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

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Abstract

Aims: Develop a population pharmacokinetic model describing propofol pharmacokinetics in (pre)term neonates and infants, that can be used for precision dosing 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 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 GA) and postpartum (by PNA/GA). The extrapolated adult (70 kg) population propofol elimination clearance (1.63 L min-1) 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 in (preterm) neonates.

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

ii. Louis Sandra[1], Anne Smits[3,4], Karel Allegaert[3,5], Johan Nicolaï[6], Pieter Annaert[1] and Thomas Bouillon[1,2]

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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.*

ii. running head: Propofol pharmacokinetics in neonates

iii. keywords: pharmacokinetics, neonates, infants, preterm, propofol, clearance maturation

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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 CYP3A4/2B6 substrate, maturational on top of morphometric effects have to be accounted for to describe the pharmacokinetics in this population.
- Former propofol pharmacokinetic analyses account for elimination clearance maturation using a 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 V1 hints towards changes in body composition not captured by overall weight.

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 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 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 GA) and postpartum (by PNA/GA). The extrapolated adult (70 kg) population propofol elimination clearance (1.63 L min^{-1}) 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 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 studied[1]. Propofol is only approved for clinical use in children 3 years of age or older[2]. Propofol is a lipophilic compound that undergoes hepatic metabolism via hydroxylation by cytochrome P450 (CYP) isoforms (CYP2B6 and CYP3A4) and glucuronidation by 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9)[3,4]. Differences in the abundance and activity of these enzymes between different age groups are reported in literature[5]. Therefore, age-dependency of size adjusted pharmacokinetic parameters (maturation) was reported earlier, and was anticipated in the current analysis. Enzyme maturation is largely complete at 2 years of age, but a prominent determinant of drug metabolism in neonates[6,7]. Maturation of propofol elimination clearance in neonates has been modeled based on postmenstrual age (PMA), the sum of gestational age (GA) and postnatal age (PNA), not always separately accounting for changes in body size/weight[8]. These simplifications may not be fully appropriate for preterm neonates. Age and weight correlate substantially in this population and may confound covariate effects[9]. 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[8,10,11].

METHODS

Ethics, trial protocols, clinical demographics, sampling and bioanalysis

Data originating from 3 studies in (pre)term neonates and infants: Allegaert et al.[8], Sepulveda et al.[12] and Smits et al.[13]were pooled for the final analysis dataset.

Allegaert et al., 2007 study[8]

Patients underwent elective chest tube removal, (semi-)elective chest tube placement or endotracheal intubation. Approval of the study protocol was granted by the local ethical board of the University Hospital Gasthuisberg, Leuven, Belgium. Patients were included after parental written informed consent was obtained. Inclusion criteria were the availability of the arterial line for sequential blood sampling and cardiovascular and respiratory stability (judged by the attending neonatologist). GA, PNA, PMA, body weight (BW), length and serum creatinine were registered upon inclusion. Propofol was administered for sedation prior to the medical procedure. 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.* infusions [14]. Analgesic therapy was titrated based on systematic evaluation of pain during the neonatal stay and was not standardized[14]. 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}. The bioanalytical method was performed on whole blood using high-performance liquid chromatography (HPLC) with a fluorescence detector. Linearity was found for standard curves of propofol in whole blood in the range of 0.02–20 μg mL^{-1}. Intra- and inter-day coefficients of variation were lower than 15%. The lower limit of quantification (LLOQ), determined as the lowest concentration with a coefficient of variation lower than 20%, was 0.02 μg mL^{-1}. A detailed description of the bioanalysis was published by Allegaert et al[8].

Sepúlveda et al, 2011 study[12]

Infants were admitted for cleft lip and cleft palate surgery. Approval of the study protocol was granted by the institutional ethics committee of the School of Medicine, Clínica Alemana, Santiago, Chile. Infants were included after parental written informed consent was obtained. 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. Age, BW and length were registered upon inclusion. GA was imputed to 38 weeks for this study only, due to absence of this covariate. 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 mg $kg^{-1}h^{-1}$ 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 remifentanil infusion at an initial rate of 0.2 µg 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 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 of 2 mL were collected. The bioanalysis method was performed on blood plasma using HPLC with a fluorescence detector using a method described by Seno et al.[15]. Linearity was found for standard curves of plasma propofol in the range of 0.1–10 µg mL^{-1}. Intra- and inter-day coefficients of variation were lower than 10%. The LLOQ was 0.1 µg mL^{-1}.

Smits et al. 2016 study[13]

Neonates admitted to the University Hospitals Leuven were eligible for inclusion when a propofol *i.v.* bolus was administered for procedural sedation for (semi-)elective endotracheal intubation. Patients were included after parental written informed consent was obtained. Approval of the study protocol was granted by the ethical board of the University Hospitals Leuven, Belgium. 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 approach[13]. 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[13]. 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}. Propofol quantification occurred by a sensitive HPLC-fluorescence method developed and validated for small volumes. Intra- and inter-day accuracy and precision were below 15%, and a LLOQ of 0.0069 µg mL^{-1} was calculated. A detailed description of the bioanalysis protocol has been published by Qi et al.[16].

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 ith individual, the relation for observation Y_{ij} is described by Equation 2.

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

Where $c_{\text{pred, }ij}$ is the predicted propofol concentration for the jth concentration of the ith 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 jth concentration of the ith 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. The effect of BW on all structural model parameters was accounted for by allometrical scaling using fixed exponents (Equation 3).

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

The allometric exponent (a) was fixed to 0.75 for clearances and 1 for volumes [17]. A reference BW of 70 kg was selected to represent mean adult BW. 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 $1_{\text{A-D}}$)[9]. An PMA-dependent Emax-type maturation term was introduced to account for elimination clearance maturation (Equation 4).

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

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 (ΔAIC=-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) [18].

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

δ is an additional shape factor. Introducing the adapted Richards equation did not improve the model fit. In order to account for the asymmetry in the observed elimination clearance in function of age, a term accounting for accelerated maturation immediately after birth, henceforth refered 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).

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

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

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).

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

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 V1, to account for the observed changes of allometrically scaled V1 in function of postnatal age.

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

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[8,11]. 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 maturatation 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 populations[11].

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 and CYP3A4) has also been observed[4]. In neonates, due to immature elimination pathways, propofol is a low extraction drug[19]. Hepatic metabolic clearance is predominantly CYP-mediated, via hydroxylation of propofol to quinol metabolites, due to the limited glucuronidation capacity in this population[20,21]. 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[22,23]. Maturational aspects and ontogeny phenomena in neonates are also observed for compounds other than propofol such as morphine (UGT2B7 substrate)[24,25]and acetaminophen

(UGT1A1/UGT1A6 substrate)[8]. 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[5,7].

Once the child is born, propofol elimination clearance will rise to adult values. This is reflected in the UGT1A9 ontogony, which has been studied on the level of protein activity, protein expression and mRNA expression, with protein expression catching up to adult levels withing 1 month to 2 years[26,27]. 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 colleagues[28] and the algorithm of Janmahasatian and colleagues[29] 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.

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/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

f. CONFLICT OF INTEREST STATEMENT

g. FUNDING INFORMATION

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h. DATA AVAILABILITY

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

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j. TABLES

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

Allegaert[8]

n = 25

Smits[13]

n = 41

Sepulveda[12]

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]

1.400 [0.580 – 4.700]]

8.000 [5.200 – 11.440]

3.050 [0.580 – 11.440]

PMA

Postmenstrual age [weeks]

36.56 [27.00 – 43.00]

30.00 [25.00 – 37.00]

77.00 [51.00 – 142.00]

38.00 [25.00 – 142.00]

PNA

Postnatal age [weeks]

1.325 [0.140 – 3.570]

0 [0 – 2.71]

39.00 [13.00 – 104.00]

1.14 [0 – 104.00]

GA

Gestational age [weeks]

37.14 [25.43 – 40.14]

29.86 [24.57 – 36.86]

38 [38 – 38]

37.14 [24.57 – 40.14]

HT

Height [cm]

49.50 [33.00 – 54.00]

39.00 [32.00 – 52.00]

68.00 [57.00 – 79.00]

50.00 [32.00 – 79.00]

GENDER

1 = male, 0 = female

1 = 20, 0 = 5

1 = 27, 0 = 14

1 = 23, 0 = 18

1 = 70, 0 = 37

PRE

Preterm patient

12

41

0

53

TER

Term patient

13

0

0

13

INF

Infant patient

0

0

41

41

Table 2: Sequential modeling workflow

Model
Three-compartment base model
Allometric fixed
Emax-type model
Richards model
Emax -type model + birth term
Richards model + birth term
GA-PNA maturation model11-2LL, minus two times log likelihood; AIC, Akaike information criterion; BIC, Bayesian-Schwa
Final model

Table 3: Final model population parameter estimates, random effect estimates expressed as standard devi-

ations, proportional residual error estimate and performance measures (objective function values) including estimate precision. All parameters were normalized to a 70 kg bodyweight

Fixed Effects
CL_{70} (L min^{-1} 70 kg^{-1})
$V1_{70}$ (L 70 kg^{-1})
$Q2_{70}$ (L min^{-1} 70 kg^{-1})
$V2_{70}$ (L 70 kg^{-1})
$Q3_{70}$ (L min^{-1} 70 kg^{-1})
$V3_{70}$ (L 70 kg^{-1})
$M_{birth,38}$
$T_{\frac{1}{2}}$ (weeks)
α
β
Standard Deviation of the Random Effects
CL_{70}
$V1_{70}$
$Q2_{70}$
V11CL_{70}, clearance of a 70 kg adult; $V1_{70}$, volume of the central compartment of a 70 kg adult; $Q2_{70}$, inter
$Q3_{70}$
$V3_{70}$
Error Model Parameters
b

k. FIGURE LEGENDS

Figure 1:

Scatter plot showing the relationship between propofol elimination clearance after three-compartment base model fit. (A) gestational age (GA, weeks), (B) postnatal age (PNA, weeks), (C) postmenstrual age (PMA, weeks) and (D) body weight (BW, kg).

Figure 2:

Goodness of fit plots; (left) observed *vs* population predicted concentrations, (right) observed *vs* individually predicted concentrations. 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 10^{th}, 50^{th} and 90^{th} percentiles for the Allegaert study[8] (left), the Sepúlveda[12] study (middle) and the Smits study[13] (right). Full lines represent the empirical percentiles. Grey dots represent the observed data.

l. APPENDICES

NA