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Inter-individual variability in propofol pharmacokinetics in preterm and term neonates

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Background. To document covariates which contribute to inter-individual variability in propofol pharmacokinetics in preterm and term neonates.

Methods. Population pharmacokinetics were estimated (non-linear mixed effect modelling) based on the arterial blood samples collected in (pre)term neonates after i.v. bolus administration of propofol (3 mg kg^{-1}, 10 s). Covariate analysis included postmenstrual age (PMA), postnatal age (PNA), gestational age, weight, and serum creatinine.

Results. Two hundred and thirty-five arterial concentration–time points were collected in 25 neonates. Median weight was 2930 (range 680–4030) g, PMA 38 (27–43) weeks, and PNA 8 (1–25) days. In a three-compartment model, PMA was the most predictive covariate for clearance ($P<0.001$) when parameterized as $[CL_{std}\cdot(PMA/38)^{11.5}]$. Standardized propofol clearance (CL_{std}) at 38 weeks PMA was 0.029 litre min^{-1}. The addition of a fixed value in neonates with a PNA of $\geq$10 days further improved the model ($P<0.001$) and resulted in the equation $[CL_{std}\cdot(PMA/38)^{11.5}+0.03]$ for neonates $\geq$10 days. Values for central volume (1.32 litre), peripheral volume 1 (15.4 litre), and peripheral volume 2 (1.29 litre) were not significantly influenced by any of the covariates ($P>0.001$).

Conclusions. PMA and PNA contribute to the inter-individual variability of propofol clearance with very fast maturation of clearance in neonatal life. This implicates that preterm neonates and neonates in the first week of postnatal life are at an increased risk for accumulation during either intermittent bolus or continuous administration of propofol.

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Although pharmacokinetics of propofol have been extensively studied in different populations of adult and paediatric age, data in neonates are still very limited. Propofol is a highly lipophilic anaesthetic compound and therefore exhibits rapid distribution from blood into s.c. fat and the central nervous system with subsequent redistribution. Elimination kinetics are triphasic and characterized by fast metabolic clearance. Although the use of propofol became standard of care for i.v. induction of anaesthesia and has been repeatedly reported in the literature, the administration of propofol is still—to the best of our knowledge—off label in neonates.[1–10]

In adults, urinary excretion of unchanged propofol only marginally (<1%) contributes to overall propofol clearance. Propofol clearance mainly depends on the hepatic blood flow (high extraction drug) with subsequent metabolism. Although multiple hepatic and extrahepatic human cytochrome (CYP) P450 isoforms (hydroxylation) are also involved in propofol metabolism, glucuronidation is the major metabolic pathway of propofol.[11 12] During paediatric life, phase I and phase II hepatic metabolism display iso-enzyme-dependent ontogeny, although there are progressive changes in body composition with subsequent effects on the relative distribution volume of

lipophilic compounds. These maturational processes are most prominent in early neonatal life.[13 14]

It is therefore to be anticipated that propofol disposition displays maturation. It was recently documented that propofol clearance (i.v. bolus administration, 3 mg kg^{-1}) in neonates was significantly lower compared with the values in toddlers and children, but we were unable to estimate any maturational trend in neonatal life.[5] In the present paper, we report on the covariates which contribute to the inter-individual variability of propofol clearance in a further extended cohort of preterm and term neonates.

Methods

Clinical characteristics, ethics, procedural sedation model, and sample collection

Neonates were included after approval of the study protocol by the local ethical board of the University Hospital Gasthuisberg, Leuven, Belgium, and after informed written consent was obtained from the parents. The decision to prescribe propofol for scheduled short procedural sedation was made by the attending neonatologist, and neonates were only considered for inclusion if an arterial line was available to enable the sequential collection of blood samples. Neonates had to be cardiovascular and respiratory stable, as judged by the attending neonatologist. Clinical characteristics were registered at inclusion [postmenstrual age (PMA, weeks), gestational age (GA, weeks), postnatal age (PNA, days), weight, and serum creatinine].

Besides elective chest tube removal, (semi)elective chest tube placement or endotracheal intubation was the indication for the administration of propofol as a sedative to ameliorate the feasibility of the procedure. Just before the procedure was initiated, propofol (3 mg kg^{-1} i.v. bolus over 10 s, Diprivan® 1%, Braun, Diegem, Belgium) was administered in addition to the analgesics already administered by either continuous (fentanyl or tramadol) or intermittent (acetaminophen) i.v. infusion.[15] This procedural sedation model has already been used to describe the pharmacodynamics of methohexital during chest tube removal in neonates.[16] Neither dose nor type of analgesic was standardized since these analgesics were titrated based on systematic evaluation of pain during neonatal stay.[15]

Blood samples were collected by arterial line up to 24 h after administration of propofol, with a specific emphasis on the very early phase (i.e. 1, 5, 15, 30, 60, 90 min and 2, 4, 8, 12 and 24 h) after initiation of administration. The total volume of blood samples in every individual neonate was limited to 1.8 ml kg^{-1}.

Drug assay

To an equivalent volume of 0.5 ml of whole blood, 50 μl of the internal standard (thymol, 10 μg ml^{-1}) and 1 ml of acetonitrile were added to precipitate the proteins. After vortexing two times for 15 s, the samples were centrifuged for 10 min at 3000 rpm. An aliquot of 200 μl of the supernatant was transferred to a microvial of 300 μl for automatic injection by an autosampler 717plus (Waters). The injection volume was 10 μl. The chromatographic system consisted of a Waters 600E pump, combined with a Waters autosampler 717plus and a fluorescence detector (Hitachi F-1000) with excitation and emission wavelengths set at, respectively, 270 and 310 nm. Chromatographic separation of propofol and the internal standard thymol was performed on a reversed phase high performance liquid chromatography column packed with Lichrosorb RP18 5 μm (125×4.0 mm ID) and the mobile phase was a mixture of acetonitrile and water (+0.1% trifluoroacetic acid) (60/40, v/v) pumped at a flow rate of 1 ml min^{-1}. Linearity was found for standard curves of propofol constructed in whole blood in the range of 0.02–20 μg ml^{-1}. Intra- and interday coefficients of variation were lower than 15%, and the lowest limit of quantitation for propofol, determined as the lowest concentration with coefficient of variation lower than 20%, was 0.02 μg ml^{-1}.

Population pharmacokinetic analysis

Data analysis

The analysis was performed using non-linear mixed effect modelling (GloboMax LLC, Hanover, MD, USA, version V release 1.1)[9] by use of the first-order conditional estimation (Method 1) with $\eta-\epsilon$ interaction. S-plus (Insightful software, Seattle, WA, USA, version 6.2) was used to visualize the data. Discrimination between different models was made by comparison of the objective function. A value of $P<0.005$, representing a decrease of 7.8 points in the objective function (χ^2 distribution), was considered statistically significant. In addition, goodness of fit plots, including observations *vs* individual predictions, observations *vs* population predictions and weighted residuals *vs* time and population predictions *vs* weighted residuals were used for diagnostic purposes. Furthermore, the confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual plots were used to evaluate the model.

Covariate analysis

The covariates PMA, PNA, GA, body weight, gender, and renal function (serum creatinine) were plotted subsequently against the individual *post hoc* parameter estimates and the weighted residuals to visualize potential relationships.

On the basis of these plots, covariates were tested for their influence and the nature of their influence which consisted of an exploration of a linear (centralized around the median value of the covariate), power, and subpopulation incorporation of each of the covariates for the involved pharmacokinetic parameter. For the subpopulation implementation, variation in the value separating the subpopulations

was also explored. The most optimal parameterization for each covariate on a specific pharmacokinetic parameter was chosen based on the objective function, although a value of $P<0.05$ representing a decrease of 3.8 points in the objective function was considered statistically significant.

Starting from the basic model without covariates, the covariate model was first built up using forward inclusion. The contribution of each covariate was confirmed by stepwise backward deletion. In the final model, all covariates associated with a significant increase in objective function (χ^2 distribution) after elimination were maintained. The choice of the model was further evaluated as described in Data analysis.

Validation

The internal validity of the population pharmacokinetic model was assessed by the bootstrap re-sampling method (repeated random sampling to produce another data set of the same size but with a different combination of individuals). Parameters obtained with the bootstrap replicates (250 times) were compared with the estimates obtained from the original data set.

Pharmacokinetic model

The parameters of a two- and three-compartment model were fitted to the log-transformed data using ADVAN3 TRANS4 and ADVAN11 TRANS4. Propofol pharmacokinetics were adequately described by a three-compartment model, parameterized in terms of volume of the central compartment (V_1), elimination clearance (CL), intercompartmental clearance between central and peripheral 1 (Q_2), peripheral volume 1 (V_2), inter-compartmental clearance between central and peripheral 2 (Q_3), peripheral volume 2 (V_3). The individual value (*post hoc* value) of the parameters of the *i*th subject was modelled by

$$\theta_i = \theta_{\text{mean}} \bullet e^{\eta_i} \quad (1)$$

where θ_{mean} is the population mean and η_i is assumed to be a random variable with zero mean and variance $\omega.^2$ The residual error was described with a proportional error model. This means for the *j*th observed log-transformed concentration of the *i*th individual, the relation (Y_{ij}):

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

where c_{pred} is the predicted transformed propofol concentration and ε_{ij} the random variable with zero mean and variance $\sigma.^2$

Results

Two hundred and thirty-five arterial concentration–time points were collected in 25 neonates. The clinical characteristics of the neonates are reported in Table 1. The sequential model building process is summarized in Table 2. On the basis of the criteria described in Methods, a three-compartment model was preferred over a two-compartment model. Scatter plots showing the relationship between propofol clearance and PMA (weeks), GA (weeks), PNA (days), and body weight (kg) of the basis model are provided in Figure 1A–D.

Table 1 Individual clinical characteristics of the 25 neonates included in the current study

Weight at inclusion (g)	2.930	(0.680–4.030)
Gestational age (weeks)	37	(26–40)
Preterm, i.e. <37 weeks at birth	10/25	
Postmenstrual age (weeks)	38	(27–43)
Postnatal age (days)	8	(1–25)
Gender (male/female)	21/4	
Serum creatinine (mg dl^{-1})	0.65	(0.4–1.03)
Indication for propofol administration		
Chest tube removal	15/25	
Chest tube placement	2/25	
Endotracheal intubation	8/25	

The introduction of PMA as a covariate for clearance using a power equation [$CL_{std}\cdot(PMA/38)^b$] further improved the model (objective function 251.28, $P<0.001$) and resulted in a more significant reduction of the objective function compared with PNA (linear, −245.42, $P<0.05$) or body weight (power model, 245.94, $P<0.05$) (Table 2). Standardized propofol clearance (CL_{std}) at 38 weeks PMA was 0.029 litre min^{-1} with a power scaling parameter *b* of 11.5 (Table 3). The addition of a fixed value in neonates with a PNA of ≥10 days further improved the model (objective function −277.5, $P<0.001$, Table 2) and resulted in the equation [$CL_{std}\cdot(PMA/38)^b+a$] for neonates ≥10 days. Variation of day 10 in days 8, 11, 12, or 13 resulted in a less significant reduction in objective function ($P<0.001$, $P<0.05$, $P<0.05$, and $P<0.05$, respectively). Upon introduction of both PMA and PNA as covariates in the final PMA+PNA model, the inter-individual variability for clearance was reduced from 322% to 84% (Table 3).

Table 2 Sequential model building process

Model	Covariates	Objective function	No. of structural parameters
Two-compartment model	—	−97.77	4
Three-compartment model	—	−235.39	6
Three-compartment model	Postmenstrual age on clearance (power model)	−251.28	7
Three-compartment model	Clearance for PNA <10 days and clearance ≥10 days	−246.81	7
Three-compartment model	PNA on clearance linear	−245.42	7
Three-compartment model	Body weight on clearance (power model)	−245.94	7
Three-compartment model	PMA on clearance (power model) plus constant if PNA ≥10 days	−277.50	8

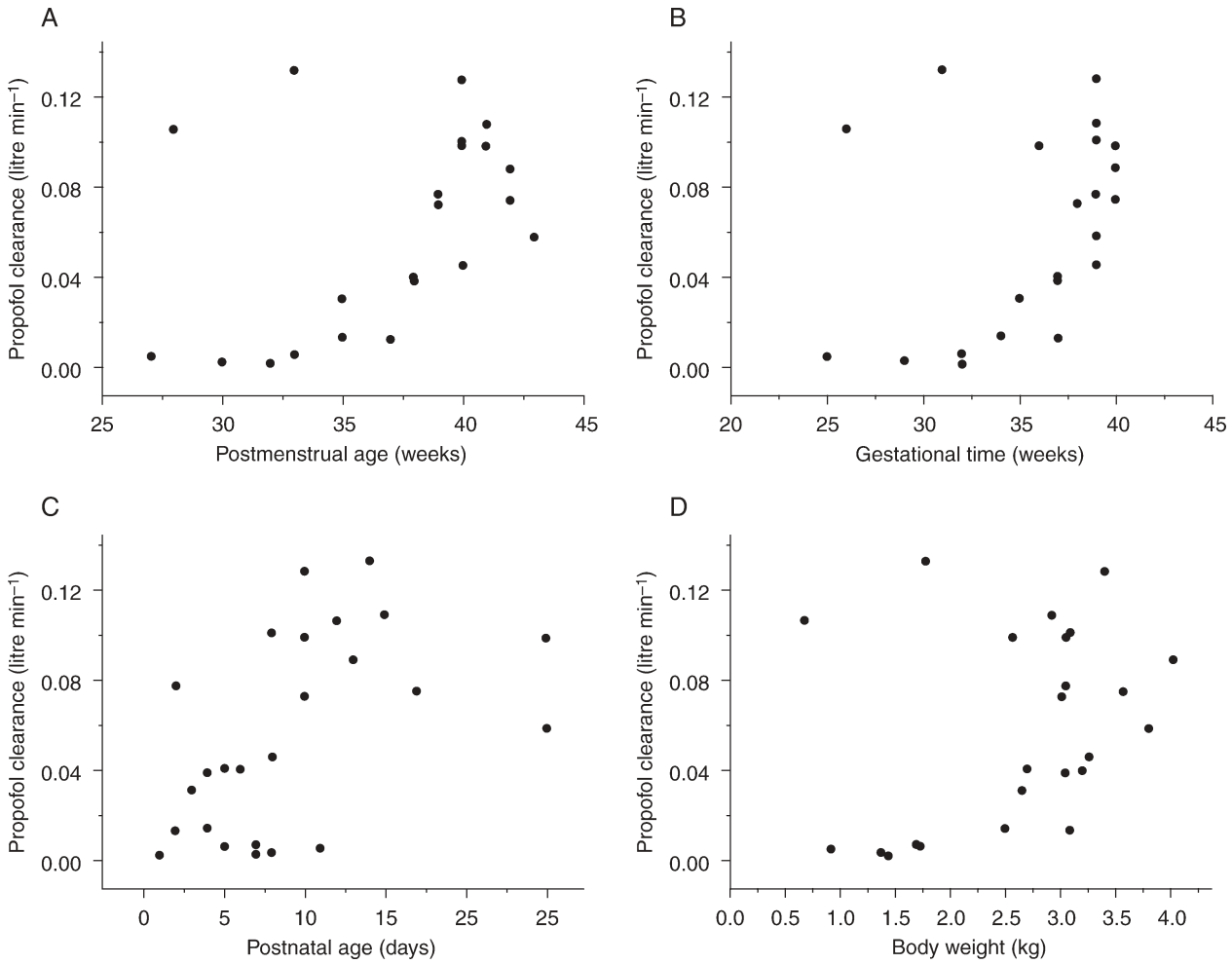

Fig 1 Scatter plot showing relationship between propofol clearance and (A) PMA (weeks), (B) GA (weeks), (C) PNA (days), and (D) body weight (kg) of the basic model.

All parameter estimates including the values on inter-individual and residual variability of the basic pharmacokinetic model, the final PMA+PNA model, and the stability of these parameters using bootstrap validation are presented in Table 3. Diagnostic plots (Fig. 2A–D) are provided to allow the evaluation of the optimal, that is, the final PMA+PNA model to the data.

Discussion

This study is the first population analysis in preterm and term neonates exploring the pharmacokinetics and its covariates following i.v. single bolus administration of propofol based on 253 observations collected in 25 neonates. It was recently documented that propofol clearance in neonates is significantly lower compared with similar observations in toddlers and children but additional maturational trends could not be unveiled.[5] On the basis of the current observations in a further extended cohort and using a population pharmacokinetic approach, both PMA and PNA contribute as covariates of the inter-individual variability in propofol clearance in neonates.

Since propofol is a highly lipophilic drug with a high hepatic extraction ratio, clearance mainly depends on hepatic blood flow with subsequent metabolic clearance. This results in more aqua-soluble compounds subsequently eliminated by renal route. Glucuronidation is the major metabolic pathway of propofol, although multiple human cytochrome P450 (CYP) isoforms also contribute to propofol metabolism.[11 12] We hypothesize that the differences in propofol clearance between neonates and infants from 4 months onwards (Table 4) at least in part reflect the still incomplete maturation of hepatic and extrahepatic phase I and phase II enzyme activities in the first month of life.[5–8] The additional impact of PNA (≥10 days) on propofol clearance hereby likely reflects ontogeny of glucuronidation activity since there are *in vivo* observations on the maturation of acetaminophen and morphine glucuronidation in early neonatal life, both illustrating the relevance of early neonatal life, that is, first week of postnatal life, on glucuronidation activity in neonates.[13 17–19]

Table 3 Parameter estimates of the basic pharmacokinetic model, the postmenstrual+postnatal age model, and the stability of the parameters using the bootstrap validation (BS). Values in parentheses are coefficient of variation of the parameter (CV); CL, elimination clearance; CL_{std}, elimination clearance in a standardized individual of 38 weeks postmenstrual age; *b*, power scaling parameter; *a*, plus clearance constant if postnatal age ≥10 days; V_1, central volume; Q_2, inter-compartmental clearance between central and peripheral 1; V_2, peripheral volume 1; Q_3, inter-compartmental clearance between central and peripheral 2; V_3, peripheral volume 2; the inter-individual variability is calculated as the square root of the exponential variance of η minus 1; ε, residual error proportional calculated as square root of the variance; −2LL, objective function

Parameter	Basic model, mean (CV%)	Postmenstrual age–postnatal age model, mean (CV%)	Bootstrap postmenstrual age–postnatal age model, BSmean (CV%)
Fixed effects			
CL (litre min^{-1})	0.028 (32)	= CL_{std}· $(PMA/38)^b$+*a* (if PNA≥10 days)	
CL_{std} (litre min^{-1})	—	0.029 (14)	0.028 (17)
b	—	11.5 (15)	10.9 (20)
a		0.030 (48)	0.036 (49)
V_1 (litre)	1.32 (17)	1.32 (17)	1.27 (23)
Q_2 (litre min^{-1})	0.036 (13)	0.036 (13)	0.036 (19)
V_2 (litre)	15.7 (17)	15.4 (15)	15.4 (26)
Q_3 (litre min^{-1})	0.092 (16)	0.088 (14)	0.090 (28)
V_3 (litre)	1.32 (19)	1.29 (18)	1.43 (37)
Inter-individual variability %			
CL	322 (35)	84 (37)	76 (53)
V_1	95 (37)	97 (32)	96 (37)
Q_2	64 (27)	65 (28)	67 (34)
CLV_1	97 (32)	73 (36)	65 (48)
Residual error %			
ε	21 (16)	21 (16)	21 (18)
Performance measures			
−2LL	−235.39	−277.50	−298.53 (14)

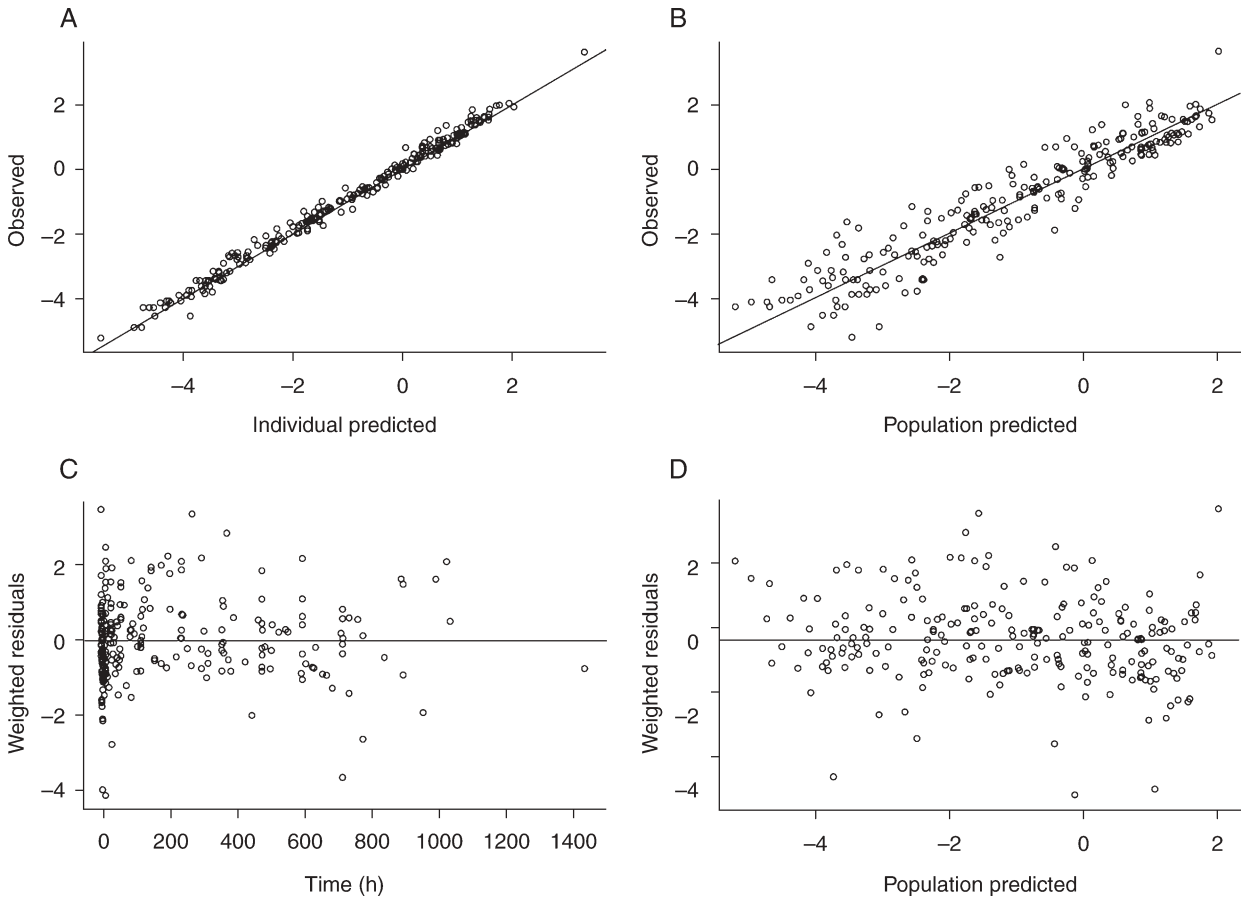

Fig 2 Diagnostic plots, allowing the evaluation of the optimal model to the data. (A) Observed *vs* individually predicted propofol concentrations; (B) observed *vs* population predicted concentrations; (C) weighted residuals *vs* time; (D) weighted residuals *vs* population predicted concentrations. Solid lines represent the line of unity.

Table 4 The pharmacokinetic estimates and clinical characteristics observed in neonates after i.v. bolus administration of propofol were compared with the estimates described by Raoof and colleagues and Murat and colleagues [standard deviation (SD)] in infants and toddlers. The estimates in neonates were based on the final PMA+PNA model in a 10-day-old neonate with PMA of 38 weeks and a weight of 3 kg (V_{ss}, distribution volume at steady state)

	Current study	Raoof and colleagues[6]	Raoof and colleagues[6]	Murat and colleagues[7]
Number of patients	25	8	6	12
Age (range)	1–25 days	4–24 months	11–43 months	1–3 yr
Weight (kg, range)	0.68–4.03	5.9–11	8.7–15	8.7–18.9
Propofol dose (mg kg^{-1})	3	2.5–3	2.5–3	3
Pharmacokinetic model	Population PK three compartment	Two-stage, open two or three compartment	Two-stage, open two or three compartment	Two-stage, open three compartment
V_{2+3} or V_{ss} (litre kg^{-1})	5.56	3.5 (SD 1.6)	2.4 (SD 1.6)	8.2 (SD 2.5)
Clearance (ml min^{-1} kg^{-1})	19.6	37.5 (SD 6.8)	38.7 (SD 6.8)	48 (SD 12)

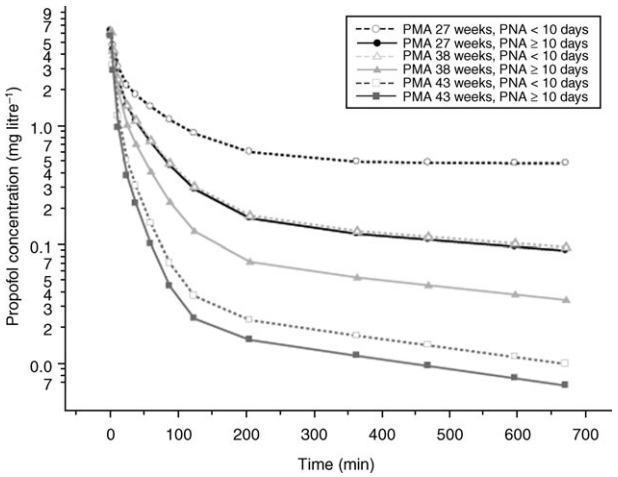

Fig 3 Simulated population propofol concentrations (line) in neonates aged 27, 38, and 43 weeks PMA and <10 days and ≥10 days PNA after a bolus dose of 9 mg in 10 s.

Guitton and colleagues demonstrated that multiple human cytochrome P450 isoforms are involved in liver metabolism of propofol based on *in vitro* microsomal adult hepatic samples. It is therefore to be anticipated that, besides maturation of glucuronidation, ontogeny of phase I process (cytochrome 2B6) also contributes to the differences in propofol clearance.[12]

The study of maturational aspects of propofol metabolism in neonates and children can therefore be of relevance beyond the drug-specific results, since these observations might provide us with additional insights into the ontogeny of various phase I and phase II processes in neonatal and paediatric life.[13] Instead of weight, PMA is the most relevant covariate for clearance of propofol with a power scaling parameter of 11.5 (CV 15%) and an additional fixed effect in neonates ≥10 days of PNA. The power scaling parameter of 11.5 hereby reflects that fast maturational changes in propofol clearance during perinatal life in this cohort related more to age than weight of which the power scaling parameter was estimated to be 0.75 by Knibbe and colleagues,[20] considering children older than 1 yr, that is, once metabolic activity is at an adult level of activity.

The current observations are of clinical relevance. The overall reduced clearance and the important inter-individual variability (322%) clearance of propofol observed in neonates make accumulation more likely during either continuous or repeated bolus administration.[21 22] Preterm neonates (PMA) and neonates in the first week of postnatal life (PNA) are even more prone to display reduced clearance. This fast maturational increase in propofol clearance is also reflected in Figure 1A–D.

Simulated population propofol concentrations (line) in neonates aged 27 weeks (black), 38 weeks (light grey), and 43 weeks (dark grey) PMA and either <10 days (dashed line) or ≥10 days (solid line) PNA after a bolus dose of 3 mg kg^{-1} in 10 s re-illustrate the impact of maturation on propofol clearance in neonates (Fig. 3). The similar concentration–time profile at the PMA of 27 weeks but ≥10 days and at the PMA of 38 weeks but <10 days hereby illustrates the additional independent impact of PNA on propofol clearance.

In conclusion, this population pharmacokinetic study on propofol disposition in preterm and term neonates confirmed the overall lower propofol clearance in neonates compared with older paediatric populations. Significant inter-individual variability (322%) in propofol clearance has been documented. PMA and PNA both contribute to the inter-individual variability of propofol clearance observed with very fast maturation of clearance in neonatal life. This implicates that PMA and neonates in the first week of postnatal life are at an increased risk for accumulation during either intermittent bolus or continuous administration of propofol.

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