Published in final edited form as:

Paediatr Anaesth. 2015 September ; 25(9): 911–923. doi:10.1111/pan.12684.

POPULATION PHARMACOKINETIC-PHARMACODYNAMIC MODELING AND DOSING SIMULATION OF PROPOFOL MAINTENANCE ANESTHESIA IN SEVERELY OBESE ADOLESCENTS

Vidya Chidambaran^{#1,2}, Raja Venkatasubramanian^{#1,3}, Senthilkumar Sadhasivam^{1,2}, Hope Esslinger¹, Shareen Cox³, Jeroen Diepstraten⁴, Tsuyoshi Fukuda^{2,3}, Thomas Inge^{2,6}, Catherijne A.J. Knibbe^{4,5}, and Alexander A. Vinks^{2,3}

¹ Division of Anesthesiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA. ² Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA ³ Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA ⁴ Department of Clinical Pharmacy, Reinier de Graaf Group, Delft, the Netherlands ⁵ Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden, the Netherlands. ⁶ Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

These authors contributed equally to this work.

Abstract

BACKGROUND—Optimal dosing of propofol to maintain appropriate anesthetic depth is challenging in severely obese (SO) adolescents. We previously reported that total body weight (TBW) is predictive of propofol clearance. This study was aimed at characterizing pharmacokinetics (PK) and pharmacodynamics (PD) of propofol in SO adolescents, using Bispectral Index (BIS), and towards developing PK/PD model-based dosing guidelines.

METHODS—A prospective PK/PD study was conducted in 26 SO children and adolescents aged 9–18 years (BMI 31–69 kg/m²), undergoing surgery with intravenous propofol anesthesia clinically titrated by providers blinded to BIS. BIS data and propofol infusion schemes were recorded. Venous blood samples collected during and after propofol infusion were assayed for propofol

Corresponding Author: V Chidambaran, 3333 Burnet Ave, MLC 2001, Cincinnati, OH 45229, USA Ph: (001) 5136361786; vidya.chidambaran@cchmc.org.

Authors' contributions: VC and RV have contributed equally to this manuscript. VC: Study design, recruitment, data collection, analysis, manuscript preparation; RV: Data analysis, manuscript preparation; SS: Study design, data collection, manuscript preparation; HE: Study conduct, data collection; SC: Data collection, sample analysis; JD: Study design; TF: Data analysis; TI: Conducted surgery, study design; CAJK: Study design, consultation for analysis; AAV: Study design, data analysis, funding, manuscript preparation.

[ClinicalTrials.gov/NCT00948597](http://www.clinicaltrials.gov/NCT00948597):

<http://www.clinicaltrials.gov/ct2/show/NCT00948597?term=propofol+cincinnati&rank=2>

Declaration of interests:

None of the authors have any disclosures.

concentrations. A propofol PK/PD model was developed using NONMEM and model-based simulations were performed to determine propofol dosing regimens targeting BIS of 50 ± 10 .

RESULTS—A 3-compartment PK model linked to a sigmoidal inhibitory Emax PD model by a first-order rate constant, adequately described the propofol concentration ($n=375$) and BIS ($n=3334$) data. TBW was the most predictive covariate for propofol clearance [CL ($L \text{ min}^{-1}$) = $1.65 \times (TBW/70)^{0.75}$]. An effect-site propofol concentration of $3.19 \mu\text{g ml}^{-1}$ was estimated for half-maximal effect, with no identifiable predictive covariates. The proposed maintenance dosing regimen targeted to a BIS of 50 ± 10 , based on our PK/PD model, was able to predict desired propofol concentrations and BIS in a representative obese teen when used in conjunction with accepted PK/PD models for children/obese adults (PK:Elefeld /PD: Cortinez), further supporting evidence for the dosing based on TBW.

CONCLUSION—This is the first study to describe the PK/PD of propofol in SO adolescents. The proposed maintenance dosing regimen for propofol uses TBW in an allometric function as a dosing scalar, with an exponent of 0.75. Our results suggest no relevant effect of obesity on the propofol concentration-BIS relationship.

Keywords

anesthetics i.v.; propofol; bariatric; bispectral index; obese; pediatric; pharmacokinetics; pharmacodynamics; simulation

INTRODUCTION

The prevalence of obesity in children in the United States is currently at a high of 16.9% (1). In line with this trend, the estimated number of adolescent weight loss surgeries performed annually between 1997 and 2003 also increased 5-fold (2). Propofol, an intravenous anesthetic, is widely used in obese children and adolescents undergoing surgery, because of rapid onset of action and ease of titration. We have previously reported that lack of dosing guidelines and clinical titration of propofol in severely obese (SO) adolescents caused overdosing associated with delayed emergence, increased postoperative somnolence and incidence of postoperative adverse respiratory events in SO children (3). On the one hand, excessive anesthetic administration results in organ hypo perfusion and low BIS values with poor outcomes (4-7), while, on the other hand, inadequate anesthesia from propofol underdosing has been reported to cause intra-operative awareness, in obese adults (8).

Physiological changes associated with obesity may affect propofol pharmacokinetics (PK) and pharmacodynamics (PD) as it is highly lipophilic drug. We have previously reported PK analysis of propofol concentration data in SO adolescents, where TBW is the most significant determinant for propofol disposition (9). However, in order to arrive at clinically meaningful dosing guidelines for propofol in this population, concomitant analysis of propofol PD effects on anesthetic depth is essential. Bispectral Index (BIS) is an accepted surrogate marker for depth of anesthesia in older children (10), and has been used previously as a marker for propofol effects in PK/PD modeling studies in children and SO adults (11). In children, propofol effects may be affected by age-dependent differences (12); additionally, in SO children, effects of obesity on propofol sensitivity are also likely. In

comparison to their leaner counterparts, SO children had lower ED95 for eyelash reflex (13). However, no evidence exists in adult literature for obesity related effects on propofol concentration-BIS relationship (14). To our knowledge, there are hitherto no PK/PD studies of propofol in the SO pediatric population; hence, we conducted this study with the aims of describing PK and PD of commonly used anesthetic propofol in SO adolescents, and to develop a PK/PD model-based dosing algorithm for individualized propofol dosing in this population.

METHODS

Study Subjects

Twenty nine SO patients aged 5 to 18 years, scheduled to undergo bariatric or other elective surgery, were enrolled provided they had a body mass index (BMI) for age >95th percentile for age (15), required propofol anesthesia for at least 60 minutes and had no known renal or liver disorders, neurological disorders or known allergy to propofol or egg lecithin. From prior work in children, it was estimated that a cohort of 20 subjects would allow adequate estimation of the primary PK variables (16). The study protocol was approved by the Cincinnati Children's Hospital institutional review board (IRB) and informed assent/consent were obtained from all participants and/or their guardians as appropriate.

Anesthetic Procedure

The anesthetic procedures are described in detail in our previous PK manuscript (9) and presented in Supplementary section for reader convenience. To summarize, all patients received standard of care anesthesia and monitoring. In addition, an age and head-size appropriate disposable BIS sensor ® XP, (Aspect Medical Systems, Norwood, MA) on the forehead was connected to the BIS monitor that was covered so anesthesia personnel were blinded to the BIS values. BIS monitoring was continued until discharge from postoperative care unit (PACU). Propofol induction was done with an infusion at a rate of 1000 µg kg⁻¹ min⁻¹ dosed to adjusted body weight (ABW) per the formula used by Servin *et. al* (Equation 1) (17). Ideal Body Weight for our population was calculated based on 50th percentile BMI for age and gender (Equation 2). This was done because for the pediatric population, BW not only depends on height, it also depends on age and sex of a growing child, and 50th percentile for age- and sex- specific BMI is the accepted median ideal or expected body weight for normally developing adolescents(18).

$$Adjusted\ BW = IBW + 0.4 \times (Total\ BW - Ideal\ BW) \quad (1)$$

$$Ideal\ BW = Ideal\ BMI \times Height(meter)^2 \quad (2)$$

Patients were asked to count, or called repeatedly in a normal voice until the induction end-point of loss of verbal contact; this was recorded as 'time to induction'. Upon loss of consciousness, endotracheal intubation was performed after administration of succinylcholine 100-150 mg. Anesthesia was maintained with clinically titrated propofol infusion, vecuronium for muscle relaxation, and fentanyl for analgesia. The propofol

infusion was discontinued when skin sutures were being placed, residual muscle relaxation reversed, trachea extubated and morphine dosed incrementally to achieve comfort, and/or a respiratory rate of 14-16/minute. Patients were followed in PACU until they met PACU discharge criteria.

Blood Sampling and Analytical Methods

Venous blood samples (1 mL) for propofol concentrations were collected prior to and 15, 30, 45, 60, 120, 180 and 240 minutes, after the start of propofol infusion; just before and at 5 or 20 minutes after any dose adjustment; just before, and at 5, 10, 15, 30, 45 and 120 minutes after discontinuation of propofol infusion. Additional blood samples were drawn 1-3, 5 and 10 min after start of propofol infusion for the last six patients to capture the rapid distribution phase better. Venous and not arterial blood samples were collected as placement of arterial lines when not clinically indicated, is considered high risk in the pediatric population and not allowed by our IRB for study purposes. Whole-blood samples were mixed thoroughly and stored at 4° C until analysis by validated high-performance liquid chromatography with fluorescence detection at 276nm and 310nm (within 1 month). The coefficients of variation for the intra-assay and inter-assay precision were less than 4.5% and 7.1%, respectively, over the concentration range from 0.05 to 10.0 µg mL⁻¹. The lower limit of quantification was 0.05 µg mL⁻¹ (19).

BIS

Real time BIS data was transferred from the monitor to a computer via USB port and included date, time, minimum and maximum BIS values, average Signal Quality Index (SQI), a measure of the signal quality for the EEG channel source; and average electromyography (EMG) which measures influence of muscle tone from forehead muscles. For the PK/PD analysis, per-second BIS data was averaged over a minute and the averaged BIS observation was assigned to the middle of the minute over which averaging was performed. Evaluable BIS data with adequate signal quality (SQI > 50) and muscle relaxation (EMG <35 decibels) were included for analysis.

Population Model Development and Evaluation

A non-linear mixed effects modeling approach (NONMEM, version 7.2., Globomax LLC, Hanover, MD) was used to develop population PK and PK/PD models using a sequential approach. First, a population PK model was estimated using propofol dosing data and patient's individual measured blood samples. In the second step, the PK/PD parameter estimation was based on simultaneous fitting of the blood concentrations (PK) and BIS (PD) data while the population PK model parameters (THETA, OMEGA and SIGMA) were fixed based on the earlier step. These methods have been previously described as a sequential method, PPP&D (Population PK Parameters & Data) by Zhang *et al.* (20). Data processing and visualization were performed using R (version 2.15). The quality of the model was evaluated using a range of criteria including objective function value (OFV), residual diagnostics and model stability considerations using bootstrap validation techniques by refitting the model to 1,000 randomly sampled bootstrap datasets.

Pharmacokinetic Model Development

Two and three compartment models were tested to fit the log-transformed propofol concentration data. The inter-individual value of the parameters of the i^{th} individual was modeled by equation 1:

$$\theta_i = \theta_{mean} * \exp^{\eta_i} \quad (3)$$

where θ_{mean} is the population mean and η_i is a random variable with a mean of zero and variance of ω^2 . Intra-individual variability was best described with an additional error model described by Equation 2:

$$Y_{ij} = \ln(C_{pred,ij}) + \varepsilon_{ij} \quad (4)$$

where Y_{ij} is the log-transformed j^{th} observation of the propofol concentration in the i^{th} individual, $C_{pred,ij}$ is the corresponding predicted concentration and ε_{ij} is the unexplained random normal error with zero mean and σ^2 variance.

Pharmacokinetic/Pharmacodynamic Model Development

The BIS data were used in concert with the PK data to examine the linkage between propofol PK and PD. BIS values were averaged over 15 seconds due to the smoothing rate on the BIS monitor. To take into account this delay in BIS measurement, we incorporated a range of time shifts (0 to 75 seconds in 7.5 second increments) for BIS relative to dosing times. An effect compartment to account for the observed lag in the BIS time profile and propofol concentrations was modeled as per equation 3.

$$\frac{dC_e}{dt} = K_{e0} \times (C_p - C_e) \quad (5)$$

where, C_p is the blood concentration in the central compartment; C_e is the effect-site concentration and k_{e0} is a linear first-order rate constant governing the drug exchange between central and effect compartments. The observed BIS values were modeled to be dependent on the effect-site propofol concentrations using a sigmoidal E_{max} model (equation 4)

$$E = E_0 - \frac{E_{max} * C_e^\gamma}{EC_{50}^\gamma + C_e^\gamma} \quad (6)$$

where E_0 is the baseline BIS; E_{max} the maximal reduction in BIS (Baseline E_0 – minimal value of BIS E_{min}); C_e the predicted propofol effect-site concentration; γ the Hill coefficient representing the steepness of the concentration-response relationship; and EC_{50} the propofol effect site concentration (in $\mu\text{g ml}^{-1}$) resulting in half maximum reduction of BIS. Log normal inter-individual variability (η_i) as described in the PK model section was assumed for EC_{50} . The residual error was best characterized by an additive error model (equation 5):

$$Y_{ij} = E_{pred,ij} + \varepsilon_{i,j}^a \quad (7)$$

where Y_{ij} represents the observed BIS in the i^{th} individual at the j^{th} timepoint; $E_{pred,i,j}$ is the corresponding predicted BIS and $\varepsilon^a_{i,j}$ is the corresponding predicted residual variable with normal distribution with a mean of zero and σ^2 variance.

Covariate analysis

The individual post-hoc parameter estimates from the base PK and PK/PD model were plotted against individual covariates to identify potential relations explaining parameter variability. Tested covariates were age, sex, height, and weight scalars including BMI, lean body mass (LBM_p derived using methods described by Peters *et al.* for children (21), and LBM_J, as described by Janmasahatian and co-workers for adults)(22) and ideal body weight (IBW) (23). Potential covariates were separately evaluated in the model for statistical significance using linear, proportional and allometric equations. Significant covariates were retained in the model using a stepwise procedure with a forward inclusion criteria ($p < 0.05$; $dOFV > 3.84$ was considered statistically significant) and a backward elimination criterion ($p < 0.01$; $dOFV > 6.63$ as significant). Other model evaluation criteria like diagnostic procedures and model stability considerations were used for final model selection.

Simulation of Different Dosing Regimens

The final PK/PD model was used to perform Monte Carlo simulations with the aim of designing a simplified dosing regimen that would maintain the BIS within the desired range of 50 ± 10 , as this is the clinical range recommended for adequate depth of anesthesia (24), and has been targeted in previous studies for simulations in children and adults (12, 25, 26). One thousand hypothetical obese individuals were randomly sampled from the National Health and Nutrition Examination Survey (NHANES) database (2005-2010) (27) such that the BMI for any selected individual was higher than the 95th percentile BMI for individuals of same age. Between subject variability in both PK and PD parameters were incorporated during simulation. The simulated maintenance regimens (described in **Supplementary section**) were altered to achieve a preset BIS target of 50 ± 10 over a period of ~ 4 hours in our virtual population. Further, the derived maintenance dosing scheme was simulated for a representative SO (median age, height and weight from our study) and lean adolescent (50th percentile weight, same height and age) using the Cortinez PD model in conjunction with Eleveld allometric PK model which was superior to other tested PK models using TBW for obese adults (14, 28). We estimated the propofol effect-site concentrations based on a new k_{e0} for the Eleveld PK - Cortinez PD model such that it resulted in a peak BIS time (T_{peak}) of 2.1 minutes as T_{peak} (29) has been reported to perform better when PK and PK/PD models from separate studies were combined.

RESULTS

Patients and Data Collection

Of the 29 SO adolescent subjects enrolled in the study, three subjects were excluded (ID: 11, 16 and 19) for the following reasons: One patient withdrew from the study and two of them had missing data due to sampling errors (9). Demographic characteristics, relevant doses and durations are summarized in Table 1. The propofol PK/PD model was developed using

propofol concentration data (n=375 samples) and BIS data (n=3334 out of total recorded 3440 values). Actual propofol concentration and BIS data are presented in Figure 1.

Pharmacokinetic Analysis

PK analysis based on a 2-compartment model from data obtained in 20 SO adolescents has been published (9). A three compartment model was found superior to the 2 compartment model (dOFV= -17.81). Inclusion of inter-individual variability (IIV) on clearance resulted in significant improvement in the model fit (dOFV = -171). Incorporation of IIV on Volume and inter-compartmental clearances resulted in (i) model non-convergence; (ii) high eta-shrinkage (>15%) indicating model over-parameterization or (iii) bimodal eta (η) distributions, and were not considered further. A systematic stepwise covariate analysis indicated TBW as the best covariate predictor of clearance using an allometric function with fixed exponent of 0.75 (Table 2). The parameter estimates for the final PK model and visual predictive checks (VPC) are presented in Table 3 and Figure 2 respectively.

Pharmacodynamic Analysis

For E_0 estimation, we had values only from 6 patients (18 data points) - it was estimated at 94.8 though no IIV was estimated within these subjects. The lowest attainable BIS $E_{\min}$ was estimated and when limited to values between 0 and 100, it was found to be 0. IIV on $E_{\min}$ was not further investigated because such an inclusion would result in prediction of negative BIS values which are not practical. This is consistent with the PD parameters in other published PD studies where maximum BIS effect is fixed at 0 (14). The lowest attainable BIS ($E_{\min}$) was 0, hence $E_{\max}$ ($=E_0-E_{\min}$) was fixed at 94.8, but derived from estimated E_0 and $E_{\min}$. A recently proposed two-compartment biophase-distribution model was explored but failed to converge (25, 26). Incorporation of IIV on EC_{50} substantially improved the model fit (dOFV = -950). No clinically significant covariates for the PD parameters of propofol were found. Table 3 shows the population parameter estimates and Figure 2 the VPC for the PK/PD model.

Residual based diagnostic plots of the final model (Supplementary Figure S1) were examined to identify trends suggesting model misspecification. The population predicted BIS were in good agreement with the observations with even distribution of individual points on both sides of the unity line ($R^2=0.681$). The slight under-prediction of BIS in the lower range (BIS < 20) was traced back to over prediction of the drug effect for low values observed from a single subject. The posthoc Bayesian individual predictions of BIS were in stronger agreement with the observations with a tighter distribution of points across the unity line ($R^2=0.89$). No specific trends were observed between conditional weighted residuals and time after dose and population predicted BIS. The stability of the final model was confirmed by rerunning the estimation on 1,000 bootstrapped datasets. The median and 95% confidence interval values for all the parameters were found to be similar to that expected from the NONMEM model run with no substantial bias (Table 3). Incorporation of a time delay (7.5 – 75 seconds lag time) resulted in higher k_{e0} estimates; they were not included in the final model as model fit progressively worsened (as inferred by increase in OFV) with increasing delay. The model with no delay had the lowest OFV and was eventually chosen as the best PK/BIS model.

Simulations and Comparison

Based on simulations, propofol induction dose of 1.4 mg/kg Adjusted body weight (ABW) followed by infusion rate $155 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 20 min, $120 \mu\text{g kg}^{-1} \text{min}^{-1}$ for the next 20 min and finally $85 \mu\text{g kg}^{-1} \text{min}^{-1}$ using a dosing weight of $70 \times (\text{TBW}/70)^{0.75} \text{ kg}$, was found to be appropriate for anesthetic maintenance in hypothetical SO population yielding blood concentrations of $\sim 3 \mu\text{g mL}^{-1}$ and BIS of 50 (Please refer to the **Supplemental Section** for details, Figures S2 for induction dose regression and S3 for dosing regimen predictions). Simulation predictions of propofol blood concentrations and BIS dosed as per the above scheme, for the hypothetical SO using Eleveld/Cortinez models yielded target propofol plasma concentrations of $\sim 3 \mu\text{g mL}^{-1}$ and BIS of 40-60 (Figure 3); k_{e0} of 0.4 min^{-1} and 0.63 min^{-1} resulted in a $T_{\text{peak}}=2.1 \text{ min}$ for the obese and lean subjects respectively. The same targets were achieved using the same dosing regimen in the lean teen using the Eleveld/Cortinez model.

DISCUSSION

This study was performed to address propofol dosing challenges posed by severe obesity in children and adolescents. A three compartment model best described propofol's PK with TBW being the most predictive covariate [$\text{CL (L min}^{-1}) = 1.65 \times (\text{TBW}/70)^{0.75}$]. The relation between propofol PK and PD (BIS) was adequately described by a sigmoid E_{max} model with an effect compartment. An effect site EC_{50} of $3.19 \mu\text{g mL}^{-1}$ was estimated; there was no clinically meaningful covariate to predict the effect site EC_{50} . Based on our PK/PD model, we simulated a propofol maintenance dosing regimen allometrically scaled to TBW to maintain adequate depth of anesthesia ($\text{BIS } 50 \pm 10$), and compared the use of the regimen using other accepted PK/PD models in obese and non-obese children.

PK data for a subset of the population published earlier was described using a two-compartmental model (9), since use of a three-compartment model did not result in an improved fit of the data *with comparable estimates* for propofol clearance. Exploratory PK/PD analysis for the present patient cohort was conducted using post-hoc PK parameters from both 2- and 3-compartment PK model parameters. The E_{max} PD model using the two PK models yielded similar EC_{50} values; however, k_{e0} estimated using the 2-compartment PK model (3.84 min^{-1} ; RSE: 55%) had high uncertainty, likely due to failure of a 2-compartmental model to capture the initial distribution phase. Hence, the 3-compartment model was determined to be a better choice to describe observations from the current study.

Comparison of PK/PD parameters and findings based on propofol PK/PD studies using BIS as PD parameter in children (30, 31), adults (25, 32), obese adults (14, 26) and our study are presented in Table 4. Consistent with published reports in obese and non-obese adults (17, 26, 33) and our previous conclusions from PK analysis of a subset of this study population (9), TBW was found to be the only weight scalar that significantly affected variations in propofol clearance in SO adolescents. The mean PK parameter estimate for clearance ($1.65 \text{ L min}^{-1} \text{ per } 70 \text{ kg}$) is also consistent with what we have reported before (1.72 L min^{-1} for a 70 kg individual) (9). Our present model uses an allometric function with a fixed exponent of 0.75 – this is close to previously reported exponent values of 0.72 (26) and 0.8 (9), and consistent with allometric theory (34). The fixed exponent was preferred over the estimated

exponent reported in our previous PK analysis (9) to prevent overparameterisation. Previously, linear (17, 33) and allometric (35) relationships between TBW and volume of distribution (V1) of propofol have been suggested. However, we did not observe any improvement in the model with incorporation of weight scalars as covariates on V1, thus supporting the conclusions by Eleveld *et. al.* that “V1 appears independent of weight for weights > about 30 kg”(28) .

BIS-effect site concentration data was well explained with a sigmoid $E_{\max}$ model without covariates, similar to other reports in children and adults (31, 36). Although two-compartment biophase-distribution models have been previously reported for propofol in lean (25) as well as SO adults (26), our data supported a mono-exponential first-order process. The two-compartment function is generally explained to be due to re-distribution of the drug in the central nervous system, more prominent after bolus injections and large infusion rate changes. Since a fairly steady propofol infusion rate with only small infusion rate changes was maintained during anesthesia, this might explain why we did not find CNS redistribution requiring a two-compartment effect-site model. The EC_{50} values presented in Table 4 are all within a narrow range of 2.12 to 3.85 $\mu\text{g ml}^{-1}$; besides, the EC_{50} in this study (3.19 $\mu\text{g ml}^{-1}$) is similar to that reported for lean children who were 14 years or older (3.3 $\mu\text{g ml}^{-1}$) undergoing middle ear surgery and obese adults (3.2 $\mu\text{g ml}^{-1}$) (12, 14). Similar to observations in obese adults, our results support the notion that obesity does not affect propofol PD in adolescents (14, 26). Although other studies found incorporation of time delays in their PD model to improve model performance (14, 30), lack of support in our data for a BIS delay could be due to the use of venous concentrations in our study which is known to lag arterial concentrations.

In clinical practice, it is customary to titrate induction dose to patient response. Although maintenance dosing is typically based on body weight and expressed as $\mu\text{g kg}^{-1}\text{min}^{-1}$, using TBW in this way for obese patients could result in overdosing and undesirable consequences (37). Servin *et. al.* used ABW to circumvent this problem with TBW as scalar for dosing and found good results with ABW; however, their conclusions were not based on an objective PD parameter like BIS, and they did not compare allometric models with TBW for propofol PK, although they found propofol clearance was correlated with TBW(17). Based on our results, we propose a propofol maintenance dosing regimen based on the nonlinear allometric relationship between clearance and TBW, as has been suggested for obese adults (14, 26). The proposed model-based dosing regimen is to be used in conjunction with muscle relaxation, midazolam premedication and fentanyl co-analgesia ($\approx 170 \mu\text{g hr}^{-1}$), as these co-medications may influence the PK/PD of propofol (38). We chose to test our proposed dosing regimen using Eleveld PKCortinez PD models as the propofol PK model developed by Eleveld *et.al.* is based on multiple studies encompassing a large population including children, teen, adults and obese adults, and had the best predictive performance when used with the Cortinez PD model for BIS predictions in obese adults (14). Ability to predict desired propofol concentrations and BIS values in the hypothetical obese and non-obese teen by simulating the developed propofol dosing regimens using accepted PK/PD model (Eleveld-Cortinez) not specifically developed for the obese teen, suggests that our proposed dosing regimen works well with a PK/PD model other than ours. Adequate

performance of PK and PD predictions for anesthetic maintenance across models for obese and lean adolescent provide further supporting evidence for the dosing based on allometry. We expect our results will serve as a guide for dosing in the SO and lean adolescent pediatric population.

One of the merits of our study is that clinical titration of propofol enabled us to capture BIS data over a wide range, unlike most other studies where propofol is titrated to target BIS ranges of 40-60 - this has allowed us to explore the full concentration-effect relationship for propofol. The downside of a clinical study is the inability to standardize opioid doses; however, opioid dosing has been reported to not affect the relation between propofol concentrations and BIS (39). We recognize that the initial small dose of midazolam could possibly affect the baseline BIS and propofol induction requirements (40). Use of venous rather than arterial samples for propofol concentration analysis could be considered a limitation of this study due to time lags between arterial and venous concentrations - in comparison to arterial concentrations, venous concentrations have been found to be lower during infusion and slightly higher after infusion was stopped (41).

In conclusion, this is the first study to describe the pharmacokinetics and pharmacodynamics of propofol in SO children and adolescents by PK/PD analysis. Simulations based on the PK/PD model lead us to propose a dosing algorithm for maintenance of propofol anesthesia in SO adolescents using TBW in an allometric function with an exponent of 0.75. This dosing schedule merits further validation in a prospective clinical study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study was funded by a Translational Research Initiative grant from Cincinnati Children's Research Foundation, Cincinnati Children's Hospital Medical Center, Cincinnati, OH. Also supported by NIH grants 1K24HD050387 (Alexander A Vinks) and the Teen-LABS Consortium (funded by cooperative agreements with the National Institute of Diabetes and Digestive and Kidney Diseases through grants U01DK072493 (Cincinnati Children's Hospital Medical Center), UM1DK072493 (Cincinnati Children's Hospital Medical Center), and UM1DK095710 (University of Cincinnati) (Thomas Inge). The findings of this study were presented in part as abstract/poster/oral presentation at the Society of Pediatric Anesthesia Annual meeting at San Antonio, 2011 and Tampa, 2013; American Society of Anesthesiology Annual Meeting, Chicago, 2011 and the American Society of Clinical Pharmacology and Therapeutics annual meeting at Indianapolis, 2013. Supported by grant K23 HD082782 Morphine Pharmacogenomics to Predict Risk of Respiratory Depression in Children CHILDREN'S HOSPITAL MEDICAL CENTER (PI:Chidambaran).

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA : the journal of the American Medical Association*. 2012; 307(5):483–90. [PubMed: 22253364]
2. Schilling PL, Davis MM, Albanese CT, Dutta S, Morton J. National trends in adolescent bariatric surgical procedures and implications for surgical centers of excellence. *Journal of the American College of Surgeons*. 2008; 206(1):1–12. [PubMed: 18155562]
3. Chidambaran V, Sadhasivam S, Diepstraten J, Esslinger H, Cox S, Schnell BM, et al. Evaluation of propofol anesthesia in morbidly obese children and adolescents. *BMC anesthesiology*. 2013; 13(1): 8. [PubMed: 23602008]

4. Kalkman CJ, Peelen LM, Moons KG. Pick up the pieces: depth of anesthesia and long-term mortality. *Anesthesiology*. 2011; 114(3):485–7. [PubMed: 21258233]
5. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesthesia and analgesia*. 2005; 100(1):4–10. [PubMed: 15616043]
6. Kertai MD, Pal N, Palanca BJ, Lin N, Searleman SA, Zhang L, et al. Association of perioperative risk factors and cumulative duration of low bispectral index with intermediate-term mortality after cardiac surgery in the B-Unaware Trial. *Anesthesiology*. 2010; 112(5):1116–27. [PubMed: 20418692]
7. Leslie K, Short TG. Low bispectral index values and death: the unresolved causality dilemma. *Anesthesia and analgesia*. 2011; 113(3):660–3. [PubMed: 21862602]
8. Igarashi T, Nagata O, Iwakiri H, Ikeda M, Uezono S, Ozaki M. [Two cases of intraoperative awareness during intravenous anesthesia with propofol in morbidly obese patients]. *Masui*. 2002; 51(11):1243–7. [PubMed: 12481451]
9. Diepstraten J, Chidambaran V, Sadhasivam S, Esslinger HR, Cox SL, Inge TH, et al. Propofol clearance in morbidly obese children and adolescents: influence of age and body size. *Clinical pharmacokinetics*. 2012; 51(8):543–51. [PubMed: 22690673]
10. Sadhasivam S, Ganesh A, Robison A, Kaye R, Watcha MF. Validation of the bispectral index monitor for measuring the depth of sedation in children. *Anesthesia and analgesia*. 2006; 102(2):383–8. [PubMed: 16428529]
11. van Kralingen S, van de Garde EM, van Dongen EP, Diepstraten J, Deneer VH, van Ramshorst B, et al. Maintenance of anesthesia in morbidly obese patients using propofol with continuous BIS-monitoring: a comparison of propofol-remifentanyl and propofol-epidural anesthesia. *Acta Anaesthesiol Belg*. 2011; 62(2):73–82. [PubMed: 21919373]
12. Rigouzzo A, Girault L, Louvet N, Servin F, De-Smet T, Piat V, et al. The relationship between bispectral index and propofol during target-controlled infusion anesthesia: a comparative study between children and young adults. *Anesthesia and analgesia*. 2008; 106(4):1109–16. table of contents. [PubMed: 18349180]
13. Olutoye OA, Yu X, Govindan K, Tjia IM, East DL, Spearman R, et al. The effect of obesity on the ED₉₅ of propofol for loss of consciousness in children and adolescents. *Anesthesia and analgesia*. 2012; 115(1):147–53. [PubMed: 22575569]
14. Cortinez LI, De la Fuente N, Eleveld DJ, Oliveros A, Crovari F, Sepulveda P, et al. Performance of propofol target-controlled infusion models in the obese: pharmacokinetic and pharmacodynamic analysis. *Anesthesia and analgesia*. 2014; 119(2):302–10. [PubMed: 24977639]
15. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007; 120(Suppl 4):S164–92. [PubMed: 18055651]
16. Wang Y, Jadhav PR, Lala M, Gobburu JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. *Journal of clinical pharmacology*. 2012; 52(10):1601–6. [PubMed: 22162537]
17. Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. *Anesthesiology*. 1993; 78(4):657–65. [PubMed: 8466066]
18. Le Grange D, Doyle PM, Swanson SA, Ludwig K, Glunz C, Kreipe RE. Calculation of expected body weight in adolescents with eating disorders. *Pediatrics*. 2012; 129(2):e438–46. [PubMed: 22218841]
19. Knibbe CA, Koster VS, Deneer VH, Stuurman RM, Kuks PF, Lange R. Determination of propofol in low-volume samples by high-performance liquid chromatography with fluorescence detection. *J Chromatogr B Biomed Sci Appl*. 1998; 706(2):305–10. [PubMed: 9551817]
20. Zhang L, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. *Journal of pharmacokinetics and pharmacodynamics*. 2003; 30(6):387–404. [PubMed: 15000421]
21. Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. *Br J Anaesth*. 2011; 106(5):719–23. [PubMed: 21498495]

22. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clinical pharmacokinetics*. 2005; 44(10):1051–65. [PubMed: 16176118]
23. Lemmens HJ, Brodsky JB, Bernstein DP. Estimating ideal body weight--a new formula. *Obesity surgery*. 2005; 15(7):1082–3. [PubMed: 16105412]
24. Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. *Anesthesiology*. 1997; 87(4):808–15. [PubMed: 9357882]
25. Bjornsson MA, Norberg A, Kalman S, Karlsson MO, Simonsson US. A two-compartment effect site model describes the bispectral index after different rates of propofol infusion. *Journal of pharmacokinetics and pharmacodynamics*. 2010; 37(3):243–55. [PubMed: 20414709]
26. van Kralingen S, Diepstraten J, Peeters MY, Deneer VH, van Ramshorst B, Wiezer RJ, et al. Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients. *Clinical pharmacokinetics*. 2011; 50(11):739–50. [PubMed: 21973271]
27. U.S. Department of Health and Human Services CfDcAP. National Health and Nutrition Examination Survey Data Hyattsville, MD2005-2010 [07/29/2013]. Available from: http://wwwn.cdc.gov/nchs/nhanes/search/nhanes05_06.aspx; http://wwwn.cdc.gov/nhanes/search/nhanes07_08.aspx; http://wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx
28. Eleveld DJ, Proost JH, Cortinez LI, Absalom AR, Struys MM. A general purpose pharmacokinetic model for propofol. *Anesthesia and analgesia*. 2014; 118(6):1221–37. [PubMed: 24722258]
29. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL. Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology*. 2003; 99(2):324–33. [PubMed: 12883405]
30. Coppens MJ, Eleveld DJ, Proost JH, Marks LA, Van Bocxlaer JF, Vereecke H, et al. An evaluation of using population pharmacokinetic models to estimate pharmacodynamic parameters for propofol and bispectral index in children. *Anesthesiology*. 2011; 115(1):83–93. [PubMed: 21555936]
31. Rigouzzo A, Servin F, Constant I. Pharmacokinetic-pharmacodynamic modeling of propofol in children. *Anesthesiology*. 2010; 113(2):343–52. [PubMed: 20613468]
32. Wiczling P, Bienert A, Sobczynski P, Hartmann-Sobczynska R, Bieda K, Marcinkowska A, et al. Pharmacokinetics and pharmacodynamics of propofol in patients undergoing abdominal aortic surgery. *Pharmacological reports : PR*. 2012; 64(1):113–22. [PubMed: 22580527]
33. Cortinez LI, Anderson BJ, Penna A, Olivares L, Munoz HR, Holford NH, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. *Br J Anaesth*. 2010; 105(4):448–56. [PubMed: 20710020]
34. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annual review of pharmacology and toxicology*. 2008; 48:303–32.
35. Schuttler J, Ihmsen H. Population pharmacokinetics of propofol: a multicenter study. *Anesthesiology*. 2000; 92(3):727–38. [PubMed: 10719952]
36. Jeleazcov C, Ihmsen H, Schmidt J, Ammon C, Schwilden H, Schuttler J, et al. Pharmacodynamic modelling of the bispectral index response to propofol-based anaesthesia during general surgery in children. *Br J Anaesth*. 2008; 100(4):509–16. [PubMed: 18270231]
37. Gaszynski T, Strzelczyk J, Machala W, Gaszynski W. Reduction of a total propofol consumption in morbidly obese patients during general anesthesia due to BIS monitoring. *Obesity surgery*. 2005; 15(7):1084. author reply 5. [PubMed: 16105413]
38. Vuyk J, Mertens MJ, Olofsen E, Burm AG, Bovill JG. Propofol anesthesia and rational opioid selection: determination of optimal EC50-EC95 propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology*. 1997; 87(6):1549–62. [PubMed: 9416739]
39. Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E. Effects of fentanyl, alfentanil, remifentanyl and sufentanyl on loss of consciousness and bispectral index during propofol induction of anaesthesia. *Br J Anaesth*. 2001; 86(4):523–7. [PubMed: 11573626]
40. Cressey DM, Claydon P, Bhaskaran NC, Reilly CS. Effect of midazolam pretreatment on induction dose requirements of propofol in combination with fentanyl in younger and older adults. *Anaesthesia*. 2001; 56(2):108–13. [PubMed: 11167469]

41. Wang YP, Cheng YJ, Fan SZ, Liu CC. Arteriovenous concentration differences of propofol during and after a stepdown infusion. *Anesthesia and analgesia*. 1994; 79(6):1148–50. [PubMed: 7978440]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

- **What is already known:** Total body weight is predictive of propofol clearance in severely obese adolescents but effect of obesity on propofol pharmacodynamics in this population is unknown.
- **What this study adds:** Obesity does not affect the propofol concentration - Bispectral Index relationship in severely obese adolescents.
- **Clinical implications:** Simulations based on the pharmacokinetic-pharmacodynamic model lead us to propose a propofol dosing algorithm to maintain adequate anesthetic depth during propofol anesthesia in severely obese adolescents. This is an important step towards addressing propofol dosing challenges in this population.

Figure 1.

Propofol concentration and BIS-time plots for the study cohort. Time 0 is the start of propofol infusion. Panel A shows measured propofol concentrations over time from 26 patients with actual measurements marked by open ended-circles (≈ 14 samples/patient). Panel B represents BIS data in 1-minute increments from 23 subjects in the cohort (≈ 144 data points/patient). BIS data from 3 subjects were excluded from analysis because sevoflurane was used for anesthetic induction in one individual who did not want to have their venous catheter placed while awake (ID: 8); and inability to retrieve all recorded data from the BIS monitor for the remaining two (ID: 3 and 25).

Figure 2.

Prediction Corrected Visual Predictive Check of PK (propofol concentrations) and PD (BIS) based on developed PK/PD models. Prediction Corrected Visual Predictive Check is presented as means of simulation diagnostics for the (A) 3-Compartmental PK model and (B) Pharmacokinetic-Pharmacodynamic model. The PK and PK/PD model were simulated $n=1000$ times and the dependent variable was subject to prediction and variance correction to account of differences due to titrated individual dosing and differences in length of surgery. The darker solid black line represents the median prediction corrected observations and darker dashed black lines present the 5th and 95th percentiles of the prediction corrected observations. Similarly, the thinner solid black line represents the model simulated median values and the thinner dashed black lines present the 5th and 95th percentiles of the same. The shaded grey area in the middle represents 90% confidence interval for the model simulated median values while the lighter shaded grey areas represent the 90% confidence interval for the model simulated 5th/95th percentiles (bottom and top shaded areas). The prediction corrected observations are represented by grey circles. Time after most recent dose/infusion rate change was used as the independent variable.

Figure 3.

Predictions of plasma propofol concentrations and BIS, based on simulations using proposed propofol dosing regimen for a representative SO (median age, height and weight from our study) and lean adolescent (50th percentile weight, same height and age). Panel A represents predicted propofol concentrations and Panel B represents BIS values during and after maintenance of propofol anesthesia over a 60 minute period, for a hypothetical obese (Total Body Weight = 130 kg, Adjusted Body Weight = 78.7 kg) and lean (Total Body Weight = 53.4 kg, Adjusted Body Weight = 48.1 kg) female of the same age (15.7 years of age) and height (166 cm). In each panel, median predictions based on our developed PK/PD model for the obese adolescent is given by the black line; the Eleveld-Cortinez PK/PD model based prediction for the obese adolescent is given by the gray colored line, and the lean adolescent is represented by the dotted line. The dosing regimen proposed maintains adequate propofol concentrations and BIS levels in conjunction with either model.

Table 1

Characteristics of 26 severely obese subjects participating in the study

	Mean	Range	SD
Sex (F - M)		16 - 10	
Age (Years)	15.7	9 - 18	2.1
Total Body weight (Kg)	131	70 - 189	31.7
Body Mass Index (Kg/m ²)	48	31 - 69	9.7
Ideal Body Weight (Kg)	60	39 - 78	10.9
Lean Body Mass _P (Kg)	77.0	46.6 - 102.6	14.4
Lean Body Mass _J (Kg)	64.2	38.4 - 87.3	13.9
Adjusted Body Weight (Kg)	91.8	55.5 - 121	17.2
Duration of propofol infusion (hours)	2.3	0.68 - 4.83	0.99
Time to induction (minutes)	1.3	0.5 - 2.6	0.5
Fentanyl equivalent dose ($\mu\text{g h}^{-1}$) [‡]	170	60 - 295	65

LBM_P = Lean Body Mass (Peters, 2011); **LBM_J** = Lean Body Mass (Janmasahatian, 2005); **TBW** = Total Body Weight;

[‡]Fentanyl equivalent dose includes morphine/hydromorphone doses at end of surgery, equivalents calculated as fentanyl 100 μg $\approx$ morphine 10mg $\approx$ hydromorphone 2mg)

Table 2

Stepwise covariate analysis for the pharmacokinetic model of propofol in 26 severely obese adolescents.

Model Description	Covariate model	OFV	OFV
2 compartment model	-	-303.74	
3 compartment model	-	-309.79	-6.05
2 compartment model + IIV on CL and V	-	-463.29	-153.5
Base Model : 3 compartment model + IIV on CL	-	-481.10	-171.31
Base Model + IBW on CL	$CL_i = CL_{pop} \left(\frac{IBW}{58.7} \right)^{0.75}$	-483.46	-2.36
Base Model + LBM _J on CL	$CL_i = CL_{pop} \left(\frac{LBM_J}{59.2} \right)^{0.75}$	-487.7	-6.6
Base Model + ABW on CL	$CL_i = CL_{pop} \left(\frac{ABW}{70} \right)^{0.75}$	-493.3	-12.2
Base Model + LBM _P on CL	$CL_i = CL_{pop} \left(\frac{LBM_P}{53} \right)^{0.75}$	-494.5	-13.4
2 Compartmental Model + IIV on CL and V ₁ + TBW on CL	$CL_i = CL_{pop} \left(\frac{TBW}{70} \right)^{0.8}$	-481.13	-0.03
Base Model + TBW on CL with 0.75 exponent	$CL_i = CL_{pop} \left(\frac{TBW}{70} \right)^{0.75}$	-498.55	-17.45
Base Model + TBW on CL with 0.8 exponent	$CL_i = CL_{pop} \left(\frac{TBW}{70} \right)^{0.80}$	-499.04	-17.94

OFV = objective function value; **OFV** = Change in OFV; **IIV** = Interindividual Variability; **CL** = Plasma Clearance; $i = i^{th}$ individual; **CL_{pop}** = Population mean value for clearance; **BMI** = Body mass index; **LBM_P** = Lean Body Mass as described by Peter *et. al.*, 2011; **LBM_J** = Lean Body Mass, based on Janmahasatian's formula, 2005; **TBW** = total body weight; **IBW** = Ideal Body Weight; For all above models, eta and epsilon shrinkages ranged between 2.1 - 7.4% and 2.9 - 5.2 % respectively.

Table 3

Population pharmacokinetic and pharmacodynamic parameters for the final PK/PD model in severely obese adolescents.

	Parameter	Model Estimate		Non-parametric Bootstrap	
		Estimate	95 % CI ^{**}	Median	95 % CI ^{††}
PK Model	$CL_{70\text{ kg}} (\text{L min}^{-1})^*$	1.65	1.37 - 1.93	1.62	1.29 - 1.86
	$V_c (\text{L})$	14.0	6.8 - 21.2	14.7	8.6 - 25.4
	$Q_2 (\text{L min}^{-1})$	4.0	2.5 - 5.5	4.0	2.6 - 5.8
	$V_2 (\text{L})$	56.9	31.2 - 82.3	55.9	31.4 - 84.7
	$Q_3 (\text{L min}^{-1})$	1.50	1.02 - 1.97	1.58	1.12 - 2.16
	$V_3 (\text{L})$	247	51 - 443	279	129 - 539
	γ	0.75	Fixed	0.75	-
	Inter-individual Variability				
	ω_{CL}^2	0.043	0.004 - 0.081	0.045	0.015 - 0.102
	Proportional Residual Error				
	σ_{prop}^2	0.085	0.06 - 0.11	0.083	0.059 - 0.11
PK-PD Model	Parameter	Estimate	95 % CI^{**}	Median	95 % CI^{††}
	$K_{e0} (\text{min}^{-1})$	0.58	0.33 - 0.82	0.58	0.39 - 1.02
	$EC_{50} (\mu\text{g/ml})$	3.19	2.85 - 3.53	3.19	2.88 - 3.58
	γ_{Hill}	1.45	1.27 - 1.63	1.44	1.30 - 1.69
	E_{max}	94.83	Fixed	94.83	-
	E_{min}	0	Fixed	0	-
	Inter-individual Variability				
	ω_{EC50}^2	0.081	0.045 - 0.12	0.078	0.045 - 0.12
	Additive Residual Error				
	σ_a^2	32.3	24.1 - 40.6	32.02	24.5 - 40.9

Model parameters for the final 3-compartment PK model with clearance normalized to allometrically scaled total body weight, and the E_{max} effect-compartment PD model relating propofol concentration to bispectral index. Model parameter estimates are compared with non-parametric bootstrap results. **CL₇₀** = Clearance normalized to a 70 kg individual

* CL in the i^{th} individual CL_i is given by $CL_{70\text{ kg}} \times (\text{TBW}/70)^{0.75}$. V_1 = volume of distribution of the central compartment; V_2 = volume of distribution of the first peripheral compartment; V_3 = volume of distribution of the second peripheral compartment; Q_2 = inter-compartmental clearance from the central compartment to the first peripheral compartment; Q_3 = inter-compartmental clearance from the central compartment to the second peripheral compartment ω^2 and σ^2 : Respective variances. γ : Allometric exponent for clearance. γ_{Hill} : Hill coefficient; **BIS**: Bispectral index; E_{max} : Maximal reduction in BIS; **EC₅₀**: Propofol concentration at half-maximum effect; E_{min} : Minimal BIS attainable due to propofol; **k_{e0}**: first-order equilibrium constant linking the central pharmacokinetic compartment to the effect-site compartment.

** Confidence interval estimated based on standard error estimates.

†† The 2.5th and 97.5th percentile of the bootstrap parameter estimates.

Table 4
Comparison of pharmacokinetic-pharmacodynamic (PK-PD) parameters from propofol PK/PD studies with bispectral index (BIS) as PD parameter in different populations.

Population studied	Reference (surgical cohort, Blood draw)	Subjects (N, age, weight range, median weight)	PK model	V1 (L)	V2 (L)	V3 (L)	CL L/min	Q2 (L/min)	Q3 (L/min)	PD Model	k _{e0} /min	T1/2 Ke0	EC ₅₀ Mcg/ml	γ	E _{max}	E ₀	Conclusions
Children	Coppens ²⁶ Dental surgery Venous	28, 4-11 yr, 18-54 kg 21.5 kg	3 compt model with PK parameters scaled to TBW	12.18	16.38	66.57	2.05	5.32	1.74	Sigmoid Emax model	0.79 (0.33-3.30) *	0.88 (2.10-0.21) *	3.85 (2.78-4.52) *	1.50 (1.02-2.07) *			Using population PK models from the literature instead of the 'true' PK model led to better predictions of BIS; Best performance with Schnider PK model
	Riguozzo ²⁷ Middle ear surgery Venous	16 children (6-12yr) 13 adults (13-35y)	4 PK models compared	In children, the predicted concentration/effect relationships were best described with Schnider PK model (fixed V1, CL scaled to Lean Body Mass, TBW and Height) – no parameters estimated							0.272 (A) 1.770 (C)	2.55 (A) 0.39 (C)	3.07 (A) 3.71 (C)	-	E _{min} 0	95.8 (A) 95.2 (C)	Puberty was found to be a covariate for K _{e0} and Ce ₅₀ .
	Wiczling ²⁸ AAA surgery Venous	10 males 50-75 yr; 50-92 kg #	2 compt model – no covariates	24.7	112	.	2.64	0.99	-		0.240	2.89	2.19	1 fixed	E _{min} fixed to 1	97	The body weight, age, blood pressure and gender were not identified as statistically significant covariates for all PK/PD parameters
Adults	Bjornsson ²⁵ Healthy volunteers Arterial	21; 19-47 yr; 52-97 kg 70 kg	4 compt model # with lag-time 5.23 s	2.88 4.47	12.4	71.2	1.6 1.29	0.68	0.46	2-compt effect-site model	0.16 k _{e12} 0.114 k _{e21} 0.021	**	2.55	2.93	90.4	93	The model predicted CL to increase by 0.73% for every kilogram difference from the median weight (70 kg);

Population studied	Reference (surgical cohort, Blood draw)	Subjects (N, age, weight range, median weight)	PK model	V1 (L)	V2 (L)	V3 (L)	CL L/min	Q2 (L/min)	Q3 (L/min)	PD Model	k _{e0} /min	T1/2 Kd0	EC ₅₀ Mcg/ml	γ	E _{max}	E ₀	Conclusions
Obese Adults	Van Kralingen ²⁴ Bariatric surgery Arterial	20; 45(12) yr, 98-167 kg 124 kg	3 compt, CL allometrically scaled to TBW – exponent 0.72	2.55	12.53	60.40	2.33	1.66	0.92		0.095 k _{e12} 0.05 k _{e21} 0.049	***	2.12	8.76	62.1	92	No covariates for other PK/PD parameters.
	Cortinez ⁸ Bariatric surgery Arterial	20; 21-53 yr 85-141 kg Scaled to 70 kg	5 PK models tested; Eleveld superior to other tested models using TBW; CL allometrically scaled to TBW – exponent 0.75	8.1	29	134	1.53	1.42	0.61	Emax with time lag of 0.44 minutes	0.190	3.65	3.29	1.59	E _{min} fixed to 0	97	The Eleveld allometric 3 compt model is based on age, healthy vs. patient, weight and gender covariates for CL, V2, V3, CL, V2, V3, Q2, Q3. No relevant effect of obesity on propofol concentration–BIS relationship
Obese Children	This study Bariatric surgery Venous	26; 9-18 yr, 70-189 kg 129.5 kg	3 compt model, CL allometrically scaled to TBW – exponent 0.75	7.57	30.76	133.51	1.65	2.52	0.95	Sigmoid Emax model	0.58	1.20	3.19	1.45	94.8	94.8	TBW is the major determinant of CL using allometric function with an exponent of 0.75. No significant covariates for other PK/PD parameters.

Volumes and Clearances from different studies were standardized to a 70 Kg individual using allometric coefficients of 1 and 0.75 respectively as per the median weight reported in the study.

Abbreviations: V1 = volume of distribution of the central compartment; V2 = volume of distribution of the first peripheral compartment; V3 = volume of distribution of the second peripheral compartment; V4 = volume of distribution of the second peripheral compartment; CL=Clearance; Q2 = inter-compartmental clearance from the central compartment to the first peripheral compartment; Q3 = inter-compartmental clearance from the central compartment to the second peripheral compartment; ke0: first-order equilibrium constant linking the central pharmacokinetic compartment to the effect-site compartment. ke12 = rate constant from the central to the peripheral effect-site compartment; ke21 = rate constant from the peripheral to the central effect-site compartment; EC50: Propofol concentration at half-maximum effect; γ: Hill coefficient; BIS: Bispectral index; Emax: Maximal reduction in BIS; Emin: Minimal BIS attainable due to propofol; C=Child; compt=compartment; TBW=Total Body Weight

No weight scaling was performed as median weights not reported

* Range provided for the parameter estimated using different models.

A two bio phase compartment model was developed and Ke0 cannot be directly translated to T1/2 Ke0.