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RESEARCH REPORT

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A manual propofol infusion regimen for neonates and infants

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Abstract

Aims: Manual propofol infusion regimens for neonates and infants have been determined from clinical observations in children under the age of 3 years undergoing anesthesia. We assessed the performance of these regimens using reported age-specific pharmacokinetic parameters for propofol. Where performance was poor, we propose alternative dosing regimens.

Methods: Simulations using a reported general purpose pharmacokinetic propofol model were used to predict propofol blood plasma concentrations during manual infusion regimens recommended for children 0-3 years. Simulated steady state concentrations were 6-8 $\mu g.mL^{-1}$ in the first 30 minutes that were not sustained during 100 minutes infusions. Pooled clinical data (n = 161, 1902 plasma concentrations) were used to determine an alternative pharmacokinetic parameter set for propofol using nonlinear mixed effects models. A new manual infusion regimen for propofol that achieves a steady-state concentration of 3 $\mu g.mL^{-1}$ was determined using a heuristic approach.

Results: A manual dosing regimen predicted to achieve steady-state plasma concentration of 3 $\mu g.mL^{-1}$ comprised a loading dose of 2 $mg.kg^{-1}$ followed by an infusion rate of 9 $mg.kg^{-1}.h^{-1}$ for the first 15 minutes, 7 $mg.kg^{-1}.h^{-1}$ from 15 to 30 minutes, 6 $mg.kg^{-1}.h^{-1}$ from 30 to 60 minutes, 5 $mg.kg^{-1}.h^{-1}$ from 1 to 2 hours in neonates (38-44 weeks postmenstrual age). Dose increased with age in those aged 1-2 years with a loading dose of 2.5 $mg.kg^{-1}$ followed by an infusion rate of 13 $mg.kg^{-1}.h^{-1}$ for the first 15 minutes, 12 $mg.kg^{-1}.h^{-1}$ from 15 to 30 minutes, 11 $mg.kg^{-1}.h^{-1}$ from 30 to 60 minutes, and 10 $mg.kg^{-1}.h^{-1}$ from 1 to 2 hours.

Conclusion: Propofol clearance increases throughout infancy to reach 92% that reported in adults (1.93 L.min.70 kg^{-1}) by 6 months postnatal age and infusion regimens should reflect clearance maturation and be cognizant of adverse effects from concentrations greater than the target plasma concentration. Predicted concentrations using a published general purpose pharmacokinetic propofol model were similar to those determined using a new parameter set using richer neonatal and infant data.

KEYWORDS

anesthetic techniques, anesthetics, infants, infusion, intravenous, neonates, pediatrics, propofol, TIVA

1 | INTRODUCTION

There are few practical recommendations for propofol infusion in neonates and infants, attributable to scarce pharmacokinetic parameters estimates in this cohort. The lower age limit is 1-3 years for pharmacokinetic parameter estimates programmed in common target controlled infusion (TCI) devices that use Paedfusor[1,2] and Kataria[3] parameter sets.

A manual infusion regime derived to maintain stable blood plasma concentrations of 3 $\mu g.mL^{-1}$ using the Kataria parameter set are commonly used in children.[4] Extrapolation of this regime to neonates and infants is unsuitable since maturational aspects of propofol metabolism in this population pose them at risk of propofol accumulation and consequent plasma concentrations greater than 3 $\mu g.mL^{-1}$.[5-8] Steur and colleagues developed manual propofol infusion regimens for neonates and infants from clinical observations in children 0-3 years undergoing anesthesia.[9] Although the authors report that the dosages provided with these schemes were sufficient for most children and allowed rapid recovery times, there is uncertainty about propofol plasma concentrations reached in this population. In addition, suggested propofol induction doses of 3-5 $mg.kg^{-1}$ are associated with hypotension in neonates.[10]

A pharmacokinetic-pharmacodynamic (PKPD) parameter set that is theoretically applicable to neonates, infants and children, has recently been published by Eleveld and colleagues.[11] The authors analyzed propofol PK data and BIS data from 1033 patients of a wide age range (27 weeks postmenstrual age to 88 years) with data obtained from 30 published studies. Although growth and maturational aspects of propofol disposition are incorporated in the estimated parameters, the assessment of pharmacokinetic covariates such as fat mass and the use of BIS as a surrogate electroencephalographic measure of depth of anesthesia remains uncertain in neonates and infants and might bias model predictions in this population.[12,13]

We aimed to evaluate the manual propofol infusion regimens[9] published for neonates and infants using the pharmacokinetic propofol parameter set estimated by the general purpose model.[11] This general purpose model included a limited cohort of neonates and so we developed a simple pharmacokinetic model from previously published propofol studies in children 0-11 years to propose alternative manual infusion guidelines that targeted a plasma concentration of 3 $\mu g.mL^{-1}$ in neonates and infants; infusion regimens consistent with previously used pediatric manual infusion regimens.[4] This methodology uses a basic tenant of pharmacology known as the target concentration approach where an understanding of pharmacokinetics is used to predict a dose that achieves a target concentration, associated with a target effect.[14-16]

What is already known about this subject

- Propofol infusion regimens for neonates and infants have been developed from clinical observations in children 0-3 years undergoing anesthesia.
- These regimens have not been reviewed using published neonatal and infant pharmacokinetic parameters.

What this study adds

- A pharmacokinetic parameter set using current propofol infusion regimens in neonates predicted propofol plasma concentrations 6-8 $\mu g.mL^{-1}$ in the first 30 minutes that were not sustained during 100 minutes infusions.
- Reevaluation of propofol plasma time-concentration profiles led to alternative dose regimens that achieve a target plasma concentration of 3 $\mu g.mL^{-1}$.
- Neonates (38-44 weeks postmenstrual age) required a loading dose of 2 $mg.kg^{-1}$ followed by an infusion rate of 9 $mg.kg^{-1}.h^{-1}$ for the first 15 minutes, 7 $mg.kg^{-1}.h^{-1}$ from 15 to 30 minutes, 6 $mg.kg^{-1}.h^{-1}$ from 30 to 60 minutes, and 5 $mg.kg^{-1}.h^{-1}$ from 1 to 2 hours.

2 | MATERIALS AND METHODS

The analysis comprised three parts:

1. Review simulated plasma concentrations in neonates and infants from infusion rates described by Steur and colleagues[9] using propofol parameter estimates contained in a general purpose model described by Eleveld and colleagues.[11]
2. Undertake a propofol population analysis in children 0-11 years using time-concentration profiles from published analyses in order to develop a simple pharmacokinetic model that describes these profiles in neonates, infants, and children.
3. Estimate infusion rates using time intervals similar to those described by McFarlan and colleagues[4] that simulate a target plasma concentration of 3 $\mu g.mL^{-1}$ using the simpler pharmacokinetic parameter model and its parameter estimates

2.1 | Simulations using Eleveld parameter estimates for neonates and infants

We investigated infusion regimens proposed by Steur.[9] Eleven individuals representing a distribution of ages from 37 weeks PMA to 3 years (Table 1) were taken from an existing data base.[17] Propofol plasma concentrations were simulated for each of these individuals based on their covariates (age, weight, height, fat-free mass) using the pharmacokinetic parameter set published by Eleveld and colleagues.[11] The Steur regimen recommended a 3-5 $mg.kg^{-1}$ induction dose. Simulation for these studies were performed in NONMEM (NONMEM 7.3, Icon Development Solutions, Ellicott City, MD, USA). Data processing and visualization steps were performed using RStudio (RStudio, Integrated Development for R, Boston, MA).

TABLE 1 Individuals used to review pharmacokinetic parameter sets in children 0-3 y

ID	PMA (wk)	Weight (kg)	Height (cm)	Sex
1	37	3.5	59.2	female
2	39	4	62.3	female
3	40	3.95	62.0	female
4	50	4.8	61.2	female
5	55	6.4	74.2	male
6	66	7.5	79.2	female
7	76	7.6	79.6	male
8	81	9	84.8	male
9	92	9.5	86.5	female
10	138	13.5	90	male
11	196	14	95	female

2.2 | Propofol pharmacokinetic parameter set derivation

Pediatric time-concentration data were pooled from five sources: Allegaert and colleagues (n = 25, PMA 27-43 weeks),[8] Murat and colleagues (n = 12, age 1-3 years)[18] Kataria and colleagues (n = 53, age 3-11 years),[3] Feuntes and colleagues (n = 30, age 1-12 years),[19] and Sepulveda (n = 41, age 3-26 months). These pooled data (1912 observations) were used for analysis. This is the biggest pediatric-specific data set available for analysis and is larger than the neonatal component of the Eleveld analysis. Propofol pharmacokinetics were described using a three-compartment mamillary model with first-order elimination. The model was parameterized in terms of clearances (CL, Q2, Q3), and volumes of distribution (V1, V2, V3). Theory-based allometric scaling[20] was used to scale pharmacokinetic parameter estimates for size and were standardized to an adult with a total body weight (TBW) of 70 kg,[21] ie,

$$\text{F size} = \left(\frac{\text{TBW}_{\text{Child}}}{70}\right)^{\text{PWR}}$$

where Fsize is the parameter (eg, CL, V, half-time; $T_{1/2}$) and PWR is the allometric exponent; ¾ for CL, 1 for V and ¼ for $T_{1/2}$. Maturation of clearance was described using a sigmoid Emax model, ie,

$$\text{CLi} = \text{CL std}\, x \frac{\text{PMA}^{\text{Hill}}}{\text{TM}_{50}^{\text{Hill}} + \text{PMA}^{\text{Hill}}}$$

The TM_{50} describes the maturation half-time, while the Hill coefficient relates to the slope of this maturation profile; CLstd is clearance standardized to a 70 kg person using allometry.

Similar models were used to explore volume parameter changes with age. Population parameter variability was described using exponential models, which is equivalent to assuming a log-normal distribution and avoids biologically inappropriate parameter values of zero or less. Residual unidentified variability (RUV) was modeled using both proportional (RUV_{PROP}) and additive residual (RUV_{ADD}) errors. The between subject variability ($\eta_{RUV,i}$) of the RUV was also estimated. Population parameters, covariate effects, and variances were estimated using the first-order conditional estimation method with interaction. Model equations were integrated using ADVAN = 11 with TRANS = 4.

The quality of fit of the pharmacokinetic model to the data was assessed by the NONMEM objective function and visual examination of plots of observed vs predicted plasma concentrations. Nonparametric bootstrap methods provided a means to evaluate parameter uncertainty.[22] A total of 1000 simulations were used to estimate confidence intervals. A prediction corrected visual predicted check[23] was used to evaluate how well the model predicted the distribution of observations.

Shrinkage was also estimated. If no data are available on a particular individual, the individual's estimate will be equal to the population value; the variance is shrinking toward zero as the quantity of information at the individual level diminishes, a phenomenon defined as η-shrinkage (Sh). When there is no shrinkage the model is correct and individual data are sufficiently abundant for individual parameter estimation. Data contain virtually no information about these parameters when shrinkage is 100% and the individual parameter values approach the typical parameter value.

2.3 | Infusion rates using time intervals similar to McFarlan that achieve a target plasma concentration of 3 μg.mL^{-1} using the new PK parameter set

Predicted propofol concentrations when using dosing regimens by Steur with the simpler parameter set were evaluated in the 11 children (Table 1). The new propofol parameter set was used to perform simulations with the intention of designing an improved dosing regimen based on the 15-minute rate changes proposed by McFarlan and colleagues. We aimed to target a propofol plasma concentration of 3 μg.mL^{-1} with deviations no greater than 5% in the 11 typical patients, while minimizing the number of rate changes required. Children were then grouped into age groups 37-44 weeks PMA, 44-52 weeks PMA, 52-92 weeks PMA (3-12 months), and 1-3 years. Simulations were performed in a population of 1000 simulated children aged from 24 weeks PMA up to 3 years of postnatal age.

3 | RESULTS

3.1 | Simulated concentrations using the Eleveld general model in neonates and infants

Use of the Eleveld general model predicted propofol plasma concentrations that were 6-8 μg.mL^{-1} in the first 30 minutes that were not sustained during 100 minutes infusions in neonates with the Steur regimen (Figure 1). Although concentrations in infants 3 months age and older achieved an initial target plasma concentration of 3 μg.mL^{-1},

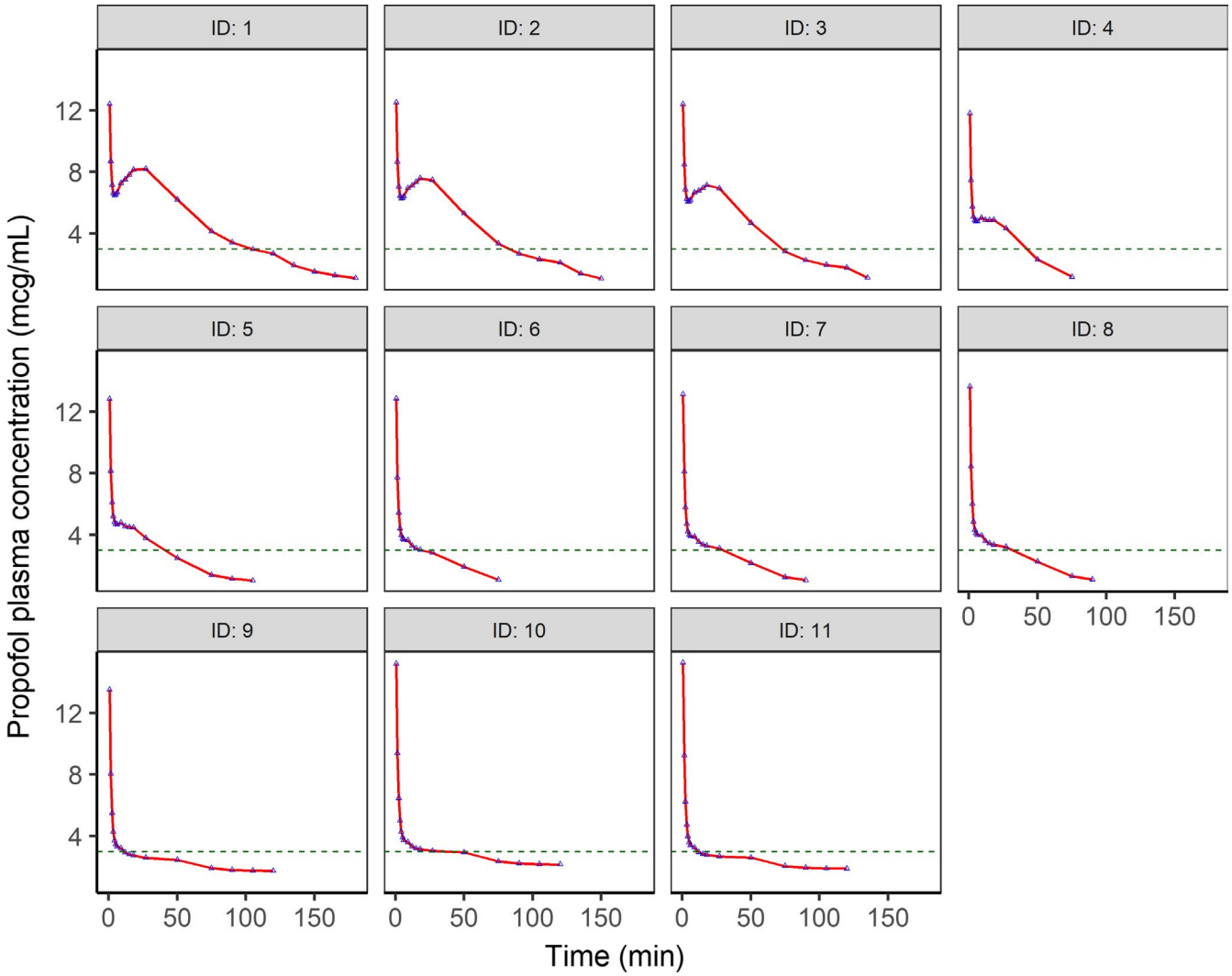

FIGURE 1 Simulated propofol plasma concentrations in 11 children aged 0-3 years using the Eleveld parameter set. Plasma concentrations when using the Steur dosing regimens with a 4 mg/kg induction dose are shown. The simulated infusions were stopped at 100 minutes after the initial bolus was given [Colour figure can be viewed at wileyonlinelibrary.com]

subsequent predicted concentrations were lower than those commonly associated with anesthesia.

3.2 | Pediatric pharmacokinetic parameter estimates

Propofol pharmacokinetics were adequately described by a three-compartment distribution model with first-order elimination. The maturation function described clearance changes during infancy; clearance was 92% that reported in adults by 6 months postnatal age (Figure 2) and was described using a maturation half-time (TM_{50}) of 42 weeks.[24] We were unable to tease out maturation changes in other parameters. Final pharmacokinetic parameter estimates and their associated population parameter variability (PPV) are shown in Table 2. Shrinkage was acceptable and less than 15% for all parameters. The correlation of between subject variability for PK parameters is shown in Table S1. Prediction corrected VPCs for propofol pharmacokinetics are shown in Figure S1.

3.3 | Infusion rates using time intervals similar to McFarlan that achieve a target plasma concentration of 3 $\mu g.mL^{-1}$ using the simpler PK parameter set

Predicted plasma concentrations in neonates and infants using infusion rates described by Steur et al. using this alternative PK parameter set are shown in Figure S2. These show plasma concentrations above 5 $\mu g.mL^{-1}$ in those infants younger than 50 weeks PMA; the dosing regimen used resulted in subsequent decreasing concentrations. These concentrations are similar to those observed using the Eleveld model (Figure 1). Infusion rates that achieve a steady-state concentration of 2 $\mu g.mL^{-1}$ and 3 $\mu g.mL^{-1}$ using the alternative PK parameter set are shown in Table 3.

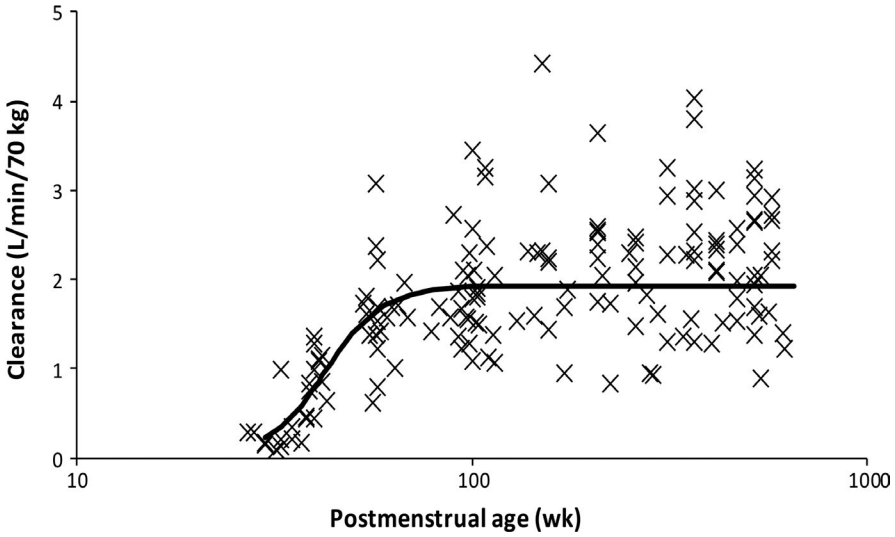

FIGURE 2 Maturation of propofol clearance with age determined by reanalysis of published pooled data. The population prediction is shown as a solid line

TABLE 2 Pediatric propofol population pharmacokinetic parameter estimates (CI is the confidence interval for the structural parameters, Sh is the shrinkage, and PPV is the population parameter variability)

	Estimate	95%CI	Sh %	PPV (%)
V1 (L/70 kg)	18.5	5.2, 23.8	8.5	41.1
V2 (L/70kg)	41.1	29.2, 58.1	9.7	23.3
V3 (L/70 kg)	230	178, 390	14.5	50.3
CL (L/min/70 kg)	1.93	1.74, 2.19	2.9	40.7
Q2 (L/min/70kg)	3.82	3.24, 7.64	11.1	47.4
Q3 (L/min/70 kg)	0.837	1.09, 1.65	6.2	69.6
TM50	42.6		–	–
Hill	5.88			–
Additive residual Error ($\mu g.mL^{-1}$)	0.012	0.0002, 0.0184		η_{RUV} 0.56
Proportional Residual Error (%)	16.9	12.5, 28.3		

TABLE 3 Manual propofol infusion rates recommended for propofol in neonates and infants under 3 y to target a propofol plasma concentration of either 2 $\mu g.mL^{-1}$ or 3 $\mu g.mL^{-1}$. Infusion rates are shown in $mg.kg.h^{-1}$

Age	Induction dose (mg/kg)	0-15 min	15-30 min	30-60 min	60 - 120 min
Target plasma concentration 2 $\mu g.mL^{-1}$					
27-44 PMA wk	1.5	6	5	4	3
44-52 PMA wk	1.5	8	7	6	6
3-12 mo	1.5	9	8	7	6
1-3 y	1.5	10	8	8	7
Target plasma concentration 3 $\mu g.mL^{-1}$					
27-44 PMA wk	2	9	7	6	5
44-52 PMA wk	2.5	11	10	9	8
3-12 mo	2.5	12	11	10	9
1-3 y	2.5	13	12	11	10

Predicted concentrations using this regimen in the 11 typical individuals are shown for both the new simple model and the Eleveld model (Figure S3). Predicted concentrations are similar with use of both models. Prediction variability for these infusion rates using this alternative parameter set is demonstrated in Figure 3. There is considerable variability associated with plasma concentration predictions, but almost half of the predictions were in the range 80%-125% of the target plasma concentration between 5 and

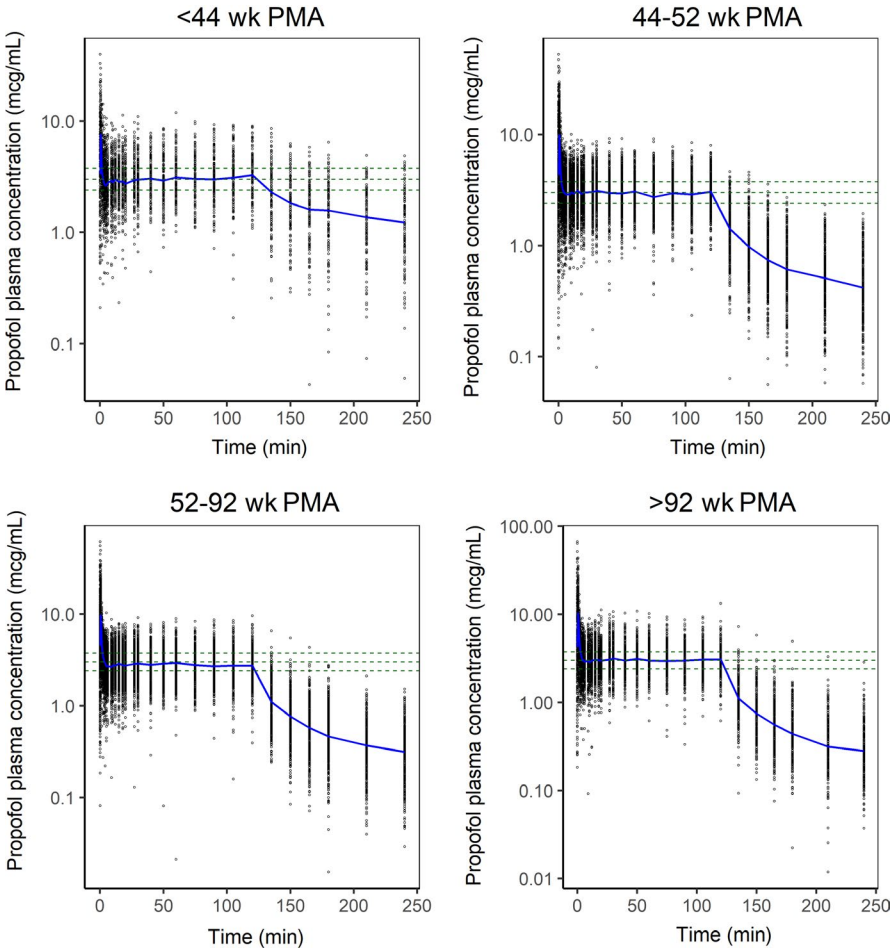

FIGURE 3 Simulated propofol plasma concentrations in 1140 children with the revised dosing regimen (Table 3) and the simpler propofol parameter set. Solid line represents median propofol concentration and black circles are individual predictions. Dashed lines show target concentration of 3 $\mu g.mL^{-1}$ and the target range (2.4-3.75 $\mu g.mL^{-1}$). There were 45% of predictions between 80% and 125% of target concentration [Colour figure can be viewed at wileyonlinelibrary.com]

90 minutes of infusion duration. Ninety percent of predictions fell within the range of 2.5-5.5 $\mu g.mL^{-1}$.

4 | DISCUSSION

Predictions of propofol plasma concentrations using the Steur regimens were higher than anticipated in the first 30 minutes with the propofol parameter set developed by the new pharmacokinetic model and by that described by Eleveld and colleagues. We anticipated that effective target concentrations (eg, 3 $\mu g.mL^{-1}$) would be achieved using the Steur regimen. However, the Eleveld model predicted initial concentrations higher than anticipated, although subsequent plasma concentrations were lower than expected. The predicted target concentration in neonates, particularly those given regional blockade or undergoing radiological scanning, may be lower and is compounded by an inability to extrapolate from adult to neonate using bispectal index as a pharmacodynamic measure.[25] There may be inaccuracy estimating fat mass from predicted equations in children younger than 3 years.[26] The role of fat mass in propofol disposition remains uncertain because clearance can be scaled satisfactorily with total body mass and allometry in adults.[27]

Consequently, we estimated propofol pharmacokinetic parameters in children 0-11 years using published data that were richer than the Eleveld model, particularly with premature and term neonates. Consequently, the slope parameter (Hill) estimate of 5.88 is less than that described by Eleveld (Hill = 9.05). Clearance increased over the first 6 months of life to reach mature values reported by others in children[3,19] and adults.[28,29] This model used only age and total body weight as covariates, ignoring any influence of fat mass. These parameter estimate differences between the new model and that by Eleveld can be observed in Figure S3. Predicted plasma concentrations using the Eleveld model were slightly higher in a 37-week PMA neonate and slightly lower in a 50-week PMA infant. However, variability of simulated predictions is large (Figure 3) and such differences between model predictions will have little impact to a clinician titrating dose to effect.

Effective clinical use of propofol infusions for anesthesia requires simple algorithms for attaining stable and relevant plasma concentrations. Review of the Steur infusion regimens were concerning because these regimens use a loading dose of 3-5 mg.kg^{-1}, a dose that is associated with hypotension in neonates[10] and predicted plasma concentrations using the revised simple model that were greater than 5 $\mu g.mL^{-1}$ in neonates, but were poorly sustained, even in infants. We selected a new dosing regimen for four groups of infants younger than 3 years of age that reflected changes in clearance with age. Predicted plasma concentrations during this infusion regimen were at steady state with a mean

concentration of 3 μg.mL^{-1} over the infusion duration of 2 hours. There is considerable variability associated with plasma concentration predictions, but almost half of the predictions were in the range 80%-125% of the target concentration between 5 and 90 minutes of infusion duration. This range has been commonly used to assume bioequivalence.[30] That this target concentration of 3 μg.mL^{-1} was only achieved in half of the infants is expected because it is essentially the ED_{50} for anesthesia and so to adequately anesthetize all patients, the dose must be increased or supplemented with other drugs (eg, opioids, benzodiazepines). Ninety percent of predictions fell within the range of 2.5-5.5 μg.mL^{-1}, a target range commonly used in clinical anesthesia. We might anticipate effect site concentrations to be similar to those observed in plasma within 5 minutes of induction, given an effect site equilibration half-time ($T_{1/2}$keo) of 2.38 minutes reported for data included[19] in this current pooled analysis.

The selection of the target plasma concentration and subsequent infusion rate depends on both the nature of the surgery and other drugs, or regional blockade used as part of the anesthetic technique. The target plasma concentration required for neonate may be less than that for an older child. Any manual infusion regimen will require adjustment for both the surgical stimulus and for pharmacokinetic-pharmacodynamic variability. Although TCI devices may overcome some of the disadvantages proposed for manual infusion regimens, both have similar depth of anesthesia and hemodynamic stability when titrated against traditional clinical signs in adults.[31] However, propofol administration in children using manual infusion guided by clinical assessment of depth of anesthesia (change in heart rate and/or blood pressure, movement) was associated with higher risks of over- or underdosage when compared to BIS-guided administrations.[32] When propofol infusion was guided by the BIS, no major difference was found between use of different pharmacokinetic parameter sets.[32] Although these principles also apply for neonates and infants there is currently no validated electroencephalographic monitor to titrate propofol administration in this population. Furthermore, a selected target of 3 μg.mL^{-1} commonly associated with adequate levels of hypnosis in young adults and children might be excessive in newborns and infants considering their immature brains.

We have no satisfactory depth of anesthesia monitor for neonates given propofol. The neonatal brain is immature. Measuring cortical response to a painful stimulus may be a good surrogate measure for anesthetic effect; however, there is little literature to inform its use in neonates. A neonate will show behavioral signs of distress when awake but vital signs under anesthesia are an unreliable measure of anesthesia depth. This could contribute to the differences observed between the Steur regimen that was determined clinically and these new regimens. Reflexes are excitable when young and relying on motor reflexes in this population is unreliable; and yet, this was the very method that Steur used to assess depth of anesthesia. Further, Steur reported a high incidence of adverse effects, consistent with plasma concentrations greater than 3-4 μg.mL^{-1}. Current animal data suggest that excess anesthetic drug exposure is toxic for the developing brain.[33]

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CONFLICT OF INTEREST

Brian Anderson and Luis Cortinez sit on the Editorial Board of the journal Pediatric Anesthesia. The authors have no other conflicts of interest to declare.

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SUPPORTING INFORMATION

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

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