Towards a system-based pharmacology approach to predict developmental changes in renal drug clearance in children

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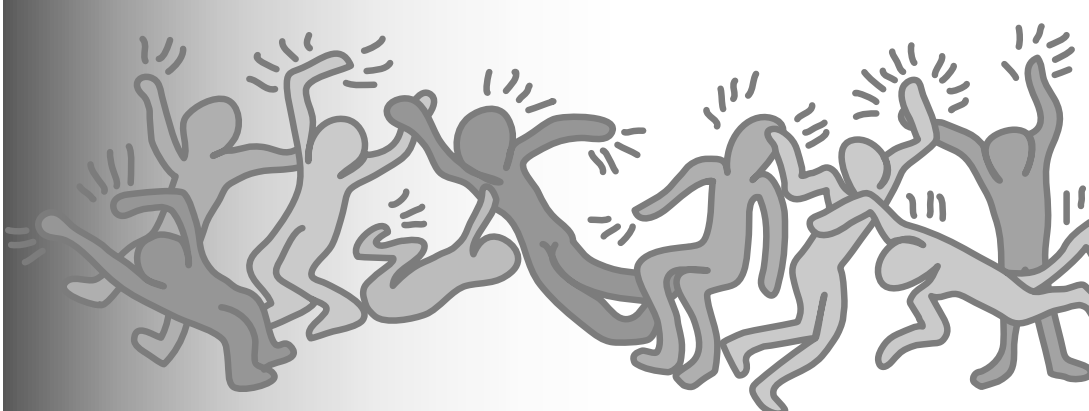
Section IV

Renal and Hepatic Elimination of Propylene Glycol in Preterm and Term Neonates



Chapter 7

Developmental Pharmacokinetics of Propylene Glycol in Preterm and Term Neonates

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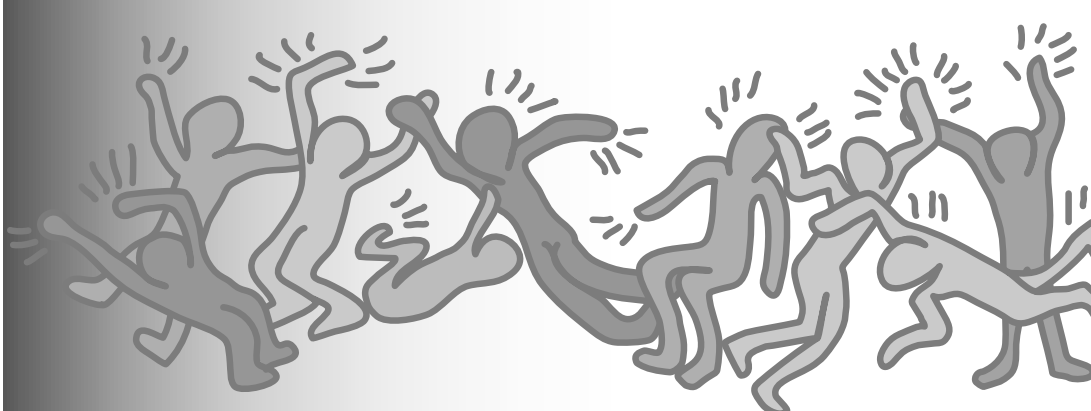
Br J Clin Pharmacol. 2013 Jan;75(1):162-71



Abstract

Aim

Propylene glycol (PG) is often applied as an excipient in drug formulations. As these formulations may also be used in neonates, the aim of this study was to characterize the pharmacokinetics of propylene glycol, co-administered intravenously with paracetamol (800mgPG/1000mg paracetamol) or phenobarbital (700mgPG/200mg phenobarbital) in preterm and term neonates.

Methods

A population pharmacokinetic analysis was performed based on 372 PG plasma concentrations from 62 (pre)term neonates (birth weight (bBW) 630-3980g, postnatal age (PNA) 1-30days) using NONMEM 6.2. The model was subsequently used to simulate PG exposure upon administration of paracetamol or phenobarbital in neonates (gestational age 24-40 weeks).

Results

In a one compartment model, birth weight and PNA were both identified as covariates for PG clearance using an allometric function ($CL_i=0.0849x\{(BWb/2720)^{1.69}x(PNA/3)^{0.201}\}$). Volume of distribution scaled allometrically with current bodyweight ($V_i=0.967x\{(BW/2720)^{1.45}\}$), and was estimated 1.77 times higher when co-administered with phenobarbital compared to paracetamol. By introducing these covariates a large part of the interindividual variability on clearance (65%) as well as on volume of distribution (53%) was explained. The final model shows that for commonly used dosing regimens, the population mean PG peak and trough concentrations ranges between 33-144 and 28-218 mg/L (peak) and 19-109 and 6-112 mg/L (trough) depending on birth weight and age of the neonates for paracetamol and phenobarbital formulations, respectively.

Conclusion

A pharmacokinetic model was developed for PG co-administered with paracetamol or phenobarbital in neonates. As such, large variability in PG exposure may be expected in neonates which are dependent on birth weight and postnatal age.

"What is already known about this subject"

Propylene glycol is commonly used as an excipient in dose forms and is ingested by neonates when administering different drugs. While propylene glycol is generally considered to be safe, toxic effects like bradycardia, lactic acidosis and convulsions have been reported. Information on the pharmacokinetics of propylene glycol in neonates is lacking to provide insights on the possible risk of toxicity.

"What this paper adds"

This study describes the pharmacokinetics of propylene glycol in preterm and term neonates co-administered with paracetamol and phenobarbital. A pharmacokinetic model was developed which identified birth weight and postnatal age as important covariates for clearance. The model was used to simulate exposure to propylene glycol co-administered with both drugs.

7.1. Introduction

Since a substantial number of drugs have poor solubility or stability, excipients are often needed. Propylene glycol (PG) is a frequently applied cosolvent to increase the solubility and/or stability of several drugs like e.g. phenobarbital, paracetamol, lopinavir, ritonavir or lorazepam, compounds which are also often administered in neonates [1]. Although propylene glycol is generally regarded as safe, concentration related toxicity has been reported in the adult, pediatric and neonatal population and may involve bradycardia, depression of the central nervous system, increase in anion gap, lactic acidosis, hepatic dysfunction or kidney injury [1-4].

Little is known on the pharmacokinetics of propylene glycol in children. In adults, it has been described that approximately 45% of the administered dose of propylene glycol is eliminated through the kidney. The other 55% is metabolized through alcohol dehydrogenase in the liver to lactate and pyruvate and eventually to carbon dioxide and water [5-7]. While the elimination half-life of propylene glycol is estimated to be 2-5 hours in adults [2, 8], prolonged elimination half-lives of 10.8-30.5 hours have been reported in preterm neonates (< 1.5 kg) [5, 9]. In particular neonates and infants are therefore potentially at increased risk for toxic effects due to a more pronounced propylene glycol exposure [10]. In spite of this, current guidelines on the use of propylene glycol in drugs or food are limited and conflicting. Although the Food

and Drug Administration (FDA) as well as the European Medicine Agency (EMA) have developed guidelines concerning the safe use of propylene glycol, these guidelines vary largely between these agencies. The FDA established an acceptable daily intake of propylene glycol of 25 mg/kg bodyweight. EMA proposed a maximum daily dose of 400 mg/kg for adults and 200 mg/kg for children [11]. This discordance in the different guidelines reflects the lack of information on the safe use of propylene glycol in general, and of specific advices for the pediatric and neonatal age ranges in particular.

To date, to our best knowledge, no pharmacokinetic studies on propylene glycol have been performed in children nor in the full spectrum of neonates. Only a limited number of pediatric reports, exploring possible toxic effects of propylene glycol, are available [3, 12-15]. In this perspective, it is of relevance that the FDA recently warned on serious health problems in premature neonates receiving Kaletra®, which contains a combination of lopinavir and ritonavir dissolved in ethanol (356.3 mg ethanol/mL) and propylene glycol (152.7 mg/mL). Adverse events as cardiac, renal and respiratory problems were reported in premature neonates, likely due to a decreased ability to eliminate either ethanol, propylene glycol or both [16, 17].

Because of the conflicting guidelines and observations on the (in)tolerabililty to PG in neonates, the aim of this study was to characterize the pharmacokinetics of propylene glycol, when co-administered with intravenous paracetamol or phenobarbital in preterm and term neonates.

7.2. Methods

7.2.1. Patients

This pharmacokinetic analysis was based on observations collected in 68 (pre) term neonates from a previously published study [1] evaluating short-term clinical and biochemical tolerability to propylene glycol co-administered with intravenous paracetamol (Paracetamol Sintetica, Mendrisio, Italy) containing 800 mg propylene glycol per 1000 mg paracetamol solution or intravenous phenobarbital (Luminal Injektionlösung, Desitin Arzneimittel, Hamburg, Germany) containing 700 mg propylene glycol per 200 mg of phenobarbital. The study was conducted at the University Hospitals Leuven (Belgium) at the neonatal intensive care unit following approval by the local ethical board (B-32220084836) and study registration (PARANEO, EUdraCT 2009-011243-39, www.clinicaltrials.gov). Neonates were included after informed written parental consent. The decision to prescribe a source of intravenous PG, either paracetamol-PG or phenobarbital-PG, was made by the

attending physician and based on the clinical needs. For paracetamol, a loading dose of 20 mg/kg was given, followed by a maintenance dose of 5-10mg/kg every 6 hours, depending on postmenstrual age [1]. For phenobarbital, a loading dose of 20 mg/kg phenobarbital was given, followed by a maintenance dose of 5 mg/kg/day [18]. The number of samples in every individual neonate ranged from 1 to 11 collected between 20 minutes until 20.5 hours after dose administration. Six patients were considered as outliers due to unexplainably high concentrations of propylene glycol, likely caused by analytical interferences after visual inspection of the individual chromatographies. The clinical characteristics of the included patients (N=62) are summarized in table 1.

7.2.2. Analytical assay

Propylene glycol concentrations were determined by high performance liquid chromatography with photodiode array detection described by Kulo *et al.* [19]. The developed accurate, specific, sensitive and rapid method was validated for quantification of propylene glycol in low volume neonatal plasma (15-46 mg/L) and urine (20-175 mg/L). Samples with concentrations higher than this were re-analysed after dilution until they fell within the calibration range. The inter-assay and intra-assay precision was between 8.1 -14.1% and 2.3 -12.7% respectively while the lower limit of quantification was 0.25 mg/L.

7.2.3. Population pharmacokinetic analysis and Model evaluation

The population pharmacokinetic analysis was performed using the non-linear mixed effect modeling software NONMEM version 6.2. (Globomax LLC, Hanover, MD, USA). S-Plus, PsN and R were used for visualization and evaluation of the models. Development of the model was performed in four different steps: (i) choice

Table 1: Clinical characteristics of the patients, receiving propylene glycol co-administered with paracetamol, phenobarbital or both, presented as median (range).

Characteristics	Paracetamol	Phenobarbital	Paracetamol + Phenobarbital
Number of patients	34	25	3
Gestational age (weeks)	38 (24-41)	34 (27-40)	36 (35-37)
Postmenstrual age (weeks)	38 (25-41)	34 (28-46)	36 (35-37)
Postnatal age (days)	3 (1-28)	2 (1-82)	3 (2-5)
Birth weight (g)	2990 (630-3820)	1965 (815-3980)	2490 (2245-2514)
Current bodyweight (g)	2990 (700-4100)	1965 (780-3980)	2435 (2145-2490)

Birth weight = weight at day of birth, current bodyweight = weight at day of blood sampling

of the structural model, (ii) choice of the statistical sub-model, (iii) covariate analysis, (iv) model evaluation. The descriptive and predictive performance between different models was evaluated by different diagnostic tools [20]. A decrease in objective function (OFV) of 3.9 points or more was considered as a statistically significant difference ($p<0.05$ based on X2 distribution) for structural and statistical models while a more stringent p value of 0.005 was used for the evaluation of covariate models. In addition, goodness-of-fit plots, including observed *versus* individual predicted, observed *versus* population predicted, conditional weighted residuals *versus* time and conditional weighted residuals *versus* population predicted, were used for diagnostic purposes. Furthermore, the total number of parameters, visual improvement of individual plots, confidence intervals of parameter estimates, and correlation matrix were assessed as diagnostic criteria during model development. Finally, ill-conditioning [21] and shrinkage [22], which may occur in pediatric analyses [20], were determined.

7.2.4. Structural model

A one and two compartment model was fitted to the data. The interindividual variability in the pharmacokinetic parameters was assumed to follow a log normal distribution. The value of a particular parameter in an individual i (*post hoc* value) is given by the following equation:

$$\theta_i = \theta_{TV} \bullet e^{\eta i} \qquad \text{(Equation 1)}$$

in which θ_{TV} is the typical value of the parameter and η_i is assumed to be a random variable with mean value zero and variance ω^2. The residual variability was best described by a proportional error model. This means for the jth observed concentration of the ith individual the relation (Y_{ij}):

$$Y_{ij} = C_{pred,ij} \bullet (1+\varepsilon_{ij}) \qquad \text{(Equation 2)}$$

where C_{pred} is the predicted concentration and ε_{ij} is a random variable with a mean of zero and a variance of σ^2.

7.2.5. Covariate analysis

To visualize potential relationships between covariates and parameter estimates, plots of the individual *post hoc* parameter estimates and weighted residuals *versus* covariates were generated. The following covariates were evaluated: gestational age, postmenstrual age, postnatal age, birth weight (weight at day of birth) and current bodyweight (weight at day of blood sampling). Potential covariates were implemented into the model using a linear or allometric equation (equation 3).

$$P_i = P_p \bullet (\frac{Cov}{Cov_{Median}})^k \qquad \text{(Equation 3)}$$

In this equation Pi represents the individual parameter estimate of the ith subject, Pp equals the population parameter estimate, Cov is the covariate and k is the exponent which was fixed to 1 for a linear function or estimated for an allometric function.

Covariates were separately implemented into the model and considered statistically significant when the OFV decreased with at least 7.8 points (p value <0.005). When more than one covariate significantly reduced the OFV, the covariate causing the largest drop in OFV was left into the model. Additional covariates had to reduce this OFV further to be retained in the model. Subsequently, the contribution of each covariate was re-evaluated in the backward deletion for which a more stringent p value <0.001 (OFV 10.83 points) was used. To select the final covariate model, the individual and population predicted values were plotted against the most predictive covariate to evaluate whether the individual predicted parameters were equally distributed around the population predicted parameters [20]. The covariate model was further evaluated as discussed previously in the section Population Pharmacokinetic analysis. Finally, the results of the model validation procedure (see below) were also considered.

7.2.6. Internal validation

For the internal validation of the final pharmacokinetic model, two different evaluation tools were used. The first method was the bootstrap resampling method to evaluate model precision and stability. The bootstrap analysis was performed in S-plus, version 6.2.1 (Insightful software, Seattle, WA) with NM.SP.interface version

05.03.01 (© by LAP&P Consultants BV, Leiden, The Netherlands) in which 1000 replicates were generated. Parameter estimates obtained in the bootstrap analysis were compared to the parameter estimates of the original dataset.

For the second internal evaluation method, the normalized prediction distribution error method (NPDE) was used, which is a simulation-based diagnostic to determine the accuracy of the model [23, 24]. The observed and simulated concentrations were compared using the NPDE package in R. A histogram of the NPDE distribution and scatterplots showing the NPDE *versus* time and *versus* predicted concentration were used to evaluate the final model.

7.2.7. Model-based simulations for propylene glycol co-administered with paracetamol or phenobarbital

Using the final PK model, simulations were performed in three different patients (birth weight 630g, 1500g and 3500g and gestational age 24, 32, 40 weeks) with a postnatal age of 1 and 28 days. The current bodyweight at a postnatal age of 28 days was 950g, 1950g and 4100 g, respectively. These three patients were selected to cover the entire population of the current study in terms of gestational age and bodyweight. The parameter estimates obtained in the final pharmacokinetic model were used to simulate concentrations of propylene glycol after administration of intravenous paracetamol (Paracetamol Sintetica, Mendrisio, Italy: 800mg PG/ 1000mg paracetamol) or intravenous phenobarbital (Luminal Injektionlösung, Desitin Arzneimittel, Hamburg, Germany: 700mg PG/ 200mg phenobarbital) in the dosing regimens applied in this study. For paracetamol, a loading dose of 20 mg/kg was given, followed by a maintenance dose of 10mg/kg every 6 hours [1]. For phenobarbital, a loading dose of 20 mg/kg phenobarbital was given, followed by a maintenance dose of 5 mg/kg/day [18].

7.2.8. Maximally acceptable levels of propylene glycol in neonates

Different approaches were applied to provide a basis for maximally acceptable concentrations of propylene glycol in neonates. First, the exposure to propylene glycol upon administration of propylene glycol as a result of paracetamol or phenobarbital was compared to levels observed in a previously published study in 68 preterm and term neonates in which tolerability of propylene glycol was evaluated and no toxic effects were reported [1]. In a second approach, a maximum concentration was defined on basis of the toxic effects related to the osmolar changes. The increase in osmolar gap can directly be linked to propylene glycol concentrations by the following relationship [2]: [osmolar gap = concentration of propylene glycol (mg/

dL) / 7.6] while osmolar gap is considered the first indicator of propylene glycol accumulation before propylene glycol toxicity appears related to other metabolic disturbances or clinical symptoms [6]. In a study of Yahwak *et al.* [25] in adults, an increase in osmolar gap of 10 mOsm/L was linked to elevated propylene glycol concentrations and an increase of 12 mOsm/L resulted in clinical changes suggestive of propylene glycol toxicity. Furthermore, in studies by Feldman *et al.* [26] and Giacoia *et al.* [27], a standard deviation of 8 mOsm/L in serum osmolality has been described in neonates. Based on these observations, we considered the maximum allowed propylene glycol plasma concentration to remain below 608 mg/L, which corresponds to a maximum change in osmolar gap of 8 mOsm/L. The proposed maximum concentration of 608 mg/L is in close agreement with previously published results by Wilson *et al.* [6] in which metabolic abnormalities were reported for concentrations ranging between 580 and 1270 mg/L [6]. However our proposed maximum concentration of propylene glycol of 608 mg/L should be viewed with caution since it is only based on findings reported in literature, for adult patients. It is therefore not validated in neonates. Finally, a third possible maximum safe concentration was identified by performing

Table II: Model-based population pharmacokinetic parameter estimates and the values obtained after the bootstrap analysis.

Parameter	Simple model without covariates Value (CV%)	Final pharmacokinetic covariate model Value (CV%)	Bootstrap final pharmacokinetic model Value (CV%)
Fixed effects			
CL (L/h) = CLp	0.060 (11.8)	-	-
CLp in CL= CLp x (bBW/median)^m x (PNA/median)^n	-	0.085 (4.9)	0.085 (5.24)
m	-	1.69 (10.2)	1.68 (11.44)
n	-	0.20 (31.9)	0.20 (37.62)
V (L) = Vp	0.90 (10.2)	-	-
Vp in V = Vp x (cBW/median)^o x p	-	0.97 (6.58)	0.97 (7.05)
o	-	1.45 (10.4)	1.45 (11.28)
p (phenobarbital)	-	1.77 (12.1)	1.79 (13.10)
Interindividual variability (ω^2)			
ω^2 (CL)	0.69 (23.9)	0.12 (26.3)	0.11 (30.91)
ω^2 (V)	0.64 (23.9)	0.18 (25.6)	0.17 (27.99)
Residual Variability (σ^2)			
σ^2 (proportional)	0.036 (12.1)	0.036 (11.8)	0.036 (11.40)

CL = Clearance, CLp = population value for clearance, V = Volume of distribution, Vp = population value for volume, bBW = bodyweight at birth, cBW = current bodyweight, PNA = postnatal age

simulations based on the guidelines for propylene glycol administration in children established by the EMA (200 mg/kg/day) and the FDA (25 mg/kg/day). To the very best of our knowledge, these guidelines are neither supported by observational data. In these simulations 100 mg or 12.5 mg of propylene glycol depending on the guidelines by the EMA or FDA, respectively was administered in three different neonates (bBW 630 g, 1500 g and 3500g) every 12 hours since drugs containing propylene glycol are often given in this manner in clinical practice in neonates. It was simulated to be given by a bolus injection over 15 min to illustrate the highest potential exposure to propylene glycol.

7.3. Results

7.3.1. Patients

The pharmacokinetic analysis was based on 372 observations obtained from 62 neonates. The number of samples taken per neonate ranged between 1-11. Thirty-four neonates received propylene glycol by intravenous administration of paracetamol compared to twenty-five neonates who received phenobarbital while three neonates receiving a combination of both paracetamol and phenobarbital. Patient characteristics are summarized in table 1.

7.3.2. Structural pharmacokinetic model

A one compartment model parameterized in terms of clearance and volume of distribution with a proportional error model best described the plasma concentrations of propylene glycol.

7.3.3. Covariate analysis

In the systematic covariate analysis, birth weight was found the most important covariate for clearance causing a drop in OFV of 82 points ($p<0.001$). Birth weight was best implemented on clearance using an allometric function in which a value of 1.69 was estimated for the exponent. When evaluating other covariates, current weight was found the most important covariate for volume of distribution using an allometric function with an estimated exponent of 1.48 (ΔOFV 48 points, $p<0.001$). Furthermore, a significant difference in volume of distribution was seen between neonates receiving phenobarbital and paracetamol. The volume of distribution was estimated to be 1.77 times higher (95% confidence interval: 1.35-2.19) for neonates receiving phenobarbital (ΔOFV 18 points, $p<0.001$). Finally, further improvement

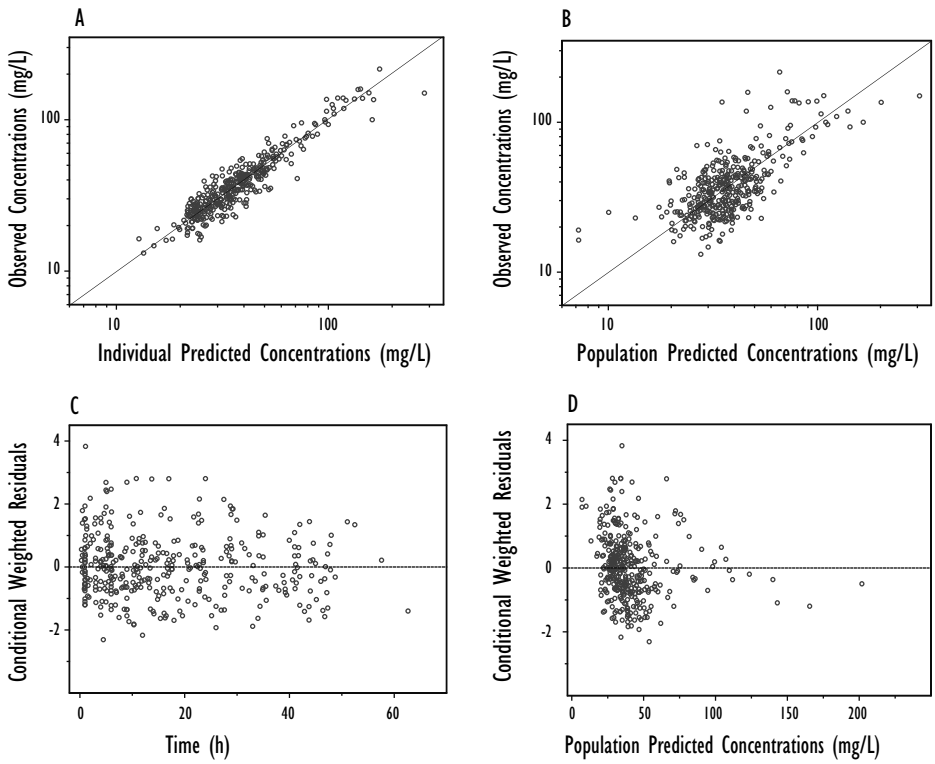


Figure 1: Diagnostic plots for the final pharmacokinetic model: (a) Observed *versus* individual predicted concentrations, (b) Observed *versus* population predicted concentrations, (c) Conditional weighted residuals *versus* time, (d) Conditional weighted residuals *versus* population predicted concentrations.

of the model fit was seen when postnatal age was introduced on clearance using an allometric function with an estimated exponent of 0.201. This last covariate was responsible for the smallest but still significant drop in the objective function (Δ OFV = 15 points, $p<0.001$). All parameter estimates of the final pharmacokinetic model are summarized in table II. The diagnostic plots are represented in figure 1. By introducing these covariates a large part of the interindividual variability on clearance (65%) as well as on volume of distribution (53%) is explained (table II). This is reflected by the estimates of interindividual variability in clearance and volume of distribution which were reduced from 0.69 to 0.12 and 0.64 to 0.18, respectively.

7.3.4. Model validation

The values for the parameter estimates obtained during the bootstrap procedure

are shown in table II. The parameter estimates obtained after bootstrapping were within 8% of the values obtained in the final pharmacokinetic model. Of the total number of runs (N=1000), 100% was successful, only 34 runs did not have a covariance step.

The results of the NPDE analysis are depicted in figure 2. The histogram follows the normal distribution indicated by the black solid line (figure 2a). No trend is seen in the NPDE *versus* time (figure 2b) and the NPDE *versus* predicted concentrations (figure2c). The plot with the individual predicted parameter estimates and population parameter estimates for clearance and volume of distribution *versus* the most predictive covariate, birth weight and current bodyweight respectively, showed that the individual predicted parameter estimates are randomly scattered around the population parameter estimates (figures not provided). The number of ill-conditioning (8.28) was far below the critical value of 1000 meaning that the final pharmacokinetic model is not over-parameterized. Finally, η-shrinkage expressed as a percentage was identified to be below 20% for clearance (14.8%) and volume of distribution (6.2%).

The model-based predicted clearance values for the final pharmacokinetic model *versus* birth weight for PNA 1, 7, 14, 21 and 28 days are shown in figure 3.

7.3.5. Model-based simulations for propylene glycol co-administered with paracetamol or phenobarbital

Concentration-time profiles of propylene glycol after standard dosing regimens of intravenous paracetamol (800mg PG/1000mg paracetamol) or phenobarbital (700mg PG/200mg phenobarbital) that were used in this study, were simulated in three different neonates (bBW 630g, 1500g and 3500g, respectively) at a postnatal

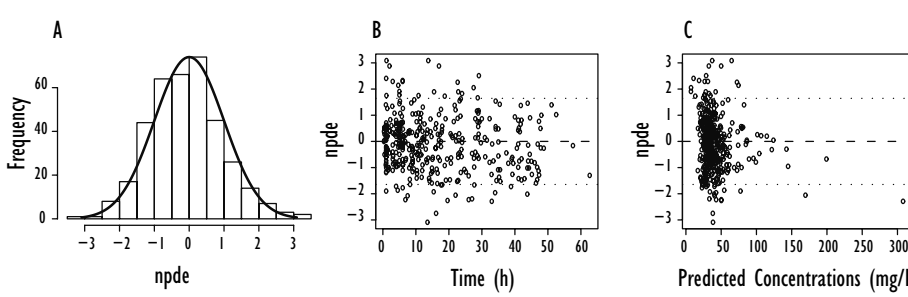


Figure 2: Results of the NPDE analysis: (a) the histogram shows the NPDE distribution, the solid line indicates a normal distribution, (b) NPDE *versus* time after first dose, (c) NPDE *versus* predicted concentrations.

Table III: Propylene glycol (PG) dosages when co-administered with paracetamol or phenobarbital in currently used dosages.

Drug	Propylene glycol content	Dosing guideline for drug	Drug-associated daily dose propylene glycol (mg/kg/day)	Ref.
IV Paracetamol 10mg/mL	800 mg PG/1000 mg paracetamol	Loading dose: 20 mg/kg	40	(1)
		Maintenance dose: 10 mg/kg every 6 hours	16-32	
IV Phenobarbital 200 mg/mL	700 mg PG/200 mg phenobarbital	Loading dose: 20 mg/kg/day	70	(18)
		Maintenance dose: 5 mg/kg/day	17.5	

age of 1 and 28 days (figure 4). The administered dose of paracetamol, phenobarbital and the corresponding dose of propylene glycol are given in table III. Figure 4 shows that population mean value for trough and peak concentration of propylene glycol co-administered with paracetamol for a neonate of 630 g at day 1 was estimated to be 109 and 144 mg/L, respectively, and for a neonates of 3500g at day 28 trough and peak concentration of propylene was estimated to be 19 and 33 mg/L, respectively.

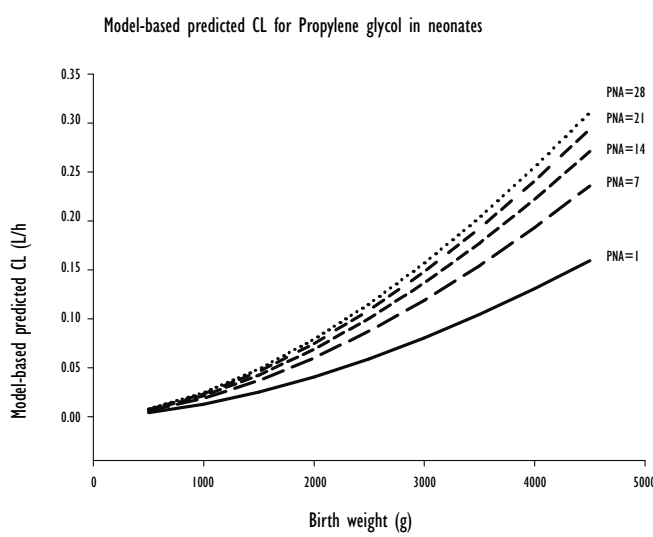


Figure 3: Model-based predicted clearance values of propylene glycol *versus* birth weight for postnatal age (PNA) of 0, 7, 14, 21 and 28 days.

The expected population mean peak and trough propylene glycol concentrations after administration of phenobarbital varied between 28-218 and 6-112 mg/L, respectively, depending on birth weight (630g-3500g) and postnatal age (1-28 days) of the neonate (table III, figure 4).

7.4. Discussion

While propylene glycol is considered to be safe and inactive, upon high concentrations toxic effects like lactic acidosis, bradycardia and convulsions may occur. The risk of propylene glycol toxicity is higher in infants and neonates compared to adults since they have a lower metabolic capacity as well as an immature renal function resulting in a lower elimination capacity. The aim of this study was to characterize the pharmacokinetics of propylene glycol and its covariates in neonates following intravenous administration.

The pharmacokinetic model developed in this study was based on 372 propylene glycol plasma concentrations obtained in 62 preterm and term neonates after administration of paracetamol, phenobarbital or both. Birth weight was found the most important covariate for clearance while an increase in clearance was seen with postnatal age. The population value for clearance of 0.0849 L/h reported here in neonates is very low compared to the clearance value reported in adults which was found to vary between 144-390 mL/min/1.73m2 (8.64-23.4 L/h/1.73m2) [5]. This may indicate that either the alcohol dehydrogenase enzyme pathway or primary renal elimination, or most likely both, are immature during the first month of life. For renal function this has been described before by studying amikacin clearance in neonates, which likely reflects glomerular filtration in neonates [28] . The model-based predicted clearance values of propylene glycol *versus* birth weight for postnatal age 1, 7, 14, 21 and 28 are shown in figure 3. Large differences in clearance values are seen between neonates of 1 kg (0.013 L/h) and neonates of 4 kg (0.13 L/h) at day of birth. This 10-fold difference in clearance is still seen one month after birth. Furthermore this figure illustrates that during the first two weeks of life the largest increase in clearance is observed. These results correspond well with the advice of the FDA to avoid Kaletra®, a propylene glycol containing oral solution in premature babies until 14 days after due date, or in full-term babies younger than 14 days postnatal age [16, 17]. Volume of distribution scaled with current weight and was estimated 1.77 times higher in neonates receiving phenobarbital compared to neonates receiving paracetamol. The volume of distribution of a neonate of 1 kg (0.23L or 0.40L) (co-administered with paracetamol or phenobarbital, respectively) was very different

compared to a neonate of 4 kg (1.69 L or 3L). This difference may possibly be explained by the fact that phenobarbital is often given to neonates after perinatal asphyxia which may lead to a change in the pharmacokinetic parameters e.g. higher volume of distribution. Unfortunately asphyxia could not be investigated as a covariate since no potential indicators (e.g. Apgar score, serum lactate concentration) were identified. The large variability in clearance and volume of distribution as a result of birth weight, PNA and current weight is reflected by the large range in expected peak and trough concentrations that can be expected upon commonly used doses of paracetamol and phenobarbital in neonates varying in birth weight between 630g and 3500g and between a PNA of 1-28 days (figure 4). The stability and predictability of the final pharmacokinetic model was demonstrated by the bootstrap (table II) as well as the NPDE (figure 2), which are both advanced validation methods for paediatric pharmacokinetic models.

Although dose-related toxic effects have been reported upon administration of propylene glycol, only a limited number of pediatric reports are available in literature. Glasgow *et al.* [13] and MacDonald *et al.* [14] described hyperosmolality and clinical symptoms of propylene glycol toxicity in small infants (< 1500 g birth weight) due

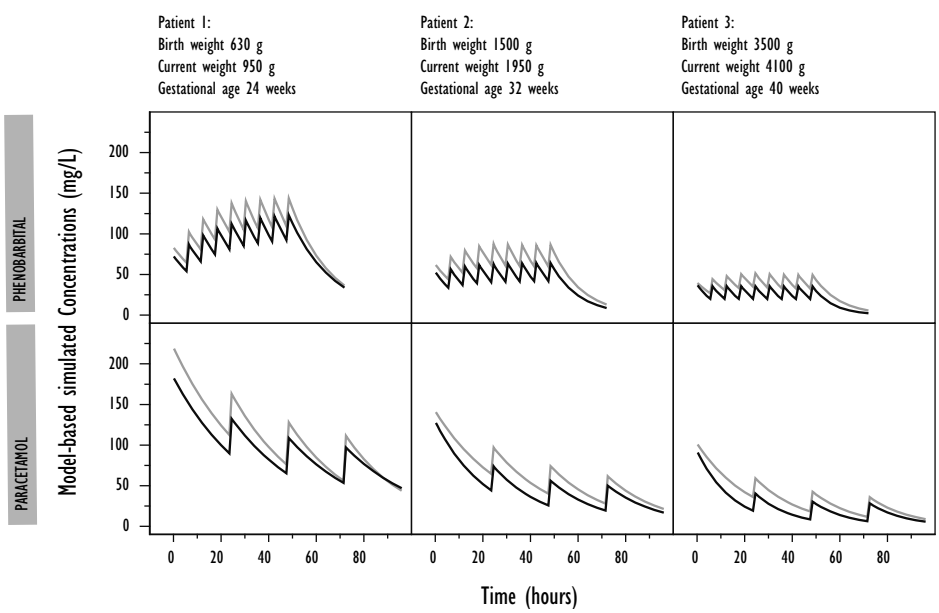


Figure 4: Model-based simulated concentration-time profiles of propylene glycol for three neonates (birth weight 630g, 1500g and 3500 g) after administration of paracetamol (800mg propylene glycol/1000mg paracetamol, upper panel) and phenobarbital (700mg propylene glycol/200mg phenobarbital, lower panel) in doses according to table III. The grey lines illustrate the concentration-time profiles for the neonates at birth. The black lines represent the concentration-time profiles at a postnatal age of 28 days (current weight 950g, 1950g and 4100g).

to very high propylene glycol exposure (3000mg/kg) in multivitamins injections. In retrospective studies of Shehab *et al.* [3] and Whittaker *et al.* [15] it was concluded that neonates at the neonatal intensive care unit are indeed exposed to potentially toxic doses of propylene glycol due to administration of commonly used drugs (e.g. phenobarbital, lorazepam, phenytoin, paracetamol) cosolved in propylene glycol but data on toxicity were not reported. In a study of Chicella *et al.* [12] a propylene glycol containing lorazepam formulation was administered to 11 infants between 1-15 months of age. In this study, there were neither clinical nor laboratory abnormalities observed, but accumulation of propylene glycol occurred during continuous infusion of lorazepam. Consequently, propylene glycol containing formulations should be used with caution in the pediatric and certainly in the neonatal age range especially when this results in high PG exposure. Based on literature, the first indicator of a risk for subsequent propylene toxicity is propylene glycol accumulation and changes in osmolar gap. Accumulation may subsequently result in biochemical changes and eventually toxic effects like e.g. bradycardia, hepatic or renal injury, depression of the central nervous system.

To provide a basis to interpret the simulated concentrations of PG co-administered with paracetamol or phenobarbital in neonates, different approaches were provided in the methods section. However to identify maximum safe concentrations, more pharmacokinetic and pharmacodynamic studies are needed in neonates, particularly with drugs containing high concentrations of propylene glycol. To illustrate this concept, simulations were performed to illustrate the potential exposure of propylene glycol co-administered with lorazepam (828mg PG/2mg lorazepam). Based on the final pharmacokinetic model of propylene glycol co-administered with paracetamol, substantially higher concentrations of PG are obtained depending on the dose of lorazepam. Simulated propylene glycol concentrations upon lorazepam in a dose of 0.015 mg/kg/h [18] (daily dose of 149 mg/kg/day of propylene glycol) varied between 540 mg/L for a neonate of 630g at day 1 and 123 mg/L for a neonate of 3500g at day 28. Upon a dose of lorazepam of 0.1 mg/kg/day as described by Chicella *et al.* [12], concentrations of propylene glycol varying between 798-3563 mg/L were obtained, depending on birth weight and postnatal age. It should be noted that these concentrations are generated under the assumption of linear pharmacokinetics of propylene glycol, while higher daily doses of propylene glycol were administered to the neonates (149 mg/kg/day or 996 mg /kg/day) with lorazepam compared to paracetamol or phenobarbital. As a result of the assumption of linear pharmacokinetics, the estimates of the exposure to propylene glycol must be considered conservative.

In case of non-linearity in pharmacokinetics, even higher exposures are expected. At least, PG accumulation upon the lorazepam dosing in neonates is in line with PG accumulation and toxicity described in adults [2, 6].

7.5. Conclusion

A pharmacokinetic model with birth weight and postnatal age as covariates for clearance was developed for propylene glycol co-administered with paracetamol or phenobarbital in preterm and term neonates. As such, large variability in exposure of propylene glycol may be expected in neonates which are dependent on birth weight and postnatal age. The model can be used to simulate concentrations of propylene glycol co-administered with paracetamol and phenobarbital in neonates. As the exact safe concentrations are still undefined, more studies are needed to characterize the pharmacokinetics of propylene glycol in neonates and children.

Acknowledgements

This study was performed within the framework of Top Institute Pharma project number D2-104.

The clinical research of K. Allegaert is supported by the Fund for Scientific Research, Flanders (Belgium) (FWO Vlaanderen) by a Fundamental Clinical Investigatorship (1800209 N). The clinical research of A. Kulo is supported by a JoinEU-SEE scholarship (2009-2010). The authors also would like to thank LAP&P Consultants for their technical support with NONMEM.

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