Performance of Propofol Target-Controlled Infusion Models in the Obese: Pharmacokinetic and Pharmacodynamic Analysis

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BACKGROUND: Obesity is associated with important physiologic changes that can potentially affect the pharmacokinetic (PK) and pharmacodynamic (PD) profile of anesthetic drugs. We designed this study to assess the predictive performance of 5 currently available propofol PK models in morbidly obese patients and to characterize the Bispectral Index (BIS) response in this population.

METHODS: Twenty obese patients (body mass index >35 kg/m^2), aged 20 to 60 years, scheduled for laparoscopic bariatric surgery, were studied. Anesthesia was administered using propofol by target-controlled infusion and remifentanil by manually controlled infusion. BIS data and propofol infusion schemes were recorded. Arterial blood samples to measure propofol were collected during induction, maintenance, and the first 2 postoperative hours. Median performance errors (MDPEs) and median absolute performance errors (MDAPEs) were calculated to measure model performance. A PKPD model was developed using NONMEM to characterize the propofol concentration–BIS dynamic relationship in the presence of remifentanil.

RESULTS: We studied 20 obese adults (mean weight: 106 kg, range: 85–141 kg; mean age: 33.7 years, range: 21–53 years; mean body mass index: 41.4 kg/m^2, range: 35–52 kg/m^2). We obtained 294 arterial samples and analyzed 1431 measured BIS values. When total body weight (TBW) was used as input of patient weight, the Eleveld allometric model showed the best ($P < 0.0001$) performance with MDPE = 18.2% and MDAPE = 27.5%. The 5 tested PK models, however, showed a tendency to underestimate propofol concentrations. The use of an adjusted body weight with the Schnider and Marsh models improved the performance of both models achieving the lowest predictive errors (MDPE = <10% and MDAPE = <25%; all $P < 0.0001$). A 3-compartment PK model linked to a sigmoidal inhibitory Emax PD model by a first-order rate constant (k_{e0}) adequately described the propofol concentration–BIS data. A lag time parameter of 0.44 minutes (SE = 0.04 minutes) to account for the delay in BIS response improved the fit. A simulated effect-site target of 3.2 μg/mL (SE = 0.17 μg/mL) was estimated to obtain BIS of 50, in the presence of remifentanil, for a typical patient in our study.

CONCLUSIONS: The Eleveld allometric PK model proved to be superior to all other tested models using TBW. All models, however, showed a trend to underestimate propofol concentrations. The use of adjusted body weight instead of TBW with the traditional Schnider and Marsh models markedly improved their performance achieving the lowest predictive errors of all tested models. Our results suggest no relevant effect of obesity on both the time profile of BIS response and the propofol concentration–BIS relationship. (Anesth Analg 2014;119:302–10)

Propofol target-controlled infusions (TCIs) enable rapid achievement and maintenance of desired concentrations, either in plasma (C_p) or at the site of effect (C_e). Although targeting C_e is the most logical approach,[1] reliable pharmacokinetic (PK) and pharmacodynamic (PD) parameter estimates are needed for this system to work properly.

Obesity is associated with important physiologic changes that can potentially affect the PK and PD profile of anesthetic drugs.[2–4] Propofol TCI models derived from nonobese people have shown poor predictive ability when used in obese patients.[5,6] Recently, new propofol PK models derived from data obtained from obese and normal weight patients have been developed.[7–9] The PK performances of these new models have not been prospectively tested. The 5 PK models we tested and their general characteristics are shown in Table 1.

Electroencephalographic (EEG) monitors are commonly used to measure the hypnotic effect of anesthetic drugs. Because of misspecifications in the propofol models in the obese, EEG monitoring is particularly recommended in this population. The Bispectral Index (BIS) monitor is one of the most extensively validated devices to measure the hypnotic effect of propofol.

This study was designed to assess the predictive performance of currently available propofol PK models in

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Table 1. General Characteristics of the 5 PK Models Tested

PK model	Covariates	Target population
Marsh[10]	TBW[a]	Adults
Schnider[11]	TBW,[a] LBM,[b] height, age	Adults, elderly
Cortínez[7]	TBW,[c] age	Adults, elderly, obese
van Kralingen[8]	TBW[c]	Adults, obese
Eleveld[9]	TBW,[c] age, gender, patient versus healthy volunteer	Children, adults, elderly, obese

PK = pharmacokinetic; TBW = total body weight; LBM = lean body mass.
[a]Parameters are linearly scaled to TBW.
[b]James equation of LBM used in Schnider model incorporates gender, TBW, and height as covariates.
[c]Parameters are allometrically scaled to TBW.

morbidly obese patients and to characterize propofol's PD profile using BIS response data. We hypothesized that newer PK models derived from data that included obese subjects should perform better than the Marsh and the Schnider models.

METHODS

This study was registered in ClinicalTrials.gov (Identifier: NCT01596387) on May 8, 2012, by Ignacio Cortínez.

After IRB approval (School of Medicine, Pontificia Universidad Católica, Santiago, Chile) and obtaining written informed consent, 20 obese patients (body mass index >35 kg/m^2) scheduled for elective laparoscopic bariatric surgery were studied. Inclusion criteria were ASA physical status II and III patients between 18 and 60 years of age. We excluded patients with allergy to study drugs, uncontrolled hypertension, heart block more than first degree, severe systemic disease, and those who had taken any drug acting in the central nervous system within 24 hours before surgery.

In the operating room, noninvasive monitoring of arterial blood pressure, electrocardiogram, and pulse oximetry were initiated. The BIS monitor (BIS VISTA™, Aspect Medical Systems, Newton, MA) was used to assess propofol's hypnotic effect. The smoothing time period of the BIS monitor was set at 15 seconds. QUATRO BIS sensor electrodes were placed according to the manufacturer's recommendations. One 20-gauge IV line was inserted in the forearm for drugs and fluid administration. A radial artery cannula (20-gauge) was placed under local anesthesia for blood sampling.

Propofol administration was started using effect-site TCI at an initial target of 4 μg/mL using the model by Cortínez et al.[7] with a k_{e0} of 0.21 per minute (time to peak effect approximately 2.2 minutes). AnestFusor© Pro Series II TCI software (School of Medicine, Universidad de Chile) was used to control a Fresenius Modular DPS infusion pump (Fresenius Vial Infusion System, Brézins, France) through a serial port of a laptop computer. The protocol target range was selected based on our experience using this model in the obese. Anesthesiologists were instructed to titrate propofol infusions to maintain BIS values between 40 and 60. Remifentanil 0.3 μg/kg/min and rocuronium 0.6 mg/kg were used to facilitate tracheal intubation. Remifentanil and rocuronium doses were based on total body weight (TBW). Patients' lungs were ventilated with a 50% oxygen/air mixture. Mechanical ventilation was adjusted to maintain end-tidal CO_2 30 to 35 mm Hg. Positive end-expiratory pressure was set at 6 to 8 cm H_2O. Anesthesiologists were instructed to maintain mean arterial blood pressure and heart rate within 20% of baseline values (preoperative values reported in the patients' clinical records) by adjusting the remifentanil infusion rates. BIS data and propofol infusion data were automatically recorded every 10 seconds using the AnestFusor program. Arterial blood samples of 2.5 mL 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.

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 C_ps were measured with high-performance liquid chromatography using the method described by Seno et al.[12] The calibration curve was linear within 0.1 to 10 mg/mL, with a coefficient of determination (r^2) of 0.9993. Plasma propofol lower limits of detection and quantification were 0.016 and 0.1 μg/mL, respectively. Intra- and interday precision at 1.0, 3.0, and 7.5 μg/mL were 2.8% and 3%, 7.5% and 5%, 3.3% and 3.5%, respectively.

Data Analysis

Performance of Propofol Models

Using the amounts and rates of propofol given during the study period, predicted propofol C_ps were simulated for each patient using the population PK parameter sets of the 5 tested models[7–11] with the program NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD).

The global predictive performance was calculated using the methodology proposed by Varvel et al.[13] Briefly, median predicted error (MDPE) is 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 performance error (MDAPE) is the median accuracy of the prediction (a value of 0 means perfect accuracy).

PKPD Modeling Analysis

A conventional 3-compartment, first-order elimination, PK model was used to fit propofol C_p data. Parameter estimates were obtained using a nonlinear mixed effects model with the program NONMEM 7.2. Population and individual parameters were estimated using the first-order conditional estimation method. The convergence criterion was 3 significant digits. Between-individual variability in volume and clearance was assumed to be log normal. Residual variability was characterized with a proportional error model.

Clearance and volume parameters estimated for each individual (post hoc Bayesian estimates) were used as input for the PD part of the analysis as described by Sheiner et al.[14] The plasma effect-site elimination rate constant (k_{e0}) was

used to link PK model predictions with BIS response data (Equation 1).

$$\frac{dC_e}{dt} = k_{e0} \times (C_p - C_e)$$

The BIS data were fit using a sigmoidal Imax model (Equation 2).

$$BIS = E_0 + (E_{max} - E_0) \times \frac{Ce^{\gamma}}{Ce^{\gamma} + Ce_{50}^{\gamma}}$$

Observed levels of BIS were related to the predicted propofol concentrations in the C_e. E_0 is the BIS value before propofol administration (awake), and Emax is the BIS value at the maximum drug effect and was assumed to be 0. $C_{e_{50}}$ is the C_e eliciting half of Emax and γ is the steepness of the concentration–response curve. A time lag to represent the delay in BIS calculation was estimated in our model. Residual variability for the BIS response data was characterized with an additive error model.

The quality of fit of the PKPD models to the data was judged by the NONMEM objective function value (OFV), visual inspection of measured versus predicted diagnostic plots, and estimates of performance errors (MDAPE and MDPE).

Results from the population models are presented as parameter estimates, together with the corresponding 95% confidence intervals. Confidence intervals were based on the likelihood profile method implemented in PLT Tools version 4 (a graphical interface for the NONMEM system, developed by Dennis M. Fisher and Steven L. Shafer, available at http://www.PLTsoft.com). TCI simulations and time to peak effect calculations (Tpeak) were performed with PKPD Tools for Excel, a freely available program developed by Charles F. Minto and Thomas W. Schnider (http://www.pkpdtools.com).

RESULTS

Twenty morbidly obese patients were studied. Demographic data are shown in Table 2. There were 13 patients with insulin resistance, 1 patient with type 2 diabetes mellitus, 5 patients with well-controlled chronic hypertension, and 2 patients with well-controlled hypothyroidism. No other relevant comorbidities were reported. The mean (SD) duration of anesthesia was 153 (49) minutes. No surgical complications were reported during the study period. Mean (SD) propofol and remifentanil consumption was 6.53 (1.11) mg/kg/h and 0.36 (0.09) μg/kg/min (TBW). Mean (SD) BIS value during anesthesia maintenance was 37.4 (8.7).

Table 2. Demographic and General Data

Age (y)	33.7 (21–53)
ASA physical status I/II (*n*)	0/20
Male/female (*n*)	3/17 (20)
Weight (kg)	106 (85–141)
Height (cm)	160 (148–178)
Body mass index (kg/m^2)	41.4 (35–52)

Values are mean (range).

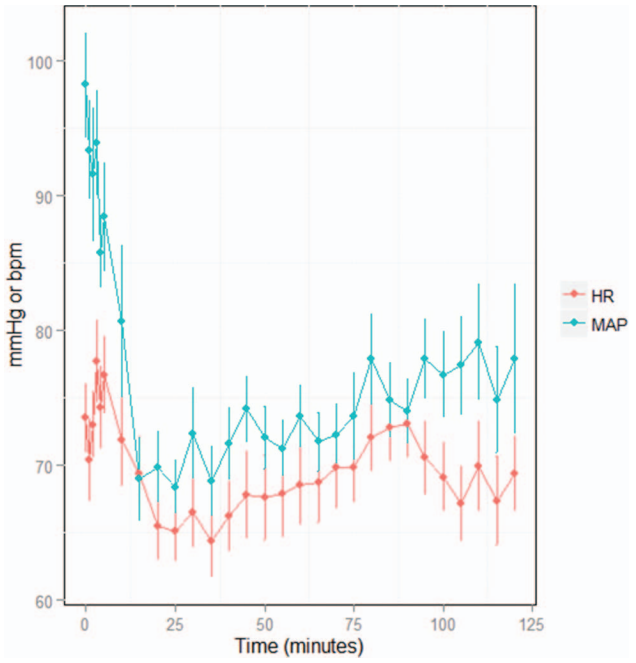


Figure 1. Time profile of mean arterial blood pressure (MAP) and heart rate (HR) values (mean ± SE) during anesthesia maintenance.

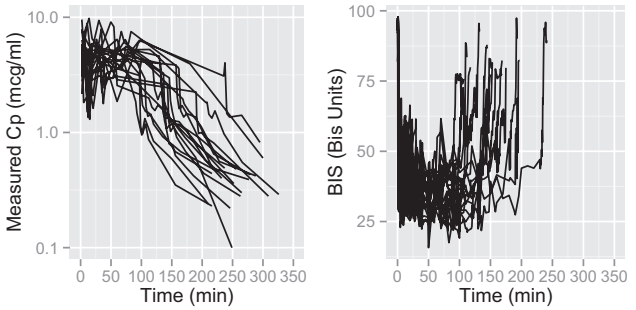


Figure 2. Time profile of measured propofol concentration (left panel) and Bispectral Index (BIS; right panel) in each individual during the study period. C_p = propofol plasma concentration.

Six patients required ephedrine (4 mg) or phenylephrine (100 μg) bolus doses to treat hypotension episodes during surgery. Mean arterial blood pressure and mean heart rate changes observed during anesthesia maintenance are summarized in Figure 1. A total of 294 propofol arterial samples and 1431 BIS values were measured. The time profiles of measured propofol concentrations and BIS values throughout the study period are shown in Figure 2.

Models Validation Analysis

The global performance of the Eleveld model was the best, when compared with models using TBW (all $P < 0.0001$), with MDPE = 18% and MDAPE = 28%. The Marsh, van Kralingen, and Cortínez models showed similar performance (all $P > 0.8$) MDAPEs and MDPEs (Table 3). In general, all models showed a trend to underestimate propofol C_ps (Fig. 3). In an attempt to improve the performance of the Marsh and the Schnider models, which were derived with data from nonobese subjects, other 2 size scalars were

Table 3. Global Performance Errors

Model	MDPE (%)	MDAPE (%)
Schnider (ABW)	8.6 [0.026] (−11.0 to 28.1)	20.1 [0.017] (9.6 to 37.4)
Marsh (ABW)	−3.5 [0.018] (−24.3 to 19.3)	21.7 [0.018] (9.5 to 40.3)
Eleveld	18.2 [0.018] (−3.1 to 38.4)*	27.5 [0.025] (14.2 to 45.2)
Marsh	36.6 [0.033] (7.9 to 70.4)*	39.9 [0.037] (20.6 to 70.4)*
van Kralingen	39.5 [0.027] (16.8 to 63.7)*	42.4 [0.021] (22.8 to 64.8)*
Cortínez	41.0 [0.024] (14.7 to 68.8)*	42.6 [0.013] (25.1 to 68.8)*
Schnider (FFM)	71.3[0.043] (34.2 to 111.7)*	71.3 [0.036] (40.2 to 111.7)*
Schnider	79.7 [0.035] (41.2 to 130.6)*	79.7 [0.029] (43.4 to 130.6)*

Values are median [SEM] (25th to 75th percentiles); nonparametric multiple comparisons performed with Kruskal–Wallis test revealed a significant effect of the model on MDPE and MDAPE ($P < 0.0001$). Post hoc comparisons were performed using Mann–Whitney *U* tests with Bonferroni correction for 28 comparisons.

ABW = adjusted body weight, FFM = fat-free mass[15]; MDPE = median performance error; MDAPE = median absolute performance error.

*$P < 0.0001$ compared with the lowest error model: MDPE (%), compared with the Marsh (ABW) model; MDAPE (%), compared with the Schnider (ABW) model.

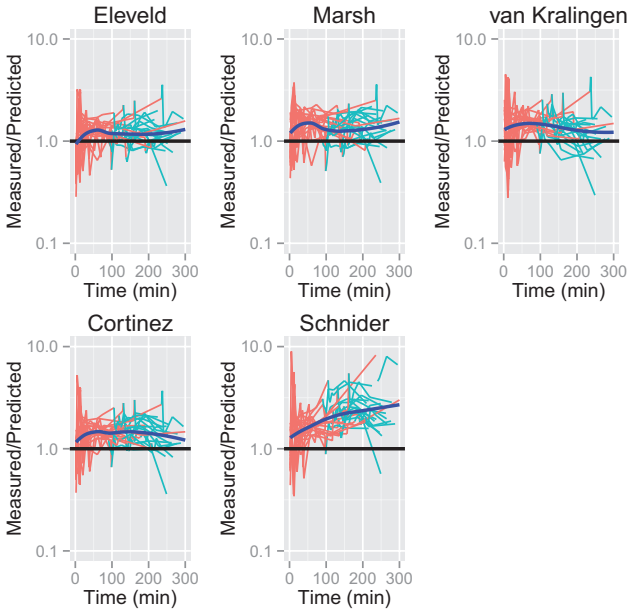


Figure 3. Goodness-of-fit plots corresponding to the observed/predicted propofol concentrations times profiles. (red = maintenance; light blue = recovery). Panels are ordered according to the magnitude of model median absolute performance error. The horizontal black line at y = 1 represents a perfect fit. The blue line is a loess (local regression) smoother (span = 0.75) used to better appreciate the errors trend.

tested. When adjusted body weight (ABW) instead of TBW was used to simulate propofol C_ps with the Marsh and the Schnider models (Fig. 4), the underestimation tendency was reversed and the models' behavior markedly improved achieving the lowest performance errors of all tested models (all $P < 0.0001$). ABW was calculated as IBW + 0.4 × (TBW − IBW), where IBW (ideal body weight) = 45.4 + 0.89 × (HT [cm] − 152.4) + 4.5 (if male).[16] The replacement of

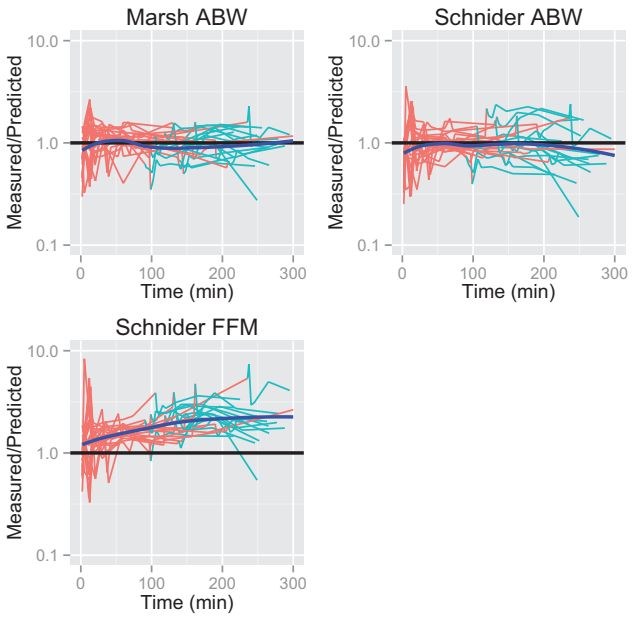


Figure 4. Goodness-of-fit plots corresponding to the observed/predicted propofol concentrations times profiles for the Marsh and Schnider models using adjusted body weight (ABW) instead of total body weight (red = maintenance; light blue = recovery). Panels are ordered according to the magnitude of model median absolute performance error (MDAPE). The horizontal black line at y = 1 represents a perfect fit. The blue line is a loess (local regression) smoother (span = 0.75). FFM indicates fat-free mass.

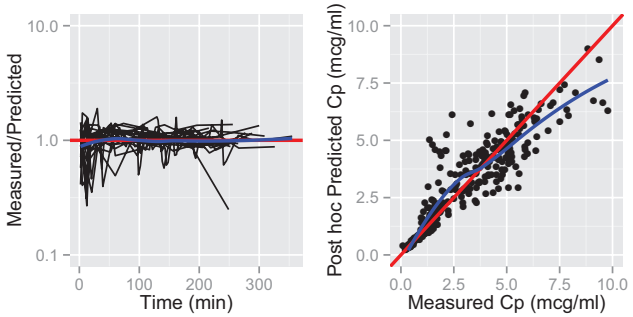


Figure 5. Goodness-of-fit plots of the new developed propofol pharmacokinetic model. The left plot corresponds to the individual observed/predicted propofol plasma concentration (C_p) times profiles. The right plot shows individual observed versus predicted propofol C_p. The horizontal line represents a perfect fit. The blue line is a loess (local regression) smoother (span = 0.75).

the James equation in the Schnider model to estimate lean body mass by the fat-free mass (FFM) equation derived by Janmahasatian et al.[15] did not improve the performance of the model ($P = 0.89$). Global performance errors of all tested models are shown in Table 3.

PKPD Analysis

A 3-compartment model without covariates was used to fit the PK data. The population MDPE [SE] and MDAPE [SE] were −1.0% (0.02) and 19% (0.02), respectively. The individual MDPE [SE] and MDAPE [SE] were 0.8% (0.01) and 13% (0.01), respectively. Diagnostic plots are shown in Figure 5. The post hoc estimates of volumes and clearances used as

Table 4. Estimated Pharmacokinetic Parameters of the Derived Model

Parameter	
V1 (L)	3.9 (1.0–34.5)
V2 (L)	16.5 (8.9–16.4)
V3 (L)	80.8 (47.7–87.6)
CL (L/min)	2.1 (1.6–2.7)
Q2 (L/min)	4.8 (3.8–6.0)
Q3 (L/min)	0.9 (0.8–1.3)

Values are median (range).

V1 = volume of central compartment; V2 = volume of the small peripheral compartment; V3 = volume of the large peripheral compartment; CL = metabolic clearance; Q2 = rapid distribution clearance; Q3 = slow distribution clearance.

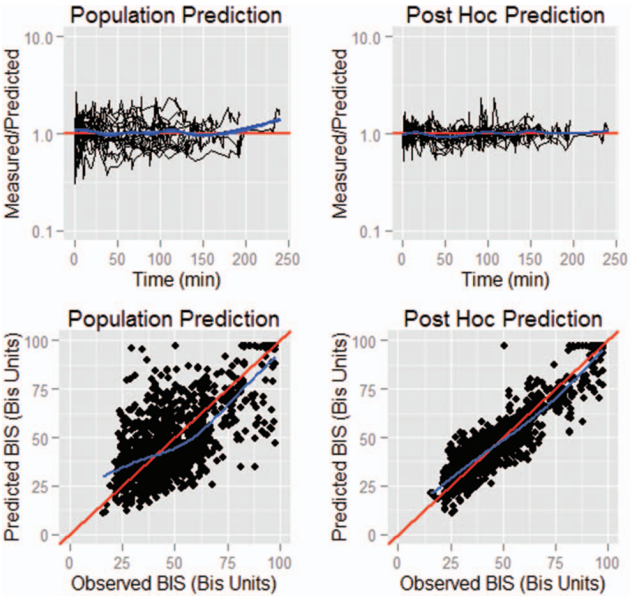


Figure 6. Goodness-of-fit plots of the new developed propofol pharmacokinetic pharmacodynamic model. The top plots correspond to the observed/predicted Bispectral Index (BIS) times profiles. The bottom plots are observed versus predicted BIS. Population predictions (left). Individual predictions (right). The horizontal red line represents a perfect fit. The blue line is a GAM (backfitting algorithm to fit a Generalized Additive Model) smoother performed with mgcv package of R program (http://cran.r-project.org/web/packages/mgcv/mgcv.pdf) and the formula = y ~ s(x, k = 5).

inputs to predict individual propofol concentrations in the PD part of the analysis are summarized in Table 4.

Diagnostic plots of the effect-site model and the sigmoidal inhibitory Emax model, used to fit the BIS data, are shown in Figure 6. The inclusion of a lag time parameter to account for the delay in BIS response improved the fit with a decrease in the OFV of 111.2. No effect of age, weight, or gender (decrease in the OFV <2) was observed in any model parameter. Estimated parameters are shown in Table 5. According to the current PKPD model parameters, derived in the presence of remifentanil, an effect-site target of 3.2 μg/mL would be required to obtain BIS of 50 for a typical patient in our study. To achieve and maintain this target, our model predicts an initial bolus dose of 1.4 mg/kg (TBW) followed by infusion rates between 5 and 4 mg/kg/h (Fig. 7). In addition, according to our PKPD model parameters, the

Table 5. Estimated Pharmacodynamic Parameters of the Derived Model

Parameter	TV	BSV (CV%)	95% CI
E_0 (BIS Units)	96.8	—	94.8–99.0
Emax (BIS units)	0 FIX	—	—
$C_{e_{50}}$ (μg/mL)	3.29	21.9%	2.95–3.69
γ	1.59	42.8%	1.29–2.00
K_{e0} (per min)	0.190	79.2%	0.13–0.26
Time lag (min)	0.44	—	0.39–0.46
Additive error (BIS units)	9.05	—	

Pharmacodynamic parameters were estimated in the presence of remifentanil. The additive error is the residual error or "noise."

CI = confidence interval; TV = typical value; BSV = between-subject variability expressed as coefficient of variation (CV%); E_0 = Bispectral Index (BIS) value before propofol administration (awake); Emax = BIS value at the maximum drug effect; $C_{e_{50}}$ = effect-site concentration eliciting half of Emax; γ = steepness of the concentration–response curve.

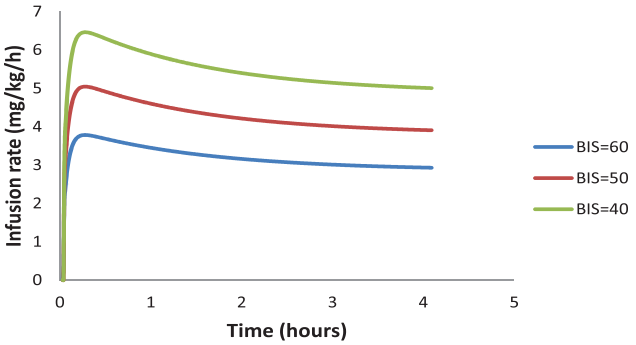


Figure 7. Simulated infusion rates after propofol bolus doses of 1.1, 1.4, and 1.8 mg/kg required to achieve and maintain target Bispectral Index (BIS) levels of 40, 50, and 60 in the presence of remifentanil. Simulation is performed based on the typical pharmacokinetic pharmacodynamic parameters of the derived model.

median time to peak effect after a rapid bolus dose would be 2.1 minutes. An additional time delay of approximately 0.4 minutes is required to observe the maximum effect in the BIS monitor due to time delays in index calculation.

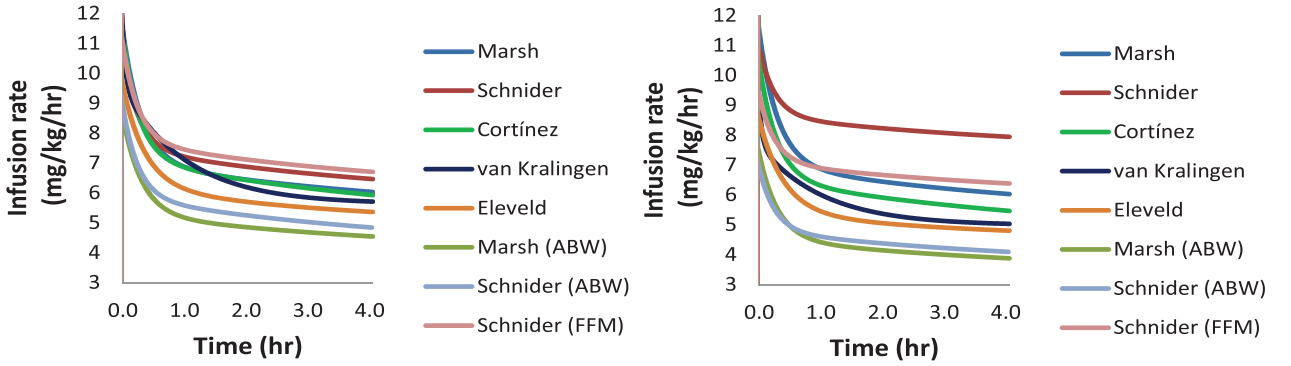
DISCUSSION

The main finding of this study is that when TBW was used as the input weight, the Eleveld allometric PK model showed the best predictive performance (all $P < 0.0001$) with errors within acceptable limits for TCI, (MDPE <10%–20% and MDAPE between 20% and 40%).[17,18] All models, however, showed a trend to underestimate propofol concentrations. The use of ABW with the Schnider and Marsh models improved both models' performances achieving the best predictive ability of all tested models (all $P < 0.0001$). In the modeling analysis, we characterized the PK/PD profile of propofol in obese patients using BIS response data and obtained results that were similar to those described in lean patients.[19,20] This finding is of great clinical importance and confirms the validity of BIS monitoring in the obese.

Previous studies support the use of TBW-based schemes during anesthesia maintenance in obese patients.[5,21,22] Similar infusion regimens adjusted to TBW for obese and lean subjects assume proportional increments in propofol volumes and clearances with weight.[6] Recent studies, however, have found allometric (nonlinear) relationships

between propofol clearances and TBW.[7–9] According to these new models, maintenance infusion schemes based on mg/kg/h should be reduced in a nonlinear fashion as weight increases. In the current study, the performance of the Marsh model, which linearly scales volumes and clearances according to TBW, was similar to that of the Cortínez and the van Kralingen allometric models. This result is consistent with the fact that these 3 models predict relatively similar infusion rates in moderately obese patients and their differences become relevant only in the heaviest patients (Fig. 8). The superiority of the Eleveld PK model in our study is therefore probably not explained from its allometric relationships but from a better characterization of other covariate effects present in the current clinical scenario. The Eleveld model uses TBW, age, gender, and patient versus healthy volunteer as covariates and resulted in the lowest infusion rates in our population. Eleveld et al.[9] found lower estimates of metabolic clearance (CL) and distributional clearances (Q2 and Q3) and a smaller peripheral volume of distribution (V3) in patients when compared with volunteers. The difference between patients and healthy volunteers is probably related to the effect of multiple factors on propofol PK, such as coadministration of other drugs, mechanical ventilation, surgery, comorbidity.

We do not have a clear explanation for the positive bias observed in all model predictions, but volumes and clearances estimated in the current PK analysis were in general lower than those described in the tested models using TBW (Table 6). Different factors need to be considered while interpreting our results. First, the relatively deep hypnotic state reached during the maintenance period might have affected propofol distribution and elimination by a decrease in cardiac output and regional blood flows.[23] Although per protocol design we instructed anesthesiologists to keep BIS values between 60 and 40, they were reluctant to set target propofol values <2 μg/mL to avoid the appearance of intraoperative awareness. Second, a PK interaction with remifentanil might also have contributed to the biased predictions. In the current study, the mean infusion dose of remifentanil was relatively high in relation to opioid doses used in earlier PK studies in obese patients.[7,8,21] Clinical studies have shown that propofol volumes of distribution and clearances decrease when propofol is administered with opioids and might result in biased predictions of TCI models.[24–26] Other studies, however, have not found an effect of remifentanil on propofol PK.[27] Last, all our patients underwent laparoscopic surgeries. The direct myocardial depressor effect of CO_2,[28] the deleterious hemodynamic effects of increased intraabdominal pressure,[29] as well as reverse Trendelenburg



BMI	Marsh (TBW)	Schnider (TBW)	Cortínez (TBW)	Van Kralingen (TBW)	Eleveld (TBW)	Marsh (ABW)	Schnider (ABW)	Schnider (FFM)
35 kg/m²	0.73	0.15	0.20	0.11	0.29	0.55	0.15	0.15
50 kg/m²	0.73	0.11	0.20	0.08	0.20	0.47	0.11	0.11

ABW = adjusted body weight; FFM = fat-free mass.

Figure 8. Simulated infusion rates to achieve and maintain a constant plasma target of 3.2 μg/mL in a 35-year-old female patient with a body mass index (BMI) of 35 kg/m² (left) or BMI of 50 kg/m² (right). Initial bolus doses mg/kg total body weight (TBW) given by these models are listed in the above table.

Table 6. Pharmacokinetic Parameters Estimated by All Models Tested for a Typical 106 kg, 160 cm, Body Mass Index 41 kg/m², 35-Year-Old Female Patient

Parameter	Marsh (TBW)	Schnider (TBW)	Cortínez (TBW)	van Kralingen (TBW)	Eleveld (TBW)	Marsh (ABW)	Schnider (ABW)	Schnider (FFM)
V1 (L)	24.2	4.27	6.78	3.03	8.21	16.87	4.27	4.27
V2 (L)	49.2	25.9	41.1	5.34	43.9	34.4	25.9	25.9
V3 (L)	306	238	358	116	141	214	238	238
CL (L/min)	2.87	3.48	2.62	2.93	2.59	2.01	2.09	3.24
Q2 (L/min)	2.71	1.72	2.49	1.64	1.94	1.89	1.72	1.72
Q3 (L/min)	1.01	0.84	1.17	1.86	0.63	0.71	0.84	0.84

V1 = volume of central compartment; V2 = volume of the small peripheral compartment; V3 = volume of the large peripheral compartment; CL = metabolic clearance; Q2 = rapid distribution clearance; Q3 = slow distribution clearance; TBW = total body weight; ABW = adjusted body weight; FFM = fat-free mass.[15]

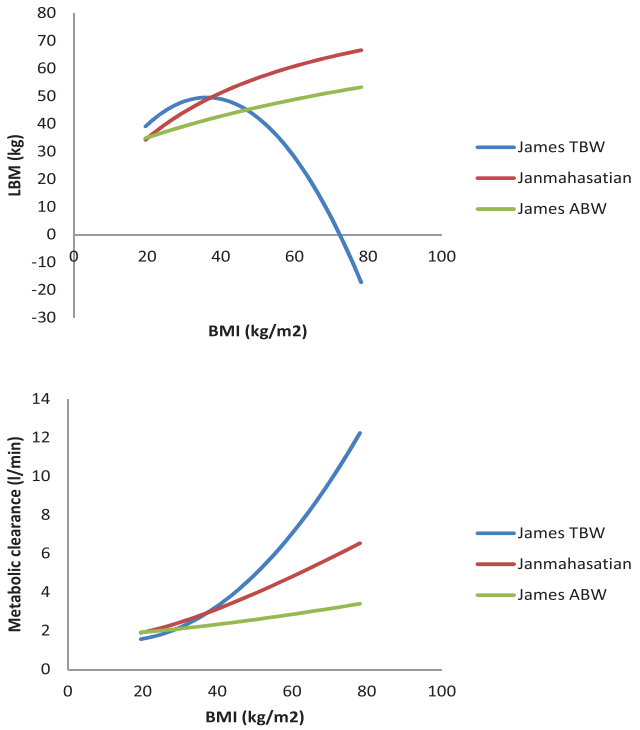


Figure 9. Simulated lean body mass (LBM) changes derived with 3 different approaches (top) and the corresponding metabolic clearances estimates by the Schnider model using these approaches in a 160-cm tall female patient as weight increases. ABW = adjusted body weight; BMI = body mass index; TBW = total body weight.

positioning[30] can all reduce cardiac output and regional blood flow and therefore very likely affected propofol distribution and elimination in this study. Although many of the tested models were derived with data from patients undergoing laparoscopic surgeries,[7–9] a formal assessment of this factor on propofol PK is needed to clarify this point.

ABW is a size descriptor developed to improve dose adjustments in obese patients.[16] This index uses IBW plus a proportion of excess of body weight, which can vary according to the physical properties of the drug.[31] In our analysis, the use of ABW with the Marsh and Schnider models improved both models' performance. In the Marsh model, the use of ABW reduced all volumes and clearances proportionally. In the case of the Schnider model, this approach reduced the error in CL, which is overestimated by this model due to the inappropriate estimation of lean body mass by the James equation for the morbidly obese.[6] Another, perhaps more rational approach[32,33] to improve the performance of the Schnider model in morbidly obese patients is to replace the James equation by that of Janmahasatian et al.[15] to estimate FFM. In our analysis, the Schnider (FFM) model performed worse than the Schnider (ABW) model since it estimated higher CLs than the ABW model (Fig. 9). Since our results contrast with previous findings,[5,22] we can only recommend the use of ABW with the Marsh and the Schnider models if EEG monitoring is available to avoid the risk of awareness.

In the PKPD part of the analysis, the 3-compartment PK model and the effect-site model parameterized with the k_{e0} were adequate to describe the time course of propofol effect measured with BIS. Since the purpose of the current PK analysis was to obtain post hoc estimates of volumes and clearances for the subsequent PD analysis, but not to derive a comprehensive population PK model for TCI use, it is our opinion that the newly developed Eleveld model using TBW or the Marsh or the Schnider models using ABW are the best options for propofol TCI in obese patients.

There have been different modeling approaches to describe BIS response data.[19,20,34] In the current PKPD analysis, we assumed a maximal propofol BIS effect of 0 since we a priori knew that propofol at higher doses than those administered in this study can reach BIS values of 0. This approach has the advantage of giving clinically meaningful $C_{e_{50}}$ estimates corresponding to BIS around 50. In addition, in our modeling strategy, we included a time lag parameter to account for possible delays in BIS response. The time lag of 0.44 minutes estimated in our final model closely agrees with commonly accepted values for this monitor, which range from 10 to 30 seconds.[34–36]

Studies in obese patients have demonstrated that the accumulation of excess visceral fat is related to several metabolic and inflammatory perturbations which might affect drug sensitivity.[37–39] While some studies have found higher pain sensitivity in obese subjects,[40] others have reported opposite results[39] or simply no effect of weight in drug PD profile.[8,41] In the current study, the conventional inhibitory Emax model used to describe BIS response data produced a good fit of the data. The current data set (only obese patients) does not allow us to identify any statistically significant relationship with weight in any model parameter (k_{e0}, E_0, $C_{e_{50}}$, γ, time lag). The $C_{e_{50}}$ estimated in our model was 3.29 μg/mL, this value is similar to the value of 3.34 μg/mL observed by Rigouzzo et al.[20] in lean adult patients using a similar modeling approach. In addition, the time profile of BIS effect represented by the predicted time to peak effect of 2.1 minutes closely agrees with the value reported by Doufas et al.[19] in nonobese subjects using the BIS monitor. In their model, the authors did not include a parameter to account for BIS time delay and found a k_{e0} of 0.17 per minute, which predicts a time to peak effect of 2.7 minutes. Our results are in agreement with that of a previous study suggesting no relevant effect of obesity in the propofol PD profile.[8]

It should be considered that the propofol PD model parameters derived in our study were estimated in the presence of remifentanil. Propofol and remifentanil have shown a synergistic PD interaction in response surface models of hypnosis and nociception.[42–44] Other studies, however, have shown a direct effect of remifentanil on the EEG, which is characterized by a decrease in high-frequency EEG activity during light propofol anesthesia but an increased activity in the extended α-band and decreased activity in the δ-band during deep anesthesia which might produce and increase in BIS.[26,45] Although in our modeling analysis we found a mild tendency toward higher propofol requirements, at higher remifentanil infusion rates (data not shown), it is our opinion that the current investigation cannot confirm or deny this association with a reasonable degree of certainty. The current model characterizes a common clinical scenario where BIS-guided propofol TCI and remifentanil, titrated according to hemodynamic variables, are administered together. Extrapolation of the current PD

model parameters to a different scenario without remifentanil is probably not appropriate.

CONCLUSIONS

We have shown that when using TBW as the weight input, the Eleveld allometric PK model derived with data from 21 previously published propofol studies including obese and non-obese subjects showed the best predictive performance with errors within acceptable limits for clinical practice. The use of ABW with the Schnider and Marsh models, however, reduced their predictive errors and transformed them into the best models in the current scenario. Our results, obtained in the presence of remifentanil, suggests no relevant effect of obesity in both the time profile of propofol effect measured with BIS and in the propofol concentration–BIS relationship.

DISCLOSURES

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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Luis I. Cortínez has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is one of the authors responsible for archiving the study files.
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