Population pharmacokinetics of propofol in neonates and infants: Gestational and postnatal age to determine clearance maturation

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Aims: Develop a population pharmacokinetic model describing propofol pharmacokinetics in (pre)term neonates and infants, that can be used for precision dosing (e.g. during target-controlled infusion) of propofol in this population.

Methods: A nonlinear mixed effects pharmacokinetic analysis (Monolix 2018R2) was performed, based on a pooled study population in 107 (pre)term neonates and infants.

Results: In total, 836 blood samples were collected from 66 (pre)term neonates and 41 infants originating from 3 studies. Body weight (BW) of the pooled study population was 3.050 (0.580–11.440) kg, postmenstrual age (PMA) was 36.56 (27.00–43.00) weeks and postnatal age (PNA) was 1.14 (0–104.00) weeks (median and min-max range). A 3-compartment structural model was identified and the effect of BW was modelled using fixed allometric exponents. Elimination clearance maturation was modelled accounting for the maturational effect on elimination clearance until birth (by gestational age [GA]) and postpartum (by PNA and GA). The extrapolated adult (70 kg) population propofol elimination clearance (1.64 L min⁻¹, estimated relative standard error = 6.02%) is in line with estimates from previous population pharmacokinetic studies. Empirical scaling of BW on the central distribution volume in function of PNA improved the model fit.

Conclusions: It is recommended to describe elimination clearance maturation by GA and PNA instead of PMA on top of size effects when analyzing propofol pharmacokinetics in populations including preterm neonates. Changes in body composition in addition to weight changes or other physio-anatomical changes may explain the changes in central distribution volume. The developed model may serve as a prior for propofol dose finding and target-controlled infusion in (preterm) neonates.

KEYWORDS
clearance maturation, infants, neonates, pharmacokinetics, preterm, propofol
1 | INTRODUCTION

Propofol is frequently used for induction of anaesthesia and procedural sedation, including off label use in (pre)term neonates. Despite its availability for almost 30 years, neonatal propofol pharmacokinetics (PK) remain poorly studied.1 As a consequence, dosing recommendations for propofol in neonates and infants are limited, at best based on manual infusion regimens for target controlled infusion.2 Propofol is only approved for clinical use in children aged 3 years or older,3 Propofol is a lipophilic compound that undergoes hepatic metabolism via hydroxylation by cytochrome P450 (CYP) isoforms (CYP2B6 and CYP2C9) and glucuronidation by 5’-diphospho-glucuronosyltransferase 1A9 (UGT1A9).4,5 Differences in the abundance and activity of these enzymes between different age groups are reported in literature.6 Therefore, age-dependency of size adjusted PK parameters (maturation) was reported earlier, and was anticipated in the current analysis. While enzyme maturation is largely complete at 2 years of postnatal age (PNA), this remains a prominent determinant of drug metabolism in neonates.7,8 It is hence evident that maturation of propofol elimination clearance in neonates requires significant attention. Elimination clearance maturation is typically accounted for via postmenstrual age (PMA). PMA is the sum of gestational age (GA), which is the duration of the pregnancy starting from the beginning of the last menstrual period and ending at birth, and PNA, which is the elapsed time after birth. The characterization of propofol elimination clearance maturation is reported in literature, and is accounted for using PMA but does not always separately account for changes in body size/weight.9 These simplifications may not be fully appropriate for preterm neonates. Age and weight correlate substantially in this population and may confound covariate effects.10 In addition, pre- and postnatal maturation are not expected to follow the same trajectory. A postmenstrual age of 38 weeks probably reflects different maturation in an 8-week-old neonate born after 30 weeks of gestation vs a full-term neonate immediately after birth. Since currently available population PK models for propofol in neonates lack granularity in this regard, we expanded these models in order to optimally capture size and maturation effects.2,9,11,12

2 | METHODS

2.1 | Ethics, trial protocols, clinical demographics, sampling and bioanalysis

Data originating from 3 studies in (pre)term neonates and infants: Allegaert et al.9 Sepúlveda et al.13 and Smits et al.14 were pooled for the final analysis dataset.

2.1.1 | Allegaert et al. 2007 study9

During this prospective study, patients underwent elective chest tube removal, (semi-)elective chest tube placement or endotracheal intubation. Inclusion criteria were the availability of the arterial line for sequential blood sampling and cardiovascular and respiratory stability (judged by the attending neonatologist). Propofol (3 mg kg\(^{-1}\)) was administered once as an intravenous (i.v.) bolus infused over 10 seconds. In addition, patients received either continuous fentanyl or tramadol or intermittent paracetamol i.v. infusions.15 Analgesic therapy was titrated based on systematic evaluation of pain during the neonatal stay and was not standardized.15 Arterial blood samples were collected 1, 5, 15, 30, 60, 90, 120, 240, 480, 720 and 1440 minutes after propofol administration. The total arterial blood volume sampled per individual neonate was limited to 1.8 mL kg\(^{-1}\).

2.1.2 | Sepúlveda et al. 2011 study13

During this prospective study, infants were admitted for cleft lip and cleft palate surgery. Inclusion criteria were American Society of Anesthesiologists I or II status, absence of respiratory, renal, hepatic or endocrine dysfunction and no familial or personal history of allergic reaction to propofol or any of its formulation constituents. Propofol was administered for the indication of generalized anaesthesia. An i.v. bolus dose of propofol 2.5 mg kg\(^{-1}\) was administered...
with subsequent i.v. continuous infusion of propofol 8 mg kg\(^{-1}\) h\(^{-1}\) maintained throughout the surgery. Anaesthesia was induced using sevoflurane 6% in oxygen. Sevoflurane administration was terminated after securing the airway with a tracheal tube to allow for mechanical ventilation. Children received remifentanil infusion at an initial rate of 0.2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). Remifentanil infusion rate was adjusted during surgery to maintain immobility and hemodynamic stability. Arterial blood samples were collected 1, 2, 3, 5, 10, 20 and 60 minutes after i.v. bolus injection, at the moment of discontinuation of the propofol infusion (end of the surgery) and at 1, 3, 5, 30, 60 and 120 minutes thereafter. Arterial blood samples were limited to 2 mL per infant.

2.1.3 Smits et al. 2016 study\(^{14}\)

During this prospective dose finding study, neonates were admitted to the University Hospitals Leuven and received a propofol i.v. bolus administration for the indication of procedural sedation during (semi-) elective endotracheal intubation. Inclusion further requested the absence of sedatives or analgesics, except paracetamol in the previous 24 hours and cardiovascular and haemodynamic stability (judged by the attending neonatologist). The propofol dose at start of the procedure, for each patient, was determined based on a dose-finding approach.\(^{14}\) Additional up-titration of the dose was allowed based on clinical need. The initial and total propofol dose ranges used in the study were 0.5–2 mg kg\(^{-1}\) and 0.5–4.5 mg kg\(^{-1}\) respectively.\(^{14}\) Blood samples for propofol quantification were collected at 3 and/or 12 hours after propofol administration. Samples (300–600 \(\mu\)L) were collected from an arterial line if present, or venous puncture. The total blood volume sampled in every neonate was limited to 1 mL kg\(^{-1}\).

2.2 Population PK analysis

The population PK analysis was performed using Monolix 2019R2 (Lixoft SAS, Antony, France), which incorporates the stochastic approximation expectation–maximization algorithm. The model was parameterized in terms of volumes \((V_j)\), elimination clearance \((CL)\) and distribution clearances \((Q_j)\). Between-subject variability (BSV) of the parameters was assumed to be log-normally distributed. The individual parameter estimate values \((\theta_i)\) are modelled according to Equation 1.

\[
\theta_i = \theta_{\text{pop}} \cdot \epsilon_i
\]

Where \(\theta_{\text{pop}}\) is the typical population parameter mean and \(\epsilon_i\) is assumed to be the random individual deviation from \(\theta_{\text{pop}}\). The random effects are log-normally distributed with zero as a mean and a variance of \(\sigma^2\). Residual error was described by a proportional error model. For the \(j\)th observed concentration of the \(i\)th individual, the relation for observation \(Y_{ij}\) is described by Equation 2.

\[
\log(Y_{ij}) = \log(\text{c}_{\text{pred},ij}) + b \cdot \log(\text{c}_{\text{pred},ij}) \cdot \epsilon_{ij}
\]

Where \(\text{c}_{\text{pred},ij}\) is the predicted propofol concentration for the \(j\)th concentration of the \(i\)th individual, \(b\) is the proportional error term and \(\epsilon_{ij}\) is assumed to be a standardized Gaussian random variables representing residual error the for the \(j\)th concentration of the \(i\)th individual, with zero as a mean and a variance of \(\sigma^2\). Covariate modeling was performed by successive inclusion starting from the base structural model, guided by \(a\) priori physiological plausibility and plots of covariates vs empirical Bayesian parameter estimates. Inclusion of covariates and selection of the modelled covariate structure was judged based on decrease in objective function values, expressed as \(2\) times log likelihood \((-2\text{LL})\), the Akaike information criterion, the Bayesian–Schwartz information criterion and visual inspection of diagnostic plots. Diagnostic plots to evaluate model fit included visual predictive checks, goodness of fit plots of both populations, and individual estimates and distributions of the random effects. All diagnostic plots were stratified by study. Additionally, the standard errors of the parameter estimates were evaluated to compare competing models.

3 RESULTS

The final analysis dataset consisted of 836 concentration–time points from 107 subjects, of whom 53 are preterm neonates, 13 are term neonates and 41 are infants. Demographics and anthropometrics of the individual studies and the pooled final analysis dataset are presented in Table 1.

The sequential model building process is summarized in Table 2. A 3-compartment structural model was selected. This 3-compartment model consisted of 1 central compartment which is subsequently connected to 2 independent peripheral compartments via Q2 and Q3. Clearance of the central compartment is reflected via CL. The effect of BW on all structural model parameters was accounted for by allometrical scaling using fixed exponents (Equation 3).

\[
\theta_i = \theta_{70,\text{pop}} \cdot \left(\frac{\text{BW}}{70}\right)^\alpha \cdot \epsilon_i
\]

The allometric exponent \((\alpha)\) was fixed to 0.75 for clearances and 1 for volumes.\(^{16,17}\) A reference BW of 70 kg was selected to represent mean adult BW, which allowed for comparison of the obtained parameter estimate values with parameter estimate values of published adult and paediatric propofol PK studies.\(^{18}\) This comparison in combination with plots of the BW corrected elimination clearance vs PMA, GA and PNA revealed the need to account for age on top of BW despite the high level of correlation between age and weight in this population (Figure 1A–D).\(^{10}\) A PMA-dependent Emax-type maturation term was introduced to account for elimination clearance maturation (Equation 4).

\[
\text{CL}_i = \text{CL}_{70,\text{pop}} \cdot \left(\frac{\text{BW}}{70}\right)^{0.75} \cdot \left(\frac{\text{PMA}}{\text{PMA}_{50} + \text{PMA}^*}\right) \cdot \epsilon_{\text{CL}_i}
\]
PMA50 is the PMA at half maximal maturation and \( \gamma \) is a Hill slope factor. Introducing this PMA-dependent Emax-type maturation term on top of the weight-proportional model improved the model fit (change in Akaike information criterion = \(-202.37\)). A generalized logistic function, better known as a Richard's curve, which is a sigmoidal function originally developed to empirically describe growth phenomena, was adapted in an attempt to account for elimination clearance maturation with improved flexibility (Equation 5).19

\[
CL_i = CL_{70, pop} \cdot \left( \frac{BW}{70} \right)^{0.75} \cdot \left( 1 - \left( 1 - \left( \frac{PMA}{PMA50} \right) \right)^{\frac{1}{\delta}} \right) - \frac{1}{\delta} \cdot e^{\eta_i} \tag{5}
\]

\( \delta \) is an additional shape factor. Introducing the adapted Richards equation did not improve the model fit. In order to account for differences in pre- and postnatal maturation of the elimination clearance, a term

\[
\text{TABLE 1} \quad \text{Selection of relevant clinical demographics and anthropometrics of both the separate studies and the pooled analysis dataset}
\]

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Description (unit)</th>
<th>Allegaert\textsuperscript{9} n = 25 Median (range)</th>
<th>Sepúlveda\textsuperscript{13} n = 41 Median (range)</th>
<th>Smits\textsuperscript{14} n = 41 Median (range)</th>
<th>Pooled n = 107 Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW</td>
<td>Body weight (kg)</td>
<td>2.56 (0.68–4.03)</td>
<td>8.000 (5.200–11.440)</td>
<td>1.400 (0.580–4.700)</td>
<td>3.050 (0.580–11.440)</td>
</tr>
<tr>
<td>PMA</td>
<td>Postmenstrual age (wk)</td>
<td>36.56 (27.00–43.00)</td>
<td>77.00 (51.00–142.00)</td>
<td>30.00 (25.00–37.00)</td>
<td>38.00 (25.00–142.00)</td>
</tr>
<tr>
<td>PNA</td>
<td>Postnatal age (wk)</td>
<td>1.325 (0.140–3.570)</td>
<td>39.00 (13.00–104.00)</td>
<td>0 (0–2.71)</td>
<td>1.14 (0–104.00)</td>
</tr>
<tr>
<td>HT</td>
<td>Height (cm)</td>
<td>49.50 (33.00–54.00)</td>
<td>68.00 (57.00–79.00)</td>
<td>39.00 (32.00–52.00)</td>
<td>50.00 (32.00–79.00)</td>
</tr>
<tr>
<td>Sex</td>
<td>1 = male, 0 = female</td>
<td>1 = 20, 0 = 5</td>
<td>1 = 23, 0 = 18</td>
<td>1 = 27, 0 = 14</td>
<td>1 = 70, 0 = 37</td>
</tr>
<tr>
<td>PRE</td>
<td>Preterm patient</td>
<td>12</td>
<td></td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>TER</td>
<td>Term patient</td>
<td>13</td>
<td></td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>INF</td>
<td>Infant patient</td>
<td>0</td>
<td></td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

\[
\text{TABLE 2} \quad \text{Sequential modelling workflow}
\]

<table>
<thead>
<tr>
<th>Model</th>
<th>Allometry</th>
<th>Covariates (equation)</th>
<th>Objective function value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>−2LL</td>
</tr>
<tr>
<td>One-compartment base model</td>
<td>None</td>
<td>None</td>
<td>1834.51</td>
</tr>
<tr>
<td>Two-compartment base model</td>
<td>None</td>
<td>None</td>
<td>921.68</td>
</tr>
<tr>
<td>Three-compartment base model</td>
<td>None</td>
<td>None</td>
<td>589.44</td>
</tr>
<tr>
<td>Allometric fixed</td>
<td>Fixed exponential scaling* of BW.</td>
<td>BW on all parameters\textsuperscript{3}</td>
<td>159.97</td>
</tr>
<tr>
<td>Emax-type model</td>
<td>Fixed exponential scaling* of BW.</td>
<td>BW on all parameters, PMA on CL\textsuperscript{4}</td>
<td>−42.40</td>
</tr>
<tr>
<td>Richards model</td>
<td>Fixed exponential scaling* of BW.</td>
<td>BW on all parameters, PMA on CL\textsuperscript{5}</td>
<td>−48.92</td>
</tr>
<tr>
<td>Emax-type model + birth term</td>
<td>Fixed exponential scaling* of BW.</td>
<td>BW on all parameters, PMA and PNA on CL\textsuperscript{6}</td>
<td>−50.17</td>
</tr>
<tr>
<td>Richards model + birth term</td>
<td>Fixed exponential scaling* of BW.</td>
<td>BW on all parameters, PMA and PNA on CL\textsuperscript{7}</td>
<td>−57.88</td>
</tr>
<tr>
<td>GA-PNA maturation model\textsuperscript{*}</td>
<td>Fixed exponential scaling* of BW.</td>
<td>BW on all parameters, GA and PNA on CL\textsuperscript{8}</td>
<td>−66.17</td>
</tr>
<tr>
<td>Final model</td>
<td>Fixed exponential scaling* of BW.</td>
<td>BW on all parameters, GA and PNA on CL, PNA on V\textsuperscript{9}</td>
<td>−81.51</td>
</tr>
</tbody>
</table>

*fixed exponential scaling of bodyweight included fixed allometric exponents of 0.75 for clearances and 1 for volumes. −2LL, −2 times log likelihood; AIC, Akaike information criterion; BIC, Bayesian–Schwartz information criterion; BW, body weight; PMA, postmenstrual age; PNA, postnatal age; GA, gestational age; CL, elimination clearance; V1, volume of the central compartment
accounting for accelerated maturation immediately after birth, henceforth referred to as the birth acceleration term, was developed and introduced on top of both the PMA-dependent Emax-type maturation model (Equation 6) and the adapted Richards maturation model (Equation 7).

\[
CL_i = CL_{\text{pop}} \cdot \left( \frac{BW}{70} \right)^{0.75} \frac{\text{PMA}'}{1 + \frac{1}{\eta} + \frac{1}{\eta} + \left( \frac{\text{PMA}'}{\text{PMA}''} + \frac{\text{PMA}'}{\text{PMA}''} \right)} \cdot e^{\eta/2}
\]

Equation 6

\[
CL_i = CL_{\text{pop}} \cdot \left( \frac{BW}{70} \right)^{0.75} \cdot \left( 1 + \frac{FB_{\text{MAX}}}{1 - e^{-\left( \frac{\text{PNA} + \text{PMA}'}{\text{PMA}''} \right)}} \right) \cdot e^{\eta/2}
\]

Equation 7

Two additional parameters were introduced to the model: \(FB_{\text{MAX}}\), the fractional increase relative to the value at birth and \(T_{\frac{1}{2}}\), the half-life of the maturation immediately after birth. Inclusion of the birth acceleration term improved the model fit for both models. No significant differences between the PMA-dependent Emax-type maturation model fit and the adapted Richards maturation model fit were observed regardless of inclusion of the birth acceleration term. In absence of a population with different gestational age, a PMA-dependent Emax-type maturation model more than adequately accounts for elimination clearance maturation. However, it was observed that postnatal maturation is influenced by the GA of the neonate. A final maturation model accounting for gestational maturation, driven by GA, and postnatal maturation, driven by PNA and GA, further improved the model fit (Equation 8).

\[
CL_i = CL_{\text{pop}} \cdot \left( \frac{BW}{70} \right)^{0.75} \cdot \left( M_{\text{birth},38} \cdot \left( \frac{\text{GA}}{38} \right) \alpha + \left( 1 - M_{\text{birth},38} \cdot \left( \frac{\text{GA}}{38} \right) \alpha \right) \cdot \left( 1 - e^{-\left( \frac{\text{PNA} + \text{PMA}'}{\text{PMA}''} \right)} \right) \right)\]

Equation 8

Where \(M_{\text{birth},38}\) is the fraction of elimination clearance maturation at the time of birth after a 38 week gestational period, \(\alpha\) is a shape factor and \(T_{\frac{1}{2}}\) is the time to achieve 50% of postnatal elimination clearance maturation (in weeks). Addition of the final maturation term on top of the weight-proportional model reduced the unexplained BSV for elimination clearance, calculated as the square root of the exponential variance of \(\eta - 1\), from 175.9% for the weight-proportional model down to 71.1% for the final maturation model. A PNA covariate effect (Equation 9) was introduced to \(V_1\), to account for the observed changes of allometrically scaled \(V_1\) in function of PNA.

\[
V_{1,i} = V_{1,\text{pop}} \cdot \left( \frac{BW \cdot e^{-\left( \frac{\text{PNA} + \text{PMA}'}{\text{PMA}''} \right)}}{70} \right) \cdot e^{\eta/2}
\]

Equation 9

Here, \(\beta\) is a shape factor. No other covariate effects were identified. The final model is the intrauterine-postnatal maturation model with a PNA covariate effect on \(V_1\). Goodness of fit plots and visual predictive checks of the final model fit are provided in Figures 2 and 3. The iterative model building process is summarized in Table 2. The population parameter estimates, interindividual variability estimates of the respective parameters, residual error estimates, precision of the estimates and objective function values of the final model fit are summarized in Table 3.
This study presents a population PK model for propofol in (pre)term neonates and infants, based on a large pooled dataset in this specific population. Traditionally, propofol elimination clearance maturation is accounted for using size (e.g., BW) and/or age (e.g., PMA) covariates only.\textsuperscript{9,12} Accounting for GA and PNA (as continuous covariates) instead of aggregation of these metrics into postmenstrual age (PMA) improves the description of the PK of propofol in a population including both (pre)term neonates and infants. In the final model, we demonstrate the necessity to account separately for GA and PNA to optimally describe the maturation of size-corrected elimination clearance in this specific population. The final maturation model accounts for the observed clearance maturation via 2 distinctive terms: a term accounting for gestational maturation of elimination clearance and a term accounting for postnatal maturation of elimination clearance. This postnatal elimination clearance maturation immediately takes over gestational elimination clearance maturation postpartum and is influenced by GA. Not unexpectedly, BSV not counted for by covariates exceeds that of adult populations.\textsuperscript{12} Our analysis was predominantly limited by its retrospective nature but mainly by the sparsity of the data collection in young preterm neonates, which is a direct consequence of the sampling regimen and the fact that only a limited sampling is feasible in these subjects. However, this study included a large subset of both term and preterm neonates. The main limit of this model is its limited application range. This model is only predictive for human neonates and infants up to age 2 years. This is a direct consequence of the parametrization of the PNA on top of BW covariate effect. Upon extrapolating the PNA to adult values, the individual V1 estimate will be physiologically implausible. The elimination
Propropofol is a highly lipophilic compound characterized by a high hepatic extraction ratio in the adult human. In adults, hepatic metabolic clearance is predominantly mediated by UGT1A9, while minor involvement of multiple CYP isoforms (e.g., CYP2B6 [lesser] and CYP2C9 [major]) has also been observed. In neonates, due to immature elimination pathways, propofol is a low extraction drug. Hepatic metabolic clearance is predominantly CYP-mediated, via hydroxylation of propofol to quinol metabolites, due to the limited glucuronidation capacity in this population. Apparently, the minor pathways for hepatic elimination of propofol in adults, represent the proportional major elimination pathways in neonates. The incomplete maturation of metabolic enzymes, both hepatic and extrahepatic phase I and II enzymes, at least partially reflect the observed elimination clearance maturation.

Maturation aspects and ontogeny phenomena in neonates are also observed for compounds other than propofol such as morphine (UGT2B7 substrate) and paracetamol (UGT1A1/UGT1A6 substrate). Studying maturational aspects and ontogeny of the human enzymatic repertoire may hence be of importance in addition to drug-specific characteristics and can lead to additional insights into the ontogeny of various phase I and II enzymatic processes in (early) neonatal maturation.

Once the child is born, propofol elimination clearance will rise to adult values. This is reflected in the UGT1A9 ontogeny, which has been studied on the level of protein activity, protein expression and mRNA expression, with protein expression catching up to adult levels within 1 month to 2 years. In addition to maturation/ontogeny, changes in body composition might influence the distribution of propofol and other compounds. Body composition changes, such as the changing composition of fat tissue, and fractional contribution of fat vs fat free mass to BW, occur continuously during neonatal aging and growth. A covariate effect of PNA on V1 was observed and is probably explained by these phenomena. A neonate can easily double its BW with accompanying changes in body composition during its first 6 months of life. Algorithms such as the algorithm of Al-Sallami and colleagues and the algorithm of Jammahasan and colleagues allow for the imputation of, respectively, fat free mass and lean bodyweight. However, these algorithms were developed using data collected from subjects outside the neonatal age range. Up to now, no algorithms to impute fat mass, fat-free mass and/or lean bodyweight down to the early neonatal age range, including preterm birth, have been reported as algorithms are limited to overall weight change prediction.

In conclusion, this study presents, to the best of our knowledge, the first propofol population PK analysis including (pre)term neonates present in this analysis dataset. Eleveld et al. had an estimated elimination clearance of 1.79 L min$^{-1}$ 70 kg$^{-1}$ and 2.10 L min$^{-1}$ 70 kg$^{-1}$ for respectively male and female patients. Elimination clearance maturation was accounted for via a sigmoidal PMA-dependent Emax-type relationship on top of a weight correction with fixed allometric exponents in the Eleveld et al. PKPD model. The CL results of this analysis are also well in line with the CL estimates of Michelet et al. (CL = 1.41 L min$^{-1}$ 70 kg$^{-1}$) and Rigby-Jones et al. (CL = 2.11 L min$^{-1}$ 70 kg$^{-1}$).

### TABLE 3

Final model population parameter estimates, random effect estimates expressed as standard deviations, proportional residual error estimate and performance measures (objective function values) including estimate precision. All parameters were normalized to a 70 kg bodyweight.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>SE</th>
<th>RSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL$^{70}$ (L min$^{-1}$ 70 kg$^{-1}$)</td>
<td>1.64</td>
<td>0.0986</td>
<td>6.02</td>
</tr>
<tr>
<td>V$^{170}$ (L 70 kg$^{-1}$)</td>
<td>21</td>
<td>1.97</td>
<td>9.37</td>
</tr>
<tr>
<td>Q$^{270}$ (L min$^{-1}$ 70 kg$^{-1}$)</td>
<td>3.86</td>
<td>0.368</td>
<td>9.54</td>
</tr>
<tr>
<td>V$^{270}$ (L 70 kg$^{-1}$)</td>
<td>43</td>
<td>1.4</td>
<td>3.25</td>
</tr>
<tr>
<td>Q$^{370}$ (L min$^{-1}$ 70 kg$^{-1}$)</td>
<td>0.518</td>
<td>0.0342</td>
<td>6.6</td>
</tr>
<tr>
<td>V$^{370}$ (L 70 kg$^{-1}$)</td>
<td>270</td>
<td>24.2</td>
<td>8.96</td>
</tr>
<tr>
<td>CL maturation model parameter estimates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M_{\text{birth},38}$</td>
<td>0.244</td>
<td>0.0256</td>
<td>10.5</td>
</tr>
<tr>
<td>$T_{\alpha} (\text{wk})$</td>
<td>4.77</td>
<td>0.923</td>
<td>19.4</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>6.71</td>
<td>0.525</td>
<td>7.83</td>
</tr>
<tr>
<td>V$^{1}$ maturation model parameter estimates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.77</td>
<td>0.118</td>
<td>15.3</td>
</tr>
<tr>
<td><strong>Standard deviation of the random effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL$^{70}$</td>
<td>0.409</td>
<td>0.0356</td>
<td>8.7</td>
</tr>
<tr>
<td>V$^{170}$</td>
<td>0.271</td>
<td>0.109</td>
<td>40.2</td>
</tr>
<tr>
<td>Q$^{270}$</td>
<td>0.484</td>
<td>0.0792</td>
<td>16.4</td>
</tr>
<tr>
<td>V$^{270}$</td>
<td>0.191</td>
<td>0.0636</td>
<td>33.3</td>
</tr>
<tr>
<td>Q$^{370}$</td>
<td>0.465</td>
<td>0.0514</td>
<td>11.1</td>
</tr>
<tr>
<td>V$^{370}$</td>
<td>0.593</td>
<td>0.0729</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Error model parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$b$</td>
<td>0.153</td>
<td>0.00545</td>
<td>3.56</td>
</tr>
</tbody>
</table>

Cl clearance of a 70-kg adult; V$^{170}$, volume of the central compartment of a 70-kg adult; V$^{270}$, volume of the first peripheral compartment of a 70-kg adult; V$^{370}$, volume of the second peripheral compartment of a 70-kg adult; M$^{\text{birth},38}$, proportion of completed maturation at birth for a 38-week gestational age neonate; $T_{\alpha}$, time to achieve 50% of postnatal clearance maturation in weeks; $\alpha$, shape (Hill) factor to scale a gestational age-dependent maturation on CL; $\beta$, shape factor to scale a postnatal age-dependent change of body weight on V$^{1}$; b, proportional error model term; SE, standard error; RSE, relative standard error. Standard errors were calculated using stochastic approximation.
and infants, spanning an age range from 25 weeks to 2 years of PNA, accounting for intrauterine (driven by GA) and postnatal (driven by PNA and GA) maturation improves the description of propofol PK in this population. Accounting for the observed PNA-dependent change of BW on V1 improves the model further. The developed model may serve as a prior for propofol dose finding in neonates and infants.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS


DATA AVAILABILITY STATEMENT

The data and code that support the findings of this study are available from the corresponding author upon kind request.

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