-1} at a rate of 20 mL·minute^{-1}. Decreasing infusion schemes of 10–8–6–5 mg·kg^{-1}·h^{-1} during 5–20–40–120 minutes were given, respectively. All doses were based on TBW. Remifentanil was adjusted during surgery to maintain cardiac rate and arterial blood pressure within 20% of basal values. Arterial blood samples (4 mL) were taken at 1, 3, 5 minutes after the propofol bolus, every 10–20 minutes during propofol infusion, and every 10–30 minutes for 2 hours after stopping propofol. HPLC was used for propofol assay. The LLOQ of propofol in plasma was 0.025 μg·mL^{-1}.

Study 3 (PK and PD Data)

We previously investigated 20 obese patients (body mass index [BMI] >35 kg/m^2), aged 21–53 years, weighing 85–141 kg scheduled for elective laparoscopic bariatric surgery.[3] Propofol administration was by TCI and adjusted to maintain bispectral index (BIS) values between 40 and 60. Remifentanil 0.3 μg·kg^{-1} minute^{-1} was administered during maintenance. Arterial blood samples for propofol assays were collected at 2, 5, 10, 30, 60, 90 minutes, at 2 and 5 minutes after new targets were set, and at 0, 2, 5, 10, 15, 30, 60, 120 minutes after stopping drug infusion. HPLC was used for propofol assay. Plasma propofol LLOQ was 0.1 μg·mL^{-1}. BIS data from this study were recorded every 15 seconds and used to derive the PD parameter estimates.

Modeling Analysis

All the PK data from studies 1 and 2 and the PKPD data from study 3 were pooled and analyzed using a simultaneous PKPD modeling approach in NONMEM. In this method, the PK and PD parameters and their variability are jointly estimated in the same step.[12]

A 3-compartment mammillary model was used to describe propofol PK (Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/C239). This model was parameterized with: V1 (central compartment), V2 (rapidly-equilibrating peripheral compartment), V3 (slowly-equilibrating peripheral compartment), Cl (elimination clearance), Q2 (distribution clearance between V1 and V2), and Q3 (distribution clearance, between V1and V3).

TBW and normal fat mass (NFM)[13] were tested as size scalars for volumes and clearances. NFM partitions TBW into fat-free mass (FFM) and a fraction of fat mass (Ffat) calculated from TBW minus FFM (Equations 1, 2). Ffat reflects the role of fat (TBM minus FFM) as a size driver for changes in volumes and clearances in addition to FFM.[13]

$$\mathrm{NFM} = \mathrm{FFM} + \mathrm{Ffat} \cdot (\mathrm{TBW} - \mathrm{FFM}) \quad (1)$$

$$\mathrm{FFM} = \mathrm{WHS}_{\max} \cdot \mathrm{HT}^2 \cdot \left[\mathrm{TBW}\left(\mathrm{WHS}_{50} \cdot \mathrm{HT}^2 + \mathrm{TBW}\right)\right], \quad (2)$$

where $\mathrm{WHS}_{\max}$ is the maximum FFM for any given height (HT, m) and WHS_{50} is the TBW value when FFM is half of $\mathrm{WHS}_{\max}$. For men, $\mathrm{WHS}_{\max}$ is 42.92 kg·m^{-2} and WHS_{50} is 30.93 kg·m^{-2} and for women $\mathrm{WHS}_{\max}$ is 37.99 kg·m^{-2} and WHS_{50} is 35.98 kg·m^{-2}.[14]

An effect compartment model (Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/C239) was used to characterize the time delay between propofol plasma concentrations (Cp) and BIS response. This model was parameterized with a single parameter keo, the plasma effect-site equilibration rate constant (Equation 3).

$$\frac{\mathrm{dCe}}{\mathrm{dt}} = \mathrm{keo} \times (\mathrm{Cp} - \mathrm{Ce}), \quad (3)$$

where Ce is the predicted propofol effect-site concentration.

A sigmoidal E_{max} model was used to fit BIS response data (Equation 4).

$$\text{BIS} = E_0 + (E_{max} - E_0) \cdot \frac{\text{Ce}^{\gamma}}{\text{Ce}^{\gamma} + \text{Ce}_{50}^{\gamma}} \quad (4)$$

E_0 is the awake BIS value, before propofol administration; E_{max} is the BIS value at the maximum drug effect, which in this study was assumed to be BIS = 0. Ce_{50} is the effect-site concentration eliciting half of $E_{max,}$ and γ is the coefficient describing the steepness of the concentration–response curve.

The model parameters were estimated with NONMEM 7. 3 (ICON Development Solutions, Ellicott City, MD). Modeling details are presented in the NONMEM control file (Supplemental Digital Content 8, Document, http://links.lww.com/AA/C274). Between-individual population parameter variability was modeled using an exponential model (Equation 5).

$$\text{Pi} = P_{GRP} \times e^{\eta i}, \quad (5)$$

where Pi is the parameter value in the *i*th patient, P_{GRP} is the group value of the parameter after accounting for predictable differences accounted by size in the population, and η is a random variable with a mean of 0 and variance of ω2. Residual unidentified variability was modeled with a proportional error model for the PK data and an additive error model for the PD part.

The minimum value of the objective function [−2·log-likelihood (−2LL)] provided by NONMEM served as a guide during model building. For 2 nested models, a decrease in the minimum value of the objective function (ΔOBJ) of 3.84 points for an added parameter was considered significant at the 0.05 level. Traditional measured versus predicted plots and prediction corrected visual predictive check (PC-VPC) plots[15] were used to assess the adequacy of model fit. In PC-VPC plots, observations and simulations are normalized by a correction factor (population baseline value divided by the individual-estimated baseline). PC-VPC analysis was performed using wings for NONMEM.

Results from the final population model are presented as parameter estimates, together with their 95% confidence interval (CI). To compute the CIs of parameter estimates, a bootstrap of 1000 new datasets was performed with the program wings for NONMEM. Between-individual population parameter variability is expressed as an apparent coefficient of variation obtained from the square root of the variance estimate [CV (%)].

Step 2: Performance Assessment

This study was registered in ClinicalTrials.gov (NCT01665079).

After institutional research and ethic committee approval (School of Medicine, Clínica Alemana, Universidad del Desarrollo, Santiago, Chile) and written informed consent, another 14 obese patients (BMI >35 kg m^2), American Society of Anesthesiologists physical status II, aged 20–60 years, who were scheduled for elective laparoscopic bariatric surgery, were prospectively studied. Recruitment was made between April and November 2011. Exclusion criteria were patients with allergy to study drugs, uncontrolled hypertension, heart block greater than first degree and those who had taken any drug acting on the central nervous system within 24 hours before surgery. In the operating room, noninvasive monitoring of arterial pressure, electrocardiogram, and pulse oximetry were initiated using the Datex AS3 monitor (Datex, Helsinki, Finland). The BIS (BIS monitor [version XP], Medtronic, Dublin 2, Ireland) was used to assess propofol hypnotic effect. The smoothing time period of the BIS monitor was set at 15 seconds. The QUATRO BIS sensor electrodes were placed per manufacturer recommendations.

One 20-gauge intravenous line was inserted in the forearm for drugs and fluid administration. The propofol infusion line was connected as close to the intravenous catheter as possible to minimize dead space. Intravenous (18-gauge) and radial artery cannulas (20-gauge) were placed under local anesthesia for blood sampling. Propofol was administered by plasma TCI, using the Cortínez PK model[6] with a Fresenius Modular DPS infusion pump connected to a Fresenius Base A (Fresenius Vial Infusion System, Brézins, France). The AnestFusor Pro Series II TCI software (School of Medicine, Universidad de Chile) was used to control the infusion pump, through a multiple RS232 interface installed in a laptop computer.

A bolus dose of propofol was first given by setting the initial plasma target between 12 and 16 $\mu g \cdot mL^{-1}$. The target selected aimed to induce a moderate depth of hypnosis to maintain airway patency and spontaneous ventilation avoiding airway manipulation during the BIS data collection period. The model used in this study gives a bolus dose of approximately 1.2 $mg \cdot kg^{-1}$ (TBW) in a typical obese patient if a plasma target of 14 $\mu g \cdot mL^{-1}$ is set. We arbitrarily allowed the attending anesthesiologist to select targets of 14 ± 2 $\mu g \cdot mL^{-1}$ based on their assessment of the risk of airway obstruction. After the patients reached the induction target, propofol infusion was stopped until the patients awoke (BIS >75). The rational for this induction-recovery transition period is that both contain relevant information to estimate the keo and PD parameters. No other drugs were given during this period. Facemask ventilation was assisted only if necessary to maintain pulse oximetry (Spo_2) >90%. Immediately after the patient awoke (BIS >75), propofol infusion was restarted at a plasma target of 4 $\mu g \cdot mL^{-1}$ for 30 minutes followed by a plasma target of 2.5 $\mu g \cdot mL^{-1}$ until the end of the surgery. We selected these 2 targets to assess model performance at relatively stable conditions within a concentration range common in TIVA. Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot minute^{-1}$ was maintained constant throughout the maintenance period. Rocuronium 0.6 $mg \cdot kg^{-1}$ was used to facilitate tracheal intubation. Surgery started after the airway was secured. Arterial blood samples for propofol assays were collected at 1, 2, 3, 5, 9, 10, 15, 20, 40, 60, and 90 minutes, after the start of propofol administration and at 0 1, 3, 5, 10, 30, 60, and 120 minutes after stopping the infusion. BIS data and propofol infusion data were automatically recorded every 5 seconds using the AnestFusor program.

Propofol Assay

Each arterial blood sample was kept on ice and centrifuged within the first hour after collection. Plasma samples were then stored at −20°C until analysis. Propofol plasma concentrations were measured with high-performance liquid chromatography using the method described by Seno et

al.[16] The calibration curve was linear within 0.1–10 μg·mL^{-1}, with a correlation coefficient (R^2) of 0.9993. The plasma propofol lower limits of detection and quantification were 0.01 and 0.1 μg·mL^{-1}, respectively. Intraday precision (CV%) at 1.0, 3.0, and 7.5 μg·mL^{-1} was 2.8%, 7%, and 3%, respectively. Interday assay precision (CV%) at 1.0, 3.0, and 7.5 μg·mL^{-1} was 3%, 5%, and 3.5%, respectively.

Data Analysis

Accuracy and bias of model predictions were calculated and reported as described by Varvel et al.[17] Briefly, median predictive error (MDPE) represents the median bias of the model (positive value means model underestimation, value of 0 means no bias and a negative value means model overestimation). The median absolute predictive error (MDAPE) represents the median accuracy of the prediction (a value of 0 means perfect accuracy), because this value is determined by adding the absolute value of all errors, the resultant number is always positive. To obtain the population MDPE and MDAPE, we first calculated the performance error (PE) for each observed and predicted value in each individual patient. The percentage PE was calculated according to the formula:

$$\mathrm{PE} = \frac{\text{measured} - \text{predicted}}{\text{predicted}} \times 100 \quad (6)$$

The series of PEs were then used to calculate, for each patient and for the entire group, the MDPE, the MDAPE of each model.

The MDPE and MDAPE were calculated for each patient i, having N_i blood samples as follows:

$$\mathrm{MDPE}_i = \mathrm{Median}\{\mathrm{PE}_{ij},\ j=1,....N_i\} \quad (7)$$

$$\mathrm{MDAPE}_i = \mathrm{Median}\ \{\left|\mathrm{PE}_{ij}\right|,\ j=1,....N_i\} \quad (8)$$

PK Predictive Performance

The predictive performances of 4 models (Cortinez new [step 1], Cortinez old,[6] Eleveld,[7] and Marsh[2]) were assessed. Infusion data and flow rates from Anestfusor were used to calculate the predicted propofol plasma concentration resulting from each set of population PK model parameters.

PD Predictive Performance

The predictive performances of the currently developed model were estimated. MDPE and MDAPE of measured and predicted BIS values were calculated during the induction and recovery period of the initial propofol bolus dose before other drugs were given.

RESULTS

Step 1

There were 47 subjects from the 3 studies who contributed 770 Cp observations and 1510 BIS observations. Demographic characteristics of these 3 studies data are summarized in Table 1.

A simultaneous PKPD modeling approach, where both the concentration and effect data were fitted simultaneously was performed.[12,18] During model selection, it was found that the use of effect-site concentrations, instead of a direct link between propofol Cp and BIS response data, resulted in a far superior fit (ΔOBJ, −1245). This confirmed the presence of hysteresis and the need of an effect-site model. The final basic PKPD model structure was characterized by a 3-compartment PK model, an effect compartment, and a sigmoidal inhibitory E_{max} model.

Table 1. Demographic and General Data Used in Steps 1 and 2

	Step 1 (n = 47)	Step 2 (n = 14)
Age (y)	39 (21–66)	48.5 (25–59)
M/F (n)	13/34	6/8
Weight (kg)	104 (76.8–160)	114(90.5–197)
Height (cm)	160 (139–185)	170.5 (148–186)
Body mass index (kg·m^{-2})	40.1 (33.3–52.8)	39.55 (35.5–76)

Values are median (range).

Volumes and clearances were not size scaled in our first PK model. Then a weight proportional model was tested producing an improvement in model fit with a decrease in OBJ of 18.173 points. The fit of the proportional TBW model was not improved by a linear NFM model (ΔOBJ, 0.708). In the NFM model, Ffat was estimated to be 0.99 for clearances and 0.99 for volumes indicating that size effect in all parameters were entirely predicted by TBW. Finally, the model fit of the linear TBW model was not improved using empirical allometric TBW relationships[6,13,19–21] (ΔOBJ, 0.309). The linear TBW model was chosen as our final size scaled PK model. Volumes and clearances were normalized to the median weight of the population studied (104 kg). No effect of age or gender was observed in volumes and clearances. The sigmoidal inhibitory E_{max} model adequately fitted the BIS data. The inclusion of a lag time parameter to account for the delay in BIS response improved the fit with a decrease in the OBJ of 89.593 points. No effect of age or gender was observed in any PD model parameter. Diagnostic plots of the final PK and PD models are shown in Supplemental Digital Content 2–3, Figure 2, http://links.lww.com/AA/C240, Figure 3, http://links.lww.com/AA/C241, respectively. Complementary PC-VPC diagnostic plots are shown in the appendix section in Supplemental Digital Content 4–5, Figure 4, http://links.lww.com/AA/C242, Figure 5, http://links.lww.com/AA/C243. The final population PK and PD parameters, their 95% CI, and interindividual variability estimates are shown in Tables 2 and 3. Parameter estimates of the current model and those of the Eleveld model in a 70- and 120-kg patients are shown in Supplemental Digital Content 6, Tables 1 and 2, http://links.lww.com/AA/C244.

Step 2

Two anesthesiologists performed the 14 cases. One of them (P.S.) was present in all cases and has long experience using TIVA-TCI. All 14 patients completed the study. Demographics and general data are shown in Table 1. No hemodynamic complications requiring the use of vasoactive drugs were reported during the study period. The average bolus dose given was 1.3 mg·kg^{-1} (range, 0.98–1.68 mg·kg^{-1}). The lowest propofol plasma target set (12 μg·mL^{-1}) was used in the patient with the highest BMI (76 kg·m^{-2}). A

Table 2. Propofol Population Pharmacokinetic Parameter Estimates (Step 1)

	Estimate	95% CI	CV (%)
V1 (L/104 kg)	4.86	3.01–8.1	86.4
V2 (L/104 kg)	47.9	33.5–59.9	59.9
V3 (L/104 kg)	196	94.49–723	60.3
Cl (L/min/104 kg)	2.33	1.54–2.6	34.5
Q2 (L/min/104 kg)	5.73	3.56–8.24	61.9
Q3 (L/min/104 kg)	0.653	0.51–1.08	30.7
Proportional residual error (%)	32.2	27.6–35.5	-

95% CI is the 95% confidence interval of the parameter estimated by bootstrap analysis.

CV is between-subject variability expressed as an apparent coefficient of variation.

Abbreviations: Cl, elimination clearance; Vl, central compartment; Q2, distribution clearance between V1 and V2; Q3, distribution clearance, between V1and V3; V2, rapidly-equilibrating peripheral compartment; V3, slowly-equilibrating peripheral compartment.

total of 269 arterial samples of propofol were analyzed in the PK performance analysis. The population MDPE and MDAPE of the 4 models tested are shown in Supplemental Digital Content 6, Table 3, http://links.lww.com/AA/C244. Measured/predicted versus time plots are shown in Figure 1. Figure 2 shows a simulation of predicted infusion rates based on TBW to reach and maintain a plasma target of 3 μg·mL^{-1} in a lean and obese patient, according to the 4 models tested.

A total of 1356 measured BIS values were analyzed in the PD performance analysis. The population MDPE and MDAPE of the final model were 0.4% (interquartile range, –10.39 to 3.85) and 11.9% (interquartile range, 9.62–18.76), respectively. The population measured/predicted BIS versus time plot is shown in Supplemental Digital Content 7, Figure 6, http://links.lww.com/AA/C245. Figure 3 shows the predicted time profiles of BIS values after 3 different bolus doses (1, 1.5, and 2 mg·kg^{-1}) given in a typical obese patient with the new developed model and a simple scheme to achieve and maintain propofol effect-site concentrations around 3 μg·mL^{-1}.

DISCUSSION

In the first step of this study, we derived a PKPD model to perform effect-site TCI in morbidly obese patients (BMI >35 kg/m^2). This model was derived exclusively using data from obese patients from 3 different studies. This new model is composed using a traditional 3-compartment PK model with volumes and clearances linearly scaled to TBW, an effect compartment model, characterized by a single parameter (keo), and a sigmoidal inhibitory E_{max} model. In the second step of the study, we assessed the predictive performance of the current model along with that of 3 previous propofol PK models. Independent data from 14 obese patients under propofol remifentanil anesthesia were used for this purpose. The new PKPD model showed a clinically acceptable PK and PD predictive performance. The Eleveld general purpose model showed the lowest predictive errors in the PK performance step. Although both models could be considered good alternatives when using plasma TCI in obese patients, only the currently developed PKPD model contains the PD information (Keo) needed to perform effect-site TCI in this population.

Size is the most relevant covariate to determine dose schemes in adult patients. Similarly, one of the main issues in PK modeling is the scaling of volumes and clearances to body size. The best size descriptor accounting for PK changes in obesity remains unknown.[22] Previous studies, however, have consistently shown that TBW is an adequate size descriptor for propofol PK, over a wide range of body sizes and compositions.[6,7,23] Those studies have described nonlinear relationships between propofol clearances and TBW characterized using allometric methods.[6,7,23] In our modeling analysis, we found that the fit of a simple linear TBW model in this cohort of obese patients was not improved by nonlinear methods (TBW allometric, NFM). This apparent difference to previous studies is because we have studied only obese patients with a relatively narrow range of body weights (77–160 kg); the curve relating clearance to weight appears "flattened" in this weight range, assuming a linear relationship.[24] Nonlinear relationships between TBW and clearance have been clearly observed when broader ranges of body sizes (ie, 5–160 kg)[7] have been explored.[6–8,24–26] Other nonlinear scaling options include body surface area,[27] lean body weight,[28] FFM,[29] and NFM.[30] Although both the allometric and linear weight models tested were equally good from a statistical point of view, we choose the linear model based on its simplicity. We know this argument is debatable because current availability of TCI pumps and/or portable PKPD simulators makes manual calculations of infusions unnecessary. This is not the case, however, in many countries, where manual infusions are the rule and the simplicity of a model facilitates manual dosing schemes calculations, decreasing the risk of dosing errors. In addition, because this model only contains data (PK and PD) from obese patients, we believe it is not correct to use it in another population even if allometry would have been used. Therefore, the clinical message is that this model should only be used in obese patients (BMI >35 kg/m^2), because back extrapolation of model predictions to lean patients might result in underdosing errors.

NFM, a relatively new size scalar for obese subjects, partitions TBW into FFM and a variable proportion of fat mass. While FFM is calculated based on equations that incorporate the effect of sex, weight, and height, the Ffat is estimated in the modeling analysis and is expected to vary according to the physical properties of the drug.[30] If Ffat is estimated to be zero, then FFM alone predicts size; if Ffat is 1 then size is predicted by TBW. In this study, we found that incorporation of NFM instead of TBW did not produce an improvement in model fit. The proportion of fat mass (Ffat) estimated by the NFM model was very close to 1, suggesting that in the current obese population, size effect in propofol volumes and clearances were entirely predicted by TBW. In contrast, in a recent study describing dexmedetomidine PK in obese and lean patients, we found that dexmedetomidine disposition was exclusively determined by lean tissues (Ffat = 0).[14] This result can be explained in part from the much higher lipid solubility of propofol (partition coefficient octanol-H_2O = 6800)[31] than dexmedetomidine (partition coefficient octanol-H_2O = 2.89)[32] and supports the validity of the NFM scalar as a comprehensive descriptor to explore PK changes in the obese.

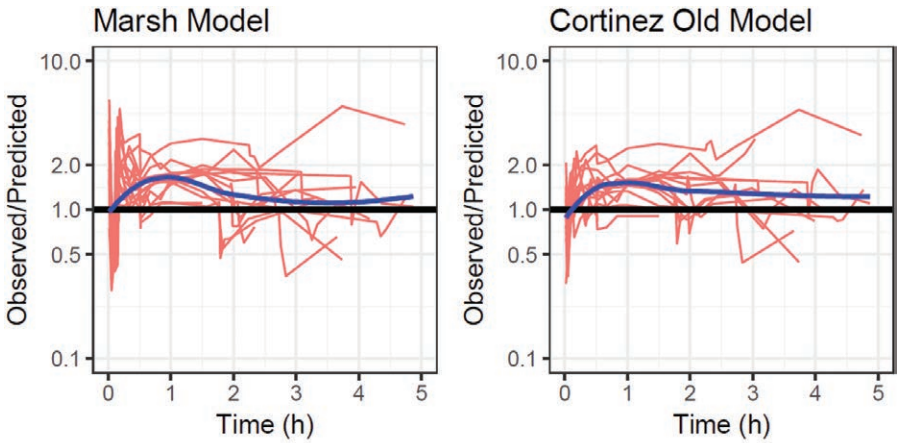

Figure 1. Goodness-of-fit plots corresponding to the measured/predicted propofol plasma concentrations time profiles, for the evaluated models in step 2. Each red line represents a patient; blue lines represent the smoother (loess) for all patients. Black line shows the perfect fit.

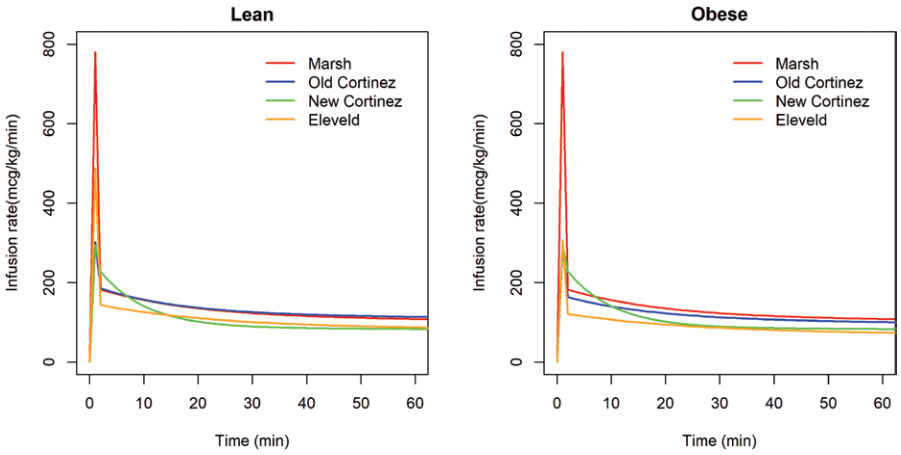

Figure 2. Simulation of predicted infusion rates of propofol based on total body weight to reach and maintain a plasma target concentration of 3 $\mu g \cdot mL^{-1}$, in a 40-y, 170-cm, male patient of 70 kg (lean) or 120 kg (obese). Note that the Marsh model predicts a bigger bolus dose than the other model's due to a too large central volume. The new model should only be used in obese patients because its use in lean patients carries the risk of underdosing.

One limitation of our study is that 2 of the datasets from which the model was derived have relatively short (2 hours) postinfusion sampling periods. Short sampling periods might result in too high elimination clearance estimates since the speed of decay of propofol concentration at that time is probably not exclusively explained by elimination but late distribution to slowly-equilibrating tissues. Our model, however, was also derived with late postinfusion samples (8 hours) from Servin et al's study and the elimination clearance predicted is in accordance with previous studies in obese.[7,8]

The performance of TCI systems depends on how well the PK model matches individual patient PK. An acceptable performance for clinical practice is commonly considered as MDPE <10%–20% and MDAPE between 20% and 40%.[33,34] One of the models assessed in the performance step was the Marsh model. It is well known that this traditional weight proportional model was derived from nonobese patients.[2] Linear per-kilogram schemes derived from lean patients can lead to overdose and adverse effects in the obese.[14,35,36] Not surprisingly, dose extrapolations based on the Marsh model have been shown to put the obese patient at risk of overdose.[37,38] In agreement, our results showed an overall positive bias for the Marsh model of 24.3%, which means that measured concentrations were on average

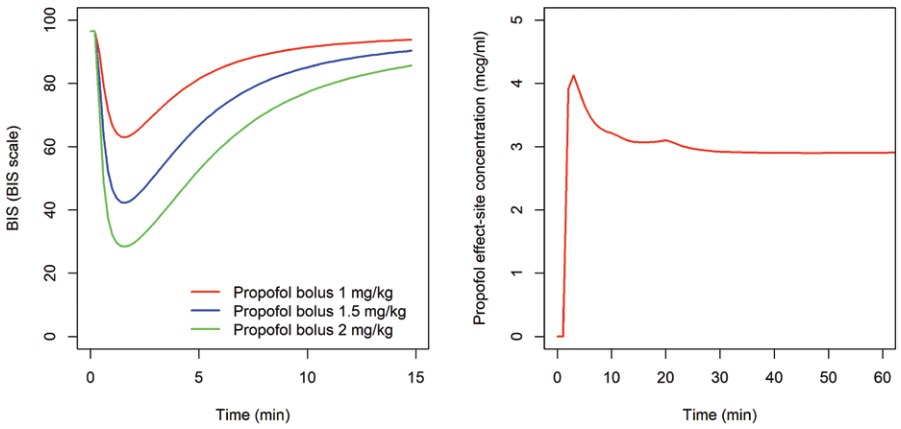

Figure 3. Predicted bispectral index (BIS) time profiles after 3 different bolus doses, in a typical obese patient (left panel). Simulated bolus plus infusions scheme to achieve propofol effect-site concentrations within 3–4 μg·mL^{-1} in a typical obese patient based on the developed pharmacokinetic pharmacodynamic model. Bolus dose of 1.5 mg·kg^{-1} followed by 3 decreasing infusion rates of 120 μg·kg^{-1}·min^{-1} (0–10 min), 100 μg·kg^{-1}·min^{-1} (10–20 min), and 80 μg·kg^{-1}·min^{-1} after 20 min (right panel). Bolus and infusions are based on total body weight.

Table 3. Propofol Population Pharmacodynamic Parameter Estimates (Step 1)

	Estimate	95% CI	CV (%)
E_0	96.5	95.2–97.9	-
E_{max}	0 FIX	-	-
Ce_{50} (mg·L^{-1})	3.4	2.81–3.85	29.2
Keo (min^{-1})	0.292	0.17–0.61	74.4
γ	2.17	1.5–2.88	66.7
Time lag (min)	0.49	-	-
Additive residual error (standard deviation)	6.71	5.54–7.72	-

95% CI is the 95% confidence interval of the parameter estimated by bootstrap analysis.
CV is between-subject variability expressed as an apparent coefficient of variation.
E_0 is the baseline BIS value before propofol administration (awake patient).
E_{max} is the BIS value at maximum propofol effect.
Ce_{50} is the effect-site concentration eliciting half of E_{max}.
Keo is the plasma effect-site equilibration rate constant.
γ is the coefficient describing the steepness of the concentration–response curve.

24% higher than those predicted by the model. Different methods have been proposed to improve the Marsh model performance in obese patients.[6,8,39] It is our opinion, however, that incorporation of new TCI models designed for obese patients is the most logical approach. The currently derived model is also a weight proportional model but, in contrast to the Marsh model, it was derived from obese patients. The predictive errors of this new model were within acceptable limits for clinical use and can be considered for propofol TCI in the obese. The current model, however, should not be used in nonobese patients because it will carry the risk of underdosing, mainly from an underestimation of propofol clearances. The Eleveld model, also tested in this study, was derived from a population which included 660 individuals with an age range from 0.25 to 88 years and weight range 5.2–160 kg. In this model, size effect in volumes and clearances was characterized by TBW using allometric (nonlinear) methods. In addition, age, sex, and study design (patients versus healthy volunteers) were also included as model covariates. In the performance step, the Eleveld model showed the lowest predictive errors of all tested models and therefore, should also be considered as another good option to perform plasma TCI in the obese. In contrast to the currently derived PKPD model, while the Eleveld model is expected to work well in a wider range of patients, it can only be used in plasma TCI mode because it was derived only with PK data.

In addition to propofol concentration data, the current model was derived using BIS data as a biomarker for propofol hypnotic effect. With this approach, the current PKPD model should be able to characterize the time course of propofol effect in obese patients allowing its use in effect-site mode. The estimated PD parameters predict that the effect-site target concentration required to keep BIS values within recommended hypnotic levels for surgery (BIS 60–40) are between 2.6 and 3.8 μg·mL^{-1}. These values are relatively similar to those described in nonobese patients.[40,41]

Although our final model showed clinically acceptable PEs, unexplained interindividual variability in model predictions should always be considered in the clinical scenario. It should be considered that the validation dataset (n = 14) is relatively small for a comprehensive model assessment. It is our opinion that only the progressive use of this model in the clinical scenario will allow a good understanding of its predictive abilities and limitations. Cautious adjustment of propofol effect-site targets based on electroencephalographic monitors and good clinical judgment are therefore needed to deal with uncertainties in model's predictions in the clinical setting.

In conclusion, we derived a propofol PKPD model to perform effect-site TCI in obese patients. The model showed an adequate PK and PD performance in an independent validation step and should be considered as a good alternative for effect-site TCI in the obese population. The new model should only be used in obese patients (BMI >35 kg/m^2), because its use in lean patients carries the risk of underdosing.

DISCLOSURES

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Contribution: This author helped design the protocol, perform the cases, analyze the data, and write the article.
Name: Pablo Sepúlveda, MD.
Contribution: This author helped design the protocol, perform the cases, and analyze the data.
Name: Augusto Rolle, MD.
Contribution: This author helped analyze the data and write the article.
Name: Pauline Cottin, PharmD.
Contribution: This author helped analyze the data and write the article.
Name: Alexandre Guerrini, PhD.

Contribution: This author helped analyze the data.
Name: Brian J. Anderson, PhD, FANZCA.
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