Sandra Louis (Orcid ID: 0000-0002-7701-289X)

Nicolai Johan (Orcid ID: 0000-0001-5479-0085)

a. i. Population pharmacokinetics of propofol in neonates and infants: gestational and postnatal age to determine clearance maturation

ii. Louis Sandra¹, Anne Smits^{3,4}, Karel Allegaert^{3,5}, Johan Nicolai⁶, Pieter Annaert¹ and Thomas Bouillon^{1,2}

¹: Drug Delivery and Disposition, KU Leuven Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium.

²: Bionotus, Niel, Belgium.

³: KU Leuven Department of Development and Regeneration, Leuven, Belgium.

⁴: Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium.

⁵: Division of Clinical Pharmacy, Erasmus Medical Center, Rotterdam, the Netherlands

⁶: Development Science, UCB BioPharma SPRL, Braine-l'Alleud, Belgium

i. corresponding author: Louis Sandra, lsandra3@its.jnj.com

i. *The authors confirm that the Principal Investigators for this paper are Anne Smits and Karel Allegaert and that they had direct clinical responsibility for patients.*

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b. STATEMENT 1: What is already known about this subject?

- Propofol is frequently used for induction of anesthesia and procedural sedation in (pre)term neonates and infants, despite being off label in this population.
- Being a UGT1A9 and CYP2C9/2B6 substrate, maturational on top of allometry effects have to be accounted for to describe the pharmacokinetics in this population.
- Former propofol pharmacokinetic analyses account for elimination clearance maturation using a postmenstrual age (PMA) dependent Emax-type maturation model.

STATEMENT 2: What this study adds?

- A propofol population pharmacokinetic analysis performed on a large dataset, originating from 107 children under the age of 2 years, including a significant proportion of preterm and term neonates.
- Accounting for gestational and postnatal age as compared to postmenstrual age, improves the description of propofol pharmacokinetics in a (pre)term neonatal and infant population.
- The identification of an age effect on weight-corrected V_1 might suggest changes in body composition different from total bodyweight are driving the change of V_1 .

c. STRUCTURED ABSTRACT

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 (TCI)) of propofol in this population.

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

Results: 836 blood samples were collected from 66 (pre)term neonates and 41 infants originating from three 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 three compartment structural model was identified and the effect of BW was modeled using fixed allometric exponents. Elimination clearance maturation was modeled 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 (RSE) = 6.02%) is in line with estimates from previous population pharmacokinetic studies. Empirical scaling of BW on the central distribution volume (V_1) 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 V_1 . The developed model may serve as a prior for propofol dose finding and TCI in (preterm) neonates.

d. MAIN TEXT

■ INTRODUCTION

Propofol is frequently used for induction of anesthesia and procedural sedation, including off label use in (pre)term neonates. Despite its availability for almost 30 years, neonatal propofol pharmacokinetics remain poorly studied¹. As a consequence, dosing recommendations for propofol in neonates and infants are limited, at best based on manual infusion regimens for target controlled infusion (TCI)². Propofol is only approved for clinical use in children 3 years of age or older³. 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 literature⁶. Therefore, age-dependency of size adjusted pharmacokinetic 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 compromises of the elapsed time after birth. The characterization of propofol elimination clearance maturation is reported in literature, and is accounted for using PMA and is not always separately accounting for changes in body size/weight⁹. These simplifications may not be fully appropriate for preterm neonates. Age and weight correlate substantially in this population and may confound covariate effects¹⁰. In addition, pre- and postnatal maturation are not expected to follow the same trajectory. A postmenstrual age of 38 weeks most likely reflects different maturation in a 8 weeks old neonate born after 30 weeks of gestation versus a full term neonate immediately after birth. Since currently available population pharmacokinetic models for propofol in neonates lack granularity in this regard, we expanded these models in order to optimally capturing size and maturation effects^{2,9,11,12}.

■ METHODS

□ 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.

▪ **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 *i.v.* bolus infused over 10 seconds. In addition, patients received either continuous fentanyl or tramadol or intermittent acetaminophen *i.v.* infusions¹⁵. Analgesic therapy was titrated based on systematic evaluation of pain during the neonatal stay and was not standardized¹⁵. Arterial blood samples were collected 1, 5, 15, 30, 60, 90, 120, 240, 480, 720 and 1440 min after propofol administration. The total arterial blood volume sampled per individual neonate was limited to 1.8 mL kg^{-1} .

▪ **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 (ASA) 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 anesthesia. An *i.v.* bolus dose of propofol 2.5 mg kg^{-1} was administered with subsequent *i.v.* continuous infusion of propofol $8 \text{ mg kg}^{-1} \text{ h}^{-1}$ maintained throughout the surgery. Anesthesia 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 remifentanyl infusion at an initial rate of $0.2 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$. Remifentanyl 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 min 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, 120 min thereafter. Arterial blood samples were limited to 2 mL per infant.

▪ **Smits et al. 2016 study¹⁴**

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 acetaminophen in the previous 24 hours and cardiovascular and hemodynamic stability (judged by the attending neonatologist). The

propofol dose at start of the procedure, for each patient, was determined based on a dose-finding approach¹⁴. 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 respectively¹⁴. Blood samples for propofol quantification were collected at 3 h and/or 12 h after propofol administration. Samples (300-600 µL) 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.

□ Population pharmacokinetic analysis

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

$$\theta_i = \theta_{\text{pop}} \cdot e^{\eta_{\theta,i}} \quad (1)$$

Where θ_{pop} is the typical population parameter mean and $\eta_{\theta,i}$ is assumed to be the random individual deviation from θ_{pop} . The random effects are log-normally distributed with zero as a mean and a variance of ω^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.

$$\log(Y_{ij}) = \log(c_{\text{pred},ij}) + b \cdot \log(c_{\text{pred},ij}) \cdot \epsilon_{ij} \quad (2)$$

Where $c_{\text{pred},ij}$ is the predicted propofol concentration for the j th concentration of the i th individual, b is the proportional error term and ϵ_{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 σ^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 modeled covariate structure was judged based on decrease in objective function values (OFV), expressed as minus two times log likelihood (-2LL), the Akaike information criterion (AIC), the Bayesian-Schwartz information criterion (BIC) and visual inspection of diagnostic plots. Diagnostic plots to evaluate model fit included visual predictive

checks (VPC), goodness of fit (GOF) plots of both population 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 also evaluated to compare competing models.

■ RESULTS

The final analysis dataset consisted of 836 concentration-time points from 107 subjects of which 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 three-compartment structural model was selected. This three-compartment model consisted of one central compartment which is subsequently connected to two 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).

$$\theta_i = \theta_{70, \text{pop}} \cdot \left(\frac{BW}{70}\right)^a \cdot e^{\eta_{\theta,i}} \quad (3)$$

The allometric exponent (a) 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 pediatric propofol PK studies¹⁸. 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. An PMA-dependent Emax-type maturation term was introduced to account for elimination clearance maturation (Equation 4).

$$CL_i = CL_{70, \text{pop}} \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot \frac{PMA^\gamma}{(PMA50^\gamma + PMA^\gamma)} \cdot e^{\eta_{CL,i}} \quad (4)$$

PMA50 is the PMA at half maximal maturation and γ is a Hill slope factor. Introducing this PMA-dependent Emax-type maturation term on top of the weight-proportional model improved the model fit ($\Delta AIC = -202.37$). 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.

$$CL_i = CL_{70,pop} \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot \left(1 - \left(1 - \left(\left(\frac{PMA}{PMA50}\right)^\gamma\right) \cdot \left(1 - \left(\frac{1}{2}\right)^{-\delta}\right)\right)^{\frac{1}{\delta}}\right) \cdot e^{\eta_{CL,i}} \quad (5)$$

δ 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 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).

$$CL_i = CL_{70,pop} \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot \frac{PMA^\gamma}{(PMA50^\gamma + PMA^\gamma)} \cdot \frac{\left(1 + FB_{MAX} \cdot \left(1 - e^{-\frac{\ln(2) \cdot PNA}{T_{\frac{1}{2}}}}\right)\right)}{1 + FB_{max}} \cdot e^{\eta_{CL,i}} \quad (6)$$

$$CL_i = CL_{70,pop} \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot \left(1 - \left(1 - \left(\left(\frac{PMA}{PMA50}\right)^\gamma\right) \cdot \left(1 - \left(\frac{1}{2}\right)^{-\delta}\right)\right)^{\frac{1}{\delta}}\right) \cdot \frac{\left(1 + FB_{MAX} \cdot \left(1 - e^{-\frac{\ln(2) \cdot PNA}{T_{\frac{1}{2}}}}\right)\right)}{1 + FB_{max}} \cdot e^{\eta_{CL,i}} \quad (7)$$

Two additional parameters were introduced to the model: FB_{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).

$$CL_i = CL_{70,pop} \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot \left(M_{birth,38} \cdot \left(\frac{GA}{38}\right)^\alpha + \left(1 - M_{birth,38}\right) \cdot \left(\frac{GA}{38}\right)^\alpha \cdot \left(1 - e^{-\frac{\ln(2) \cdot PNA \cdot \left(\frac{GA}{38}\right)}{T_{\frac{1}{2}}}}\right) \right) \cdot e^{\eta_{CL,i}} \quad (8)$$

Where $M_{birth,38}$ is the fraction of elimination clearance maturation at the time of birth after a 38 week gestational period, α 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 η minus 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 postnatal age.

$$V_{1,i} = V_{1,70,pop} \cdot \left(\frac{BW \cdot e^{\left(-\frac{PNA}{52} \cdot \beta\right)}}{70} \right) \cdot e^{\eta_{V_1,i}} \quad (9)$$

Here, β 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 Figure 2 and Figure 3. The iterative model building process is summarized in Table 2. The population parameter estimates, inter-individual 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.

■ DISCUSSION

This study presents a population pharmacokinetic 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^{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 pharmacokinetics 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 two 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 populations¹². 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. Despite, 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 until 2 years of age. 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 clearance estimate of this PK analysis, $1.64 \text{ L min}^{-1} 70\text{kg}^{-1}$, is lower but comparable with the elimination clearance estimate of a large PKPD propofol analysis, which is published by Eleveld et al.¹². The PKPD analysis of Eleveld et al. consisted of 15 433 propofol PK observations and 28 639 bispectral index PD observations collected from 1033 subjects in 30 studies¹². Both the Allegaert et al. (2007) and Sepúlveda et al. (2011) PK data were present in this analysis dataset. Eleveld et al. had an estimated elimination clearance of $1.79 \text{ L min}^{-1} 70\text{kg}^{-1}$ and $2.10 \text{ L min}^{-1} 70\text{kg}^{-1}$ 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 = $1.41 \text{ L min}^{-1} 70\text{kg}^{-1}$) and Rigby-Jones et al. (CL = $2.11 \text{ L min}^{-1} 70\text{kg}^{-1}$)^{20,21}.

Propofol 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 observed²². In neonates, due to immature elimination pathways, propofol is a low extraction drug²⁰. Hepatic metabolic clearance is predominantly CYP-mediated, via hydroxylation of propofol to quinol metabolites, due to the limited glucuronidation capacity in this population^{23,24}. 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^{21,25}. Maturation aspects and ontogeny phenomena in neonates are also observed for compounds other than propofol such as morphine (UGT2B7 substrate)^{26,27} and acetaminophen (UGT1A1/UGT1A6 substrate)⁹. 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^{6,8}.

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^{28,29}. 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 most likely 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 colleagues³⁰ and the algorithm of Janmahasatian and colleagues³¹ 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 prediction³².

In conclusion, this study presents, to the best of our knowledge, the first propofol population pharmacokinetic analysis including (pre)term neonates and infants, spanning an age range from 25 weeks to 2 years of postnatal age, accounting for intrauterine (driven by GA) and postnatal (driven by PNA and GA) maturation improves the description of propofol pharmacokinetics 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.

e. ■ ACKNOWLEDGEMENT

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f. ■ CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

g. ■ FUNDING INFORMATION

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h. ■ DATA AVAILABILITY

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

i. ■ REFERENCES

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Table 1: Selection of relevant clinical demographics and anthropometrics of both the separate studies and the pooled analysis dataset

		Allegaert ⁹ n = 25	Sepúlveda ¹³ n = 41	Smits ¹⁴ n = 41	Pooled n = 107
Covariate	Description [unit]	Median [range]	Median [range]	Median [range]	Median [range]
BW	Body weight [kg]	2.56 [0.68 – 4.03]	8.000 [5.200 – 11.440]	1.400 [0.580 – 4.700]	3.050 [0.580 – 11.440]
PMA	Postmenstrual age [weeks]	36.56 [27.00 – 43.00]	77.00 [51.00 – 142.00]	30.00 [25.00 – 37.00]	38.00 [25.00 – 142.00]
PNA	Postnatal age [weeks]	1.325 [0.140 – 3.570]	39.00 [13.00 – 104.00]	0 [0 – 2.71]	1.14 [0 – 104.00]
GA	Gestational age [weeks]	37.14 [25.43 – 40.14]	38 [38 – 38]	29.86 [24.57 – 36.86]	37.14 [24.57 – 40.14]
HT	Height [cm]	49.50 [33.00 – 54.00]	68.00 [57.00 – 79.00]	39.00 [32.00 – 52.00]	50.00 [32.00 – 79.00]
GENDER	1 = male, 0 = female	1 = 20, 0 = 5	1 = 23, 0 = 18	1 = 27, 0 = 14	1 = 70, 0 = 37
PRE	Preterm patient	12	0	41	53
TER	Term patient	13	0	0	13
INF	Infant patient	0	41	0	41

Table 2: Sequential modeling workflow

Model	Allometry	Covariates (equation)	Objective function value		
			-2LL	AIC	BIC
One-compartment base model	None	None	1834.51	1846.51	1862.26
Two-compartment base model	None	None	921.68	941.68	967.93
Three-compartment base model	None	None	589.44	615.44	650.19
Allometric fixed	Fixed exponential scaling* of BW.	BW on all parameters (3)	159.97	185.97	220.72
Emax-type model	Fixed exponential scaling* of BW.	BW on all parameters, PMA on CL (4)	-42.40	-10.40	32.36
Richards model	Fixed exponential scaling* of BW.	BW on all parameters, PMA on CL (5)	-48.92	-12.92	35.19
Emax -type model + birth term	Fixed exponential scaling* of BW.	BW on all parameters, PMA and PNA on CL (6)	-50.17	-16.17	29.27
Richards model + birth term	Fixed exponential scaling* of BW.	BW on all parameters, PMA and PNA on CL (7)	-57.88	-21.88	26.23
GA-PNA maturation model ¹	Fixed exponential scaling* of BW.	BW on all parameters, GA and PNA on CL (8)	-66.17	-34.17	8.59
Final model	Fixed exponential scaling* of BW.	BW on all parameters, GA and PNA on CL, PNA on V1 (9)	-81.51	-47.51	-2.07

*fixed exponential scaling of bodyweight included fixed allometric exponents of 0.75 for clearances and 1 for volumes. -2LL, minus two 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

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

	VALUE		STOCH. APPROX.	
	SE		RSE(%)	
Fixed Effects				
Compartmental model parameter estimates				
CL ₇₀ (L min ⁻¹ 70 kg ⁻¹)	1.64	0.0986	6.02	
V1 ₇₀ (L 70 kg ⁻¹)	21	1.97	9.37	
Q2 ₇₀ (L min ⁻¹ 70 kg ⁻¹)	3.86	0.368	9.54	
V2 ₇₀ (L 70 kg ⁻¹)	43	1.4	3.25	
Q3 ₇₀ (L min ⁻¹ 70 kg ⁻¹)	0.518	0.0342	6.6	
V3 ₇₀ (L 70 kg ⁻¹)	270	24.2	8.96	
CL maturation model parameter estimates				
M _{birth,38}	0.244	0.0256	10.5	
T _{1/2} (weeks)	4.77	0.923	19.4	
α	6.71	0.525	7.83	
V ₁ maturation model parameter estimates				
β	0.77	0.118	15.3	
Standard Deviation of the Random Effects				
CL ₇₀	0.409	0.0356	8.7	
V1 ₇₀	0.271	0.109	40.2	
Q2 ₇₀	0.484	0.0792	16.4	
V2 ₇₀	0.191	0.0636	33.3	
Q3 ₇₀	0.465	0.0514	11.1	
V3 ₇₀	0.593	0.0729	12.3	
Error Model Parameters				
b	0.153	0.00545	3.56	

CL₇₀, clearance of a 70 kg adult; V1₇₀, volume of the central compartment of a 70 kg adult; Q2₇₀, intercompartmental clearance between the central compartment and the first peripheral compartment of a 70 kg adult; V2₇₀, volume of the first peripheral compartment of a 70 kg adult; Q3₇₀, intercompartmental clearance between the volume of the central compartment and the volume of the second peripheral compartment of a 70 kg adult; V3₇₀, volume of the second peripheral compartment of a 70 kg adult; M_{birth,38}, proportion of completed maturation at birth for a 38 weeks gestational age neonate; T_{1/2}, time to achieve 50% of postnatal clearance maturation in weeks; α, shape (Hill) factor to scale a GA dependent maturation on CL; β, shape factor to scale a postnatal age-dependent change of body weight on V₁; b, proportional error model term; SE, standard error; RSE, relative standard error. Standard errors were calculated using stochastic approximation.

Figure 1:

Scatter plot showing the relationship between propofol elimination clearance after three-compartment weight-corrected model fit. (A) gestational age (GA, weeks), Spearman $\rho=0.7810$, Pearson $r = 0.7310$, (B) postnatal age (PNA, weeks), Spearman $\rho= 0.8481$, Pearson $r = 0.6891$, (C) postmenstrual age (PMA, weeks), Spearman $\rho= 0.8673$, Pearson $r = 0.7445$ and (D) body weight (BW, kg), Spearman $\rho= 0.8688$, Pearson $r = 0.8447$.

Figure 2:

Goodness of fit plots: (left) observed *vs* population predicted concentrations, $R^2 = 0.8210$, (right) observed *vs* individually predicted concentrations, $R^2 = 0.9699$. Black full lines represent the line of unity; red full line is a loess smooth. Grey dots represent the empirically Bayesian estimates (EBEs);

Figure 3:

Visual predictive check (VPC) plots with visualized 90% prediction intervals (red and blue areas) of the 10th, 50th and 90th percentiles for the Allegaert study⁹ (left), the Sepúlveda¹³ study (middle) and the Smits study¹⁴ (right). Full lines represent the empirical percentiles. Grey dots represent the observed data.

I. APPENDICES

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Accepted Article