# Chapter 8

## Low but Inducible Contribution of Renal Elimination to Clearance of Propylene Glycol in Preterm and Term Neonates

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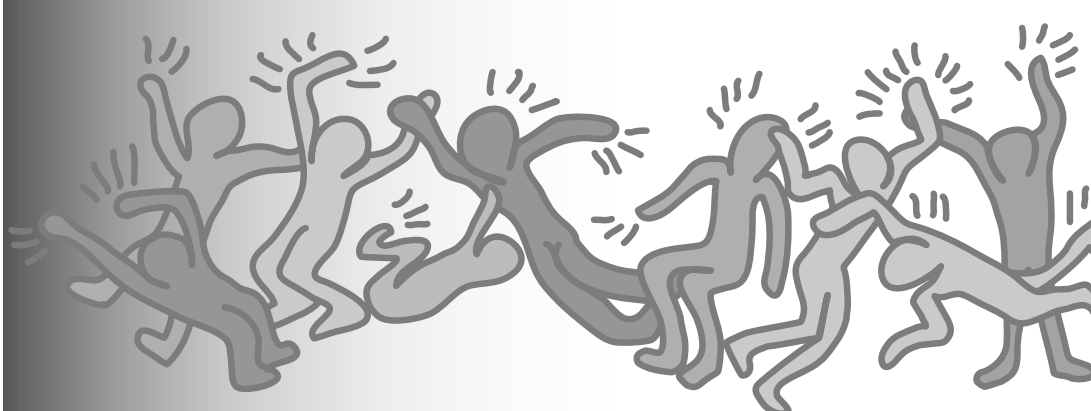


# Abstract

## Background

Despite limited information on the pharmacokinetics of excipients, propylene glycol (PG) is often used as a excipient both in adults and children. The aim of this study is to characterize renal and hepatic elimination of propylene glycol in preterm and term neonates.

## Methods

The pharmacokinetic analysis of PG was performed in NONMEM 6.2. on the basis of PG concentrations in plasma and/or urine samples for a total of 69 (pre)term neonates (birth weight 630-3980g, gestational age 24-41 weeks, postnatal age 1-29 days) who received PG co-administered with IV paracetamol (5-10 mg/kg/6 hours), phenobarbital (5 mg/kg/day) or both. To capture the time dependent trend in renal excretion of PG, different models based on time after first dose, urine volume and creatinine amount in urine were tested.

## Results

A one compartment model parameterized in terms of renal clearance, hepatic clearance and volume of distribution was found to adequately describe the observations in both plasma and urine. After the first dose, renal elimination of propylene glycol was 15% of total clearance, which increased over time to 25% at 24 hours after the first dose of PG. This increase was best described using a hyperbolic function based on time after the first dose.

## Conclusions

Renal elimination of PG in (pre)term neonates is low, particularly compared to the reported percentage of 45% in adults, but may increase with time after first dose of PG. To study whether this increase is caused by an auto-induced increase in renal secretion or a reduction of tubular reabsorption of PG, further research is needed.

## 8.1. Introduction

Propylene glycol is a frequently used excipient in many drug formulations to increase solubility and/or stability of drugs. Although excipients may be expected to be inactive compounds, toxic effects related to propylene glycol such as bradycardia, lactic acidosis, hepatic and renal dysfunction, increase in anion gap, have been described in adults, children and neonates [1-5]. As a consequence, both the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have established guidelines considering maximum daily doses of propylene glycol. However, no conformity is seen between the guidelines of both agencies [6]. While this may be explained by a lack of specific information relating to the safe use of propylene glycol, it is emphasized that the available knowledge on the pharmacokinetics of propylene glycol mainly focuses on adults. However children and certainly neonates are at increased risk for the toxic effects of propylene glycol due to accumulation of propylene glycol [7-9], which is reflected by the prolonged elimination half-life in preterm neonates (10.8-30.5 hours) [10] compared to adults (2-5 hours) [1, 11].

In adults, it is known that 45% of propylene glycol is eliminated through the renal route and 55% is metabolized in the liver by alcohol dehydrogenase (ADH) to lactate and pyruvate [8, 12, 13]. Previously it has been reported that the activity of alcohol dehydrogenase is reduced in neonates reaching adult levels at about 5 years of age [14]. Due to immaturity of the renal function, renal clearance of propylene glycol may also be expected to be lower in neonates compared to adults. Assuming that maturation processes in the liver and kidneys may differ in rate and nature, one pathway or the other may be more relevant for a specific age group resulting in for instance age-specific drug-drug interactions for the pathway concerned. Even though based on plasma observations the pharmacokinetics of propylene glycol have recently been characterized in preterm and term neonates [15], no information is available on the contribution of renal elimination to the overall clearance of propylene glycol in neonates. The aim of this study was therefore to characterize the pharmacokinetics of propylene glycol differentiating between renal elimination and hepatic metabolic pathways based on propylene glycol observations in both plasma and urine in preterm and term neonates.

## 8.2. Methods

### 8.2.1. Patients and Data

The analysis was based on data of 69 preterm and term neonates consisting of previously published observations of propylene glycol in plasma [3, 15] and observations of propylene glycol in urine. Urine samples could only be collected in neonates with a urinary bladder catheter already in place for clinical indications. An overview of the clinical characteristics is given in table 1. Propylene glycol was co-administered with either intravenous paracetamol (Paracetamol Sintetica, Mendrisio, Switzerland) 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 or both. For paracetamol, a loading dose of 20 mg/kg was given followed by a maintenance dose of 5-10 mg/kg every 6 hours. This corresponds to a dose of propylene glycol varying between 16-40 mg/kg/day. For phenobarbital, a loading dose of 20 mg/kg was given followed by a maintenance dose of 5 mg/kg/day. This corresponds to a dose of 70 mg/kg/day of propylene glycol when a loading dose is given and 17.5 mg/kg/day when a maintenance dose is given. In 46 neonates, plasma samples of propylene glycol which was co-administered with paracetamol, phenobarbital or both, was available while in 16 neonates both urine and plasma samples of propylene glycol co-administered with paracetamol were available. In 7 neonates, only urine samples of propylene glycol co-administered with paracetamol were available. Urine samples were available in 6 hour fractions collected over 24 hours. In one patient, urine was collected every 6 hours with a maximum of 48 hours instead of 24 hours after administration of the first dose. The study was conducted in Leuven NICU following approval by the local ethical board of the University Hospitals Leuven (B-32220084836).

### 8.2.2. Analytical method

Propylene glycol was determined in low volume neonate plasma (15-46 mg/L) and urine (20-175 mg/L) by high performance liquid chromatography with photodiode array detection as described by Kulo *et al* [16]. Samples with concentrations higher than the validation range were re-analyzed after appropriate dilution until they fell into the validation range. Plasma samples were diluted with drug-free human plasma and urine samples with water.

### 8.2.3. Pharmacokinetic analysis: Model development

The non-linear mixed effect modeling software (NONMEM 6.2) (Globomax LLC, Hanover, MD, USA) using the first-order conditional estimation method with the interaction option (FOCE-I) was used to perform the population pharmacokinetic analysis. Tools like 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), PsN and R (version 2.10.1) were used to visualize and evaluate the model.

The model was developed in four different steps: (i) choice of the structural model, (ii) choice of the statistical sub-model, (iii) choice of the covariate model, (iv) model evaluation. A decrease in objective function (OFV) of 3.9 points or more was considered statistically significant ($p<0.05$ based on X2 distribution, for nested models). In addition, the following goodness-of-fit plots were evaluated for diagnostic purposes: (i) observed *versus* individual predicted concentrations, (ii) observed *versus* population predicted concentrations, (iii) conditional weighted residuals *versus* time, (iv)conditional weighted residuals *versus* population predicted concentrations. Finally, the total number of parameters, visual improvement of individual plots, correlation matrix, confidence intervals of parameter estimates, ill-conditioning [17] and shrinkage [18] were assessed.

Table 1: Clinical characteristics (median (range)) of the studied patient population receiving propylene glycol (PG) co-administered with intravenous paracetamol, phenobarbital or both.

| Characteristics | All patients | Patients with plasma data only | Patients with both plasma and urine data | Patients with urine data only |
|---|---|---|---|---|
| Number of patients | 69 | 46 | 16 | 7 |
| Number of samples per patient | 1-18 | 1-11 | 5-18 | 4 |
| Co-administered drug | paracetamol, phenobarbital or both | paracetamol, phenobarbital or both | paracetamol | paracetamol |
| Gestational age (weeks) | 37 (24-41) | 35 (25-40) | 37.5 (24-41) | 37 (30-39) |
| Postmenstrual age (weeks) | 37 (25-46) | 34 (25-46) | 38 (26-41) | 38 (30-39) |
| Postnatal age (days) | 3 (1-82) | 1 (1-82) | 3 (1-28) | 2 (2-11) |
| Birth weight (g) | 2720 (630-3980) | 2200 (700-3980) | 3050(630-3600) | 2650 (1160-3315) |
| Current bodyweight (g) | 2720 (700-4100) | 2490 (700-3980) | 3030 (630-4100) | 2560 (1160-3315) |
| Urine Volume (mL/6 hours) | 48 (14-115) | - | 48 (14-0.115) | 5 (17-113) |

Birth weight = bodyweight at day of birth. Current bodyweight = bodyweight at day of blood sampling. PG = propylene glycol

*Structural model*

For the structural model, a one compartment model was developed using NONMEM VI, subroutine ADVAN6, TOL=3. The concentrations of propylene glycol in plasma were expressed as mg per L. The excretion of propylene glycol in urine was expressed as a cumulative amount in mg and calculated by multiplying the urinary concentration (mg/L) with urine volume.

*Statistical submodel*

For the statistical submodel, the interindividual variability was tested assuming a log-normal distribution in an individual *i* (*post hoc* value) and is given by the following equation:

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

in which $\theta_{TV}$ is the typical value of the parameter and $\eta_i$ is assumed to be a random variable with mean value zero and variance $\omega^2$. For the intra-individual variability and residual error, proportional (equation 2), additive (equation 3) and combination (equation 4) error models were tested:

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

$$Y_{ij} = C_{pred,ij} + \varepsilon_{ij} \qquad \text{(Equation 3)}$$

$$Y_{ij} = C_{pred,ij} \bullet (1+\varepsilon_{1,ij}) + \varepsilon_{2,ij} \qquad \text{(Equation 4)}$$

where $Y_{ij}$ is the *j*th observation in the *i*th individual, $C_{pred,ij}$ is the predicted concentration and $\varepsilon_{ij}$ is a random variable from a normal distribution with a mean of zero and estimated variance of $\sigma^2$.

*Covariate analysis*

A comprehensive covariate analysis was performed in which the following covariates were evaluated: gestational age, postmenstrual age, postnatal age, birth weight (weight at day of birth), current bodyweight (weight at day of blood or urine sampling), time after first dose, urine volume, urine volume/kg, amount of creatinine in urine (mg). Covariates were implemented into the model using a linear or power equation (equation 5):

$$P_i = P_p \bullet (\frac{Cov}{Cov_{Median}})^k$$ (Equation 5)

In this equation $P_i$ represents the individual parameter estimate of the *i*th 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 a power function. Specific covariate models that were also tested to capture the time-dependent trend in renal elimination of PG are described below under Characterization of changes in renal clearance of propylene glycol over time. A covariate was considered to be statistically significant when causing a decrease in objective function of 7.8 points (p-value <0.005). When more than 1 covariate significantly reduced the OFV, the most significant covariate was retained into the model. This model was subsequently considered as the basis for the inclusion of additional covariates. The contribution of each covariate was then re-evaluated in the backward deletion for which a more stringent p-value <0.001 (ΔOFV 10.8 points) was used. In addition, the individual and population predicted parameters were plotted against the most predictive covariate to evaluate whether the individual predicted parameters were equally distributed around the population predicted parameters [19]. Finally the covariate model was evaluated as mentioned previously under Pharmacokinetic analysis: model development, whereby the results of the Model validation were also considered.

*Characterization of changes in renal clearance of propylene glycol over time*

As a systematic trend in propylene glycol amounts in urine over time after first dose was observed, different models were tested.

*Model I.* Implementation of an (intermediate) Michaelis-Menten model [20] for renal clearance of propylene glycol.

*Model II.* Implementation of urine volume normalized to kilograms current bodyweight as a covariate on renal clearance (equation 5).

*Model III.* Implementation of both time after first dose and current bodyweight as covariates on renal clearance of propylene glycol (equation 5).

*Model IV:* Implementation of a hyperbolic model based on time after first dose on renal clearance (equation 6):

$$CL_{Ri} = CL_{max} \bullet \left( \frac{Time^{k}}{Time_{50}^{k} + Time^{k}} \right)$$

(Equation 6)

In equation 6, $CL_{Ri}$ equals the individual renal clearance of the ith subject, $CL_{max}$ represents the maximum renal clearance of propylene glycol, Time represents time after first dose, Time50 is the time after first dose at which half of the maximum clearance is reached and k is the estimated exponent. Based on observations in adults [8, 12, 13], $CL_{max}$ was fixed at 0.45/0.55 of the hepatic clearance, which indicates that renal elimination also increases in correspondence with changes in hepatic clearance.

*Model V.* Implementation of amounts of creatinine, determined in each of the 6-hourly urine fractions, as a covariate on renal clearance of propylene glycol.

### 8.2.4. Model Validation

A bootstrap 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. The parameter estimates obtained in the bootstrap were subsequently compared to the parameter estimates of the original dataset.

In addition, due to the small number of subjects in whom urine data were available, a n-1 jackknife was performed to evaluate the stability of the model when one subject with urine data at a time was removed from the dataset.

Finally the normalized prediction distribution error method (NPDE) was used as a simulation-based diagnostic. The dataset was again simulated 1000 times, after which the observed and simulated concentrations were compared using the NPDE package in R [21, 22].

### 8.2.5. Simulations

Simulations were performed in NONMEM 6.2 based on the final pharmacokinetic model to simulate renal and hepatic clearance of propylene glycol across the individuals of the current study (birth weight 630g, 1500g, 2500g and 3500g and with a postnatal age of 1 and 28 days). In the simulations, four consecutive doses of propylene glycol co-administered with paracetamol were given. Simulations were performed with the exclusion of the interindividual and residual variability in order to demonstrate the exact influence of the covariates identified in this study.

# 8.3. Results

## 8.3.1. Patients and data

Patient and data characteristics are summarized in table 1. The pharmacokinetic analysis was based on 372 plasma concentrations of propylene glycol co-administered with intravenous paracetamol, phenobarbital or both and 79 urine samples of propylene glycol co-administered with paracetamol (table 1). Postnatal age for all patients varied between 1 and 29 days, except for one patient with a postnatal age of 82 days.

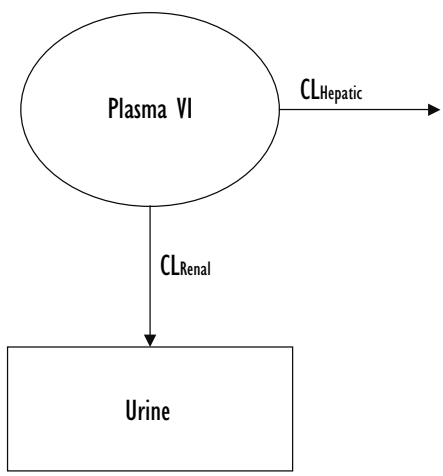



Figure 1: Schematic representation of the pharmacokinetic model of propylene glycol.

## 8.3.2. Pharmacokinetic analysis: Model development

*Structural Model*

Based on propylene glycol samples in both plasma and urine, a one compartment model was used, parameterized in terms of hepatic clearance ($CL_H$), renal clearance ($CL_R$) and volume of distribution (Vl). A schematic representation of the model is given in figure 1. A different proportional error was estimated for plasma and urine concentrations.

*Covariate Model*

*A/ Hepatic clearance of propylene glycol*

For hepatic clearance, birth weight was found as the most important covariate causing a drop in OFV of 81.5 points ($p<0.001$), when implemented using a power function. Subsequently, current bodyweight was identified as most important covariate on volume of distribution also using a power function, causing a drop in OFV of 50 points ($p<0.001$). Furthermore, the volume of distribution was estimated to be 1.71 times higher between neonates receiving phenobarbital compared to neonates receiving paracetamol, as was reported before [15]. This may possibly be explained by the fact that phenobarbital is often given to neonates after perinatal asphyxia which may cause differences in pharmacokinetic parameters like an increase in volume of distribution [15]. Finally postnatal age (PNA) was found as significant covariate on hepatic clearance. In this analysis, PNA was best implemented using a linear function, causing a drop in OFV of 20 points ($p<0.001$). After introducing these covariates, the observed plasma concentrations were well described by the model (figure 2, upper panels).

*B/ Renal clearance of propylene glycol*

When evaluating the amounts of propylene glycol in urine, a systematic trend in conditional weighted residuals *versus* time (figure 3) was seen, which could not be explained by bodyweight or PNA. To elucidate this time-dependent trend, which indicates that the excretion of propylene glycol in urine increases over time after first dose, five different models were tested as explained in the methods section.

As a first approach, a non-linear pharmacokinetic model was tested by implementation of an (intermediate) Michaelis-Menten model on renal clearance (Model I). Even though the time-dependent trend could indicate non-linear pharmacokinetic behavior of renal excretion of propylene glycol, this model did not result in an improved fit. As a second approach, urine volume (normalized to current bodyweight) was added as a covariate. This linear implementation of urine volume on renal clearance showed a significant improvement of the model illustrated by the decrease in objective function ($\Delta$OFV 26 points, $p<0.001$) and improvement of the diagnostic plots. In model III, both time after first dose and current bodyweight were implemented as covariates on renal clearance using power functions. Compared to model II, a higher drop in objective function was seen in model III ($\Delta$OFV 69 points, $p<0.001$), which was also reflected by visual improvement of the diagnostic plots. In model IV, implementation of the hyperbolic model based on time after first dose in

model IV, resulted in a drop in objective function of 67 points ($p<0.001$). In model V, no correlation was found between the amount of propylene glycol and creatinine in urine. Therefore implementation of creatinine did not result in an improved fit.

Based on the results, model III and model IV were identified as the best models to describe the time-dependent trend in the excretion of propylene glycol in urine. Although model IV had a slightly higher objective function compared to model III ($\Delta$ OFV = 2 points, $p>0.05$)), model IV was chosen as the best model since model IV was able to describe the data evenly well with one parameter less compared to model III. This hyperbolic function included an exponent and a parameter to describe the time after the first dose when 50% of the maximum renal clearance is reached, which were estimated to be 0.69 and 42.2 hours, respectively (table 2).

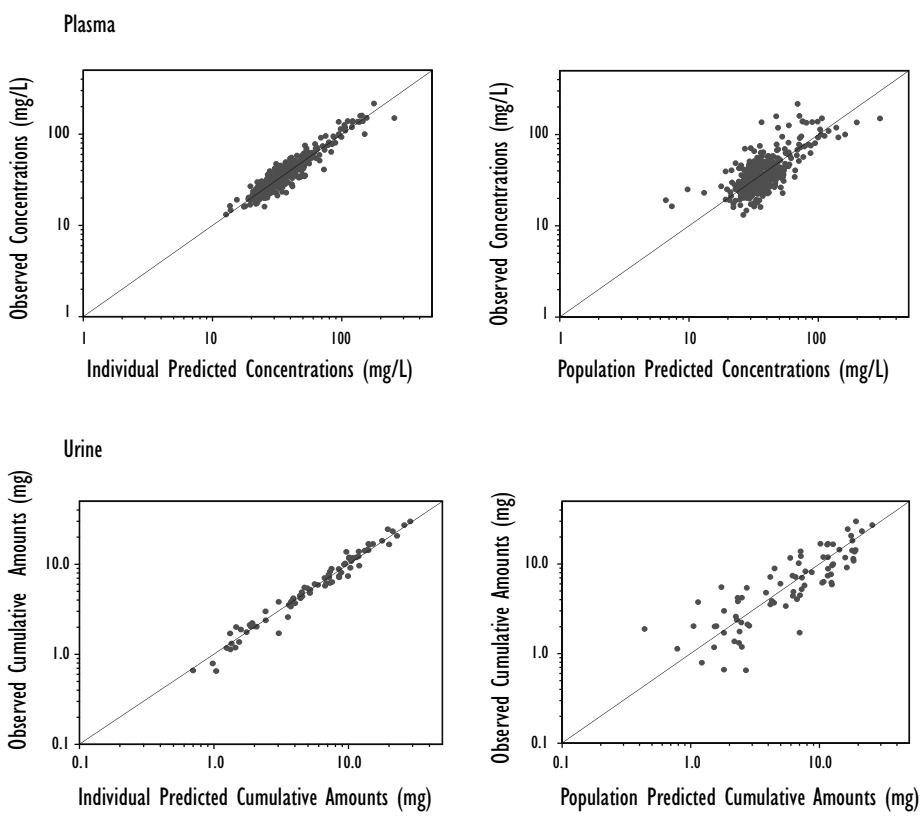



Figure 2: Observed *versus* individual predicted concentrations/amounts (left panels) and population predicted concentrations/amounts (right panels) of propylene glycol for plasma (upper panels) and urine (lower panels) observations for the final model.

Table II: Population pharmacokinetic parameter estimates of the simple model without covariates, the final pharmacokinetic model, the bootstrap analyis and n-1 jackknife analysis.

| Parameter | Simple model without covariates | Final pharmacokinetic model | Bootstrap final pharmacokinetic model | n-1 Jackknife final pharmacokinetic model |
|---|---|---|---|---|
| | Value (CV%) | Value (CV%) | Value (CV%) | Value (CV%) |
| Objective function | 2464 | 2230 | - | - |
| **Fixed effects** | | | | |
| $CL_H$ (L/h) = $CL_H$ p | 0.045 (15.0) | - | - | - |
| $CL_H$ p in CL = $CL_H$ p x (bBW/median)$^m$ x (1+(PNA/median)xn) | - | 0.056 (8.1) | 0.055 (9.4) | 0.056 (8.1) |
| m | - | 1.68 (10.5) | 1.69 (11.7) | 1.68 (10.5) |
| n | - | 0.12 (41.9) | 0.13 (46.0) | 0.12 (41.9) |
| V (L) = Vp | 0.92 (9.6) | - | - | |
| Vp in V = Vp x (cBW/median)$^o$ x p | - | 1.01 (6.5) | 1.01 (6.5) | 1.01 (6.5) |
| o | - | 1.46 (10.2) | 1.46 (10.6) | 1.46 (10.1) |
| p | - | 1.71 (11.8) | 1.71 (13.0) | 1.71 (11.8) |
| $CL_R$ (L/h) = $CL_R$ p | 0.0098 (11.8) | - | - | - |
| $CL_R$ = CLmax x ((time)$^q$/ ((time50)$^q$ +(time)$^q$)) | - | - | - | - |
| CLmax | | 0.45/0.55 x $CL_H$ | 0.45/0.55 x $CL_H$ | 0.45/0.55 x $CL_H$ |
| Time50 | - | 42.2 (49.8) | 51.4 (75.7) | 42.1 (50.9) |
| q | - | 0.69 (17.3) | 0.71 (21.7) | 0.66 (17.7) |
| **Interindividual variability ($\omega^2$)** | | | | |
| $\omega^2$ CL | 1.01 (25.9) | 0.16 (31.4) | 0.15 (36.3) | 0.16 (31.5) |
| $\omega^2$ V | 0.61 (23.4) | 0.17 (24.2) | 0.16 (24.9) | 0.17 (24.3) |
| $\omega^2$ CLU | 0.35 (32) | 0.33 (32.5) | 0.31 (37.6) | 0.34 (33.1) |
| **Residual variability ($\sigma^2$)** | | | | |
| $\sigma^2$ plasma (proportional) | 0.037 (12.1) | 0.034 (12.5) | 0.034 (12.8) | 0.034 (12.6) |
| $\sigma^2$ urine (proportional) | 0.069 (25.5) | 0.032 (33.0) | 0.031 (36.6) | 0.032 (33.3) |

$CL_H$= hepatic clearance, $CL_H$ p = population value for hepatic clearance, V = Volume of distribution, Vp = population value for volume of distribution, $CL_R$ = renal clearance, $CL_R$ p = population value for renal clearance, CLmax = maximum renal clearance = 0.45/0.55 x CL, bBW = bodyweight at birth, cBW = current bodyweight, PNA = postnatal age, time = time in hours after administration of the first dose of propylene glycol, time50 = time at which 50% of the maximum clearance is reached.

The parameter estimates of the final pharmacokinetic model are summarized in table 2. Figure 2 depicts (a) the observed *versus* the individual predicted concentrations/amounts and (b) the observed *versus* the population predicted concentrations/amounts for plasma and urine observations. In figure 3, the conditional weighted residuals *versus* time for the urine samples are illustrated for the simple without covariates and the final model. By introducing these covariates, 69% of the interindividual variability in hepatic clearance, 53% in volume of distribution and 3% in renal clearance was explained (table 2). In figure 4, the population estimates of renal and hepatic clearance *versus* birth weight for a postnatal age of 1 and 28 days are illustrated. Renal excretion of propylene glycol in neonates proved 15, 20, 23 and 25% of total clearance at 6, 12, 18 and 24 hours after the administration of the first dose respectively. At 30, 36, 42 and 48 hours after administration of the first dose, these percentages would be 27, 28, 29 and 30%, respectively. In figure 5, total clearance, hepatic clearance and renal clearance of propylene glycol is presented in four different neonates (birth weight 630g, 1500g, 2500g and 3500g) at a postnatal age of 1 and 28 days.

### 8.3.3. Model Validation

The results of the bootstrap analysis (N=1000) showed that the median estimated values based on re-sampled data were within 9% of the estimated values of the final pharmacokinetic model except for the estimated value of time at which 50% of the maximum renal clearance is reached, which was within 18%. All CV percentages were below 50%, except for the estimated value of time at which 50% of the maximum renal clearance was reached for which the CV percentage amounted 75%. As this may be explained by the small number of individuals in which urine data

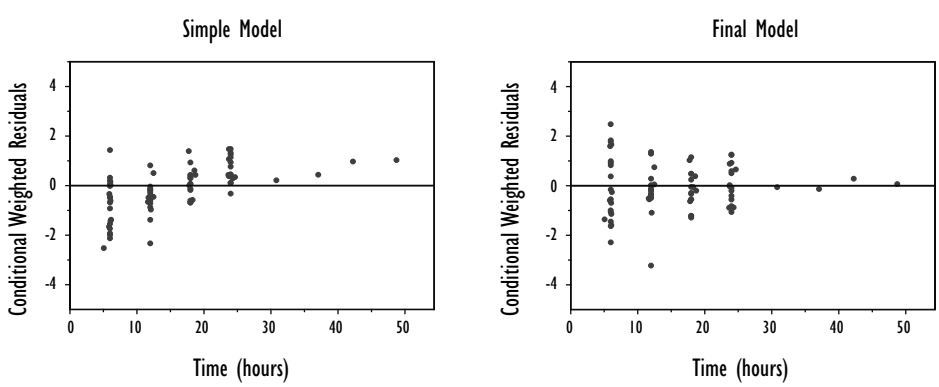



Figure 3: Conditional weighted residuals *versus* time for amounts of propylene glycol in urine for the simple (left panel) and the final (right panel) model.

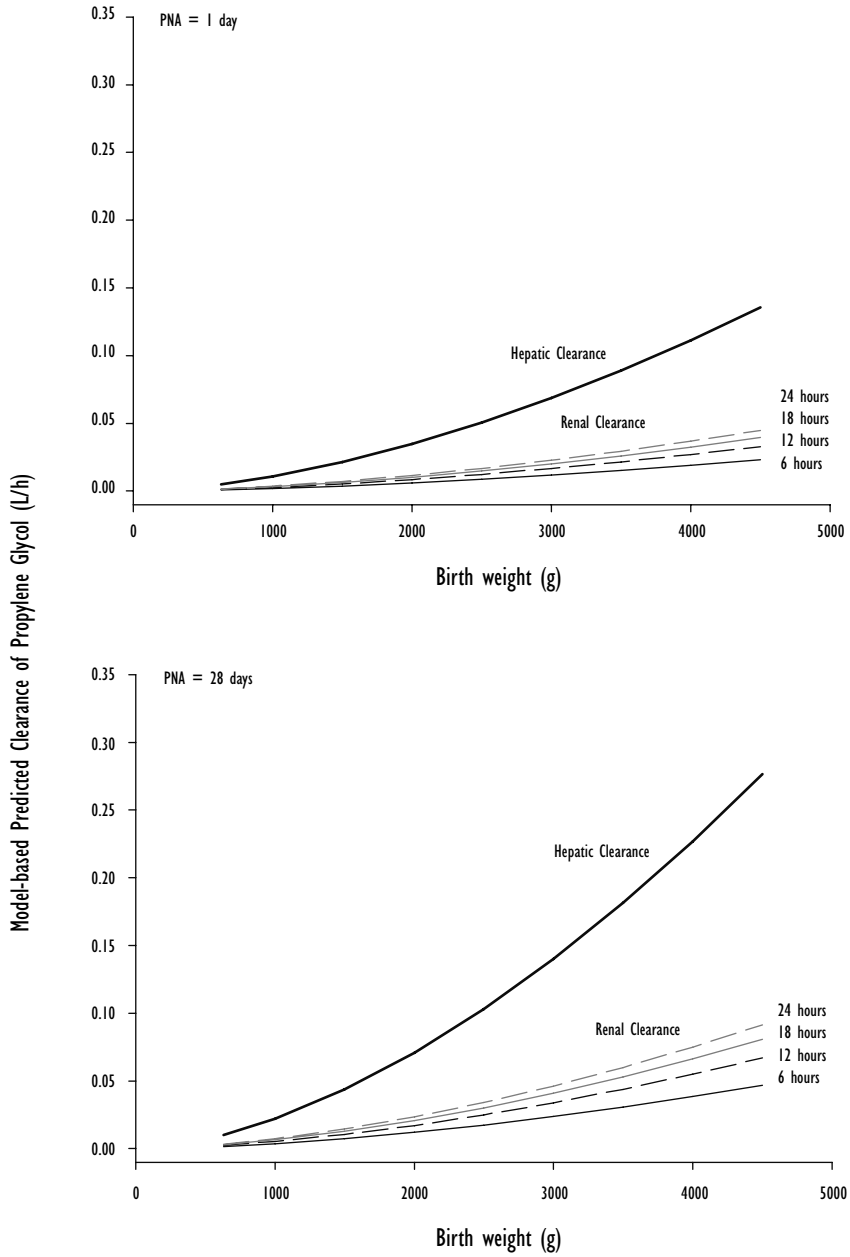



Figure 4: Model-based predicted hepatic (black line) and renal (grey lines) clearance of propylene glycol *versus* birth weight for typical neonates with a post-natal age of 1 day (upper panel) and of 28 days (lower panel). The different grey lines for renal clearance show how renal clearance changes with time after first dose of propylene glycol.

were available, a n-1 jackknife was performed, in which parameter estimates are recomputed leaving out the urine data of 1 patient at a time. In a total of 23 datasets, the values for the parameter estimates obtained were within 3% of the estimates of the final pharmacokinetic model. The CV percentage of the estimated value of time at which 50% of the maximum clearance was reached was 50.9% while the other CV percentages of the estimated parameters were all below 50%.

The results of the normalized prediction distribution error (NPDE) method analysis for the plasma and urine concentrations showed that the model can predict the median concentrations in plasma and urine since the histograms follow the normal distribution. Furthermore no trend was seen in the NPDE *versus* time and NPDE *versus* predicted concentrations (figure 6).

On the basis of the condition number of 32.9, it was concluded that the model was not over-parameterized. The percentage of $\eta$-shrinkage was identified to be 21% on hepatic clearance, 9% on volume of distribution and 37% on renal clearance. The plots illustrating the most predicted covariate, birth weight, current bodyweight and time after first dose *versus* the individual and population predicted parameter estimates for hepatic clearance, volume of distribution and renal clearance, respectively, showed that the individual parameter estimates were randomly scattered around the population parameter estimates (Supplement figure 1).

## 8.4. Discussion

Although propylene glycol is often used as an excipient in drug formulations and is regarded to be safe, toxic effects (e.g. bradycardia, lactic acidosis, convulsions) have been reported in the adult and pediatric age range upon administration of propylene glycol. In adults it is known that about 45% of propylene glycol is eliminated through the renal function and 55% of the administered dose of propylene glycol is metabolized in the liver to lactate and pyruvate [8, 12, 13]. Due to immaturity of the renal function, renal clearance of propylene glycol may be expected to be lower in neonates compared to adults. Therefore the aim of this study was to characterize the contribution of renal clearance *versus* hepatic clearance of propylene glycol in neonates based on excreted amounts of PG in urine.

Based on the final pharmacokinetic model, renal elimination of propylene glycol in neonates was low compared to hepatic elimination and increased over time after first dose of PG. The latter was best described using a hyperbolic function based on time

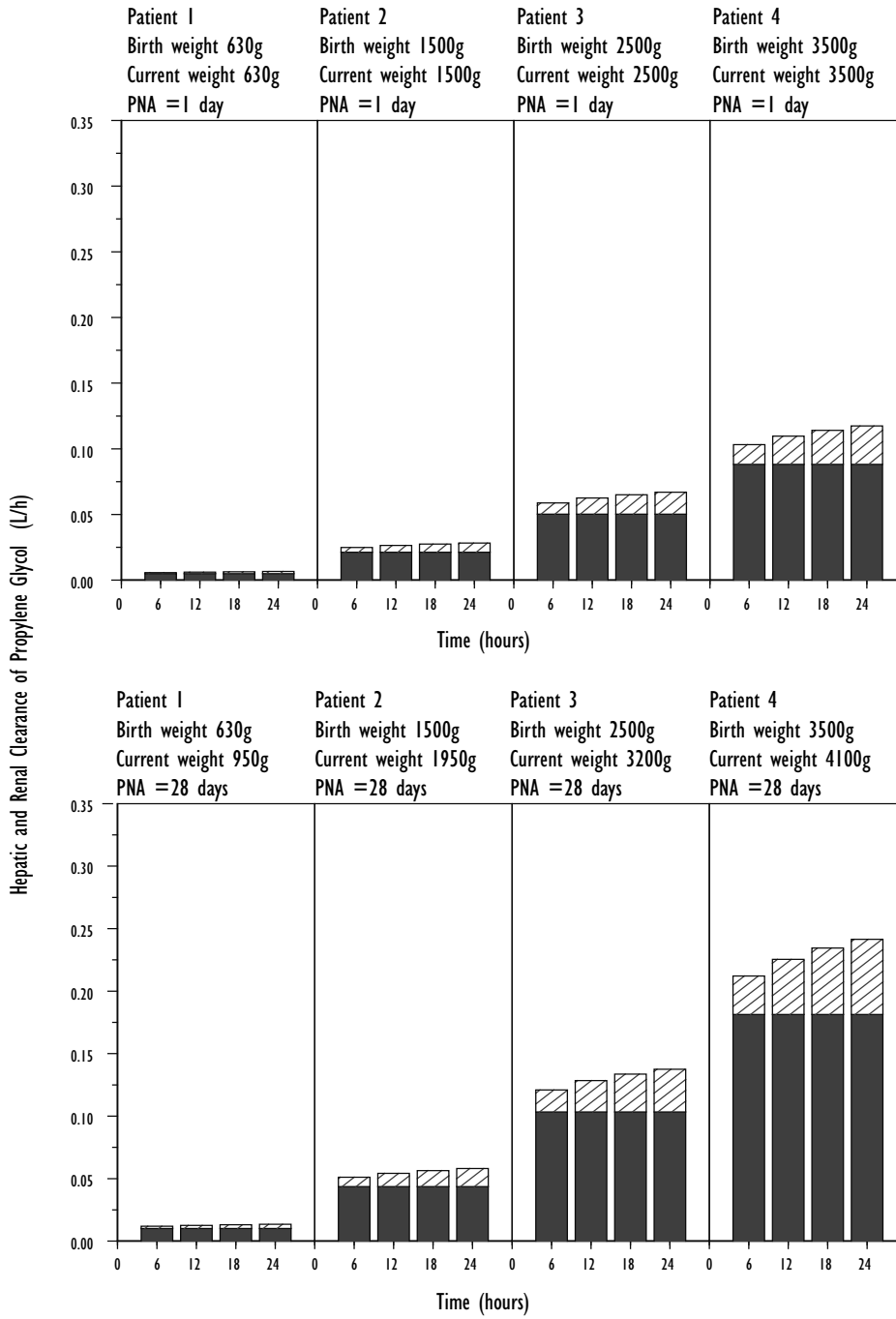



Figure 5: Hepatic (grey) and renal (striped) clearance of propylene glycol for four typical neonates with birth weight 630g, 1500g, 2500g and 3500g and a postnatal age of 1 day (upper panels) and of 28 days (lower panels).

after first dose. Based on this hyperbolic model, renal elimination of propylene glycol was estimated to be 15, 20, 23 and 25% of total clearance at 6, 12, 18 and 24 hours after the administration of the first dose respectively (figure 4 and 5). At 48 hours after the first dose, this percentage of renal elimination of propylene glycol increased even further to 30%. Despite this increase over time after dose, renal elimination of propylene glycol in neonates still remains substantially lower compared to adults, for which renal clearance of propylene glycol was reported to be 45%. The consequence of this finding is that maturational changes in the ratio between renal and metabolic clearance may influence the magnitude of drug-drug interactions. As in neonates hepatic clearance of propylene glycol proves the most important elimination route, drug-drug interactions for the alcohol dehydrogenase enzyme will become more important in neonates compared to adults. In this perspective, the advice of the FDA to avoid Kaletra®, a propylene glycol containing solution, in premature babies until 14 days after their due data or in full-term neonates younger than 14 days of postnatal age is of relevance. Kaletra® is a solution, which contains a combination of lopinavir and ritonavir solved in ethanol (356.3 mg ethanol/mL Kaletra®) and propylene glycol (152.7 mg/mL Kaletra®). Adverse events as heart, kidney and breathing problems were reported in premature neonates, which were likely due to a decreased ability to eliminate either ethanol or propylene glycol or both [23, 24]. Since both alcohols are metabolized by ADH in the liver, the high concentration of ethanol may possibly interfere with the metabolism of propylene glycol since ethanol has the highest affinity for ADH. While in adults this probably will be compensated by the renal route, in neonates this route is still immature which may result in accumulation of propylene glycol. As such, the results of this study may indicate that due to maturational changes, some drug interactions are of more relevance for specific age categories.

In the current analysis, it was found that the elimination of propylene glycol increased with time after first dose, independently of bodyweight or postnatal age of the neonate. To describe this increase in renal elimination of propylene glycol different models were tested: I) Model describing non-linear pharmacokinetics using an (intermediate) Michaelis-Menten model, II) Model with urine volume normalized to current bodyweight implemented as covariate on renal clearance, III) Model with both time after first dose and current bodyweight, implemented as covariates on renal clearance, IV) Model using a hyperbolic model based on time after first dose, V) Model with amount of creatinine as covariate on renal clearance of propylene glycol. Implementation of urine volume in the second model (Model II) caused a significant decrease in objective function which can be explained by the fact that similar to excretion of PG, urine volume increased over time as well. This time dependent increase in urine volume may potentially be induced by the osmotic

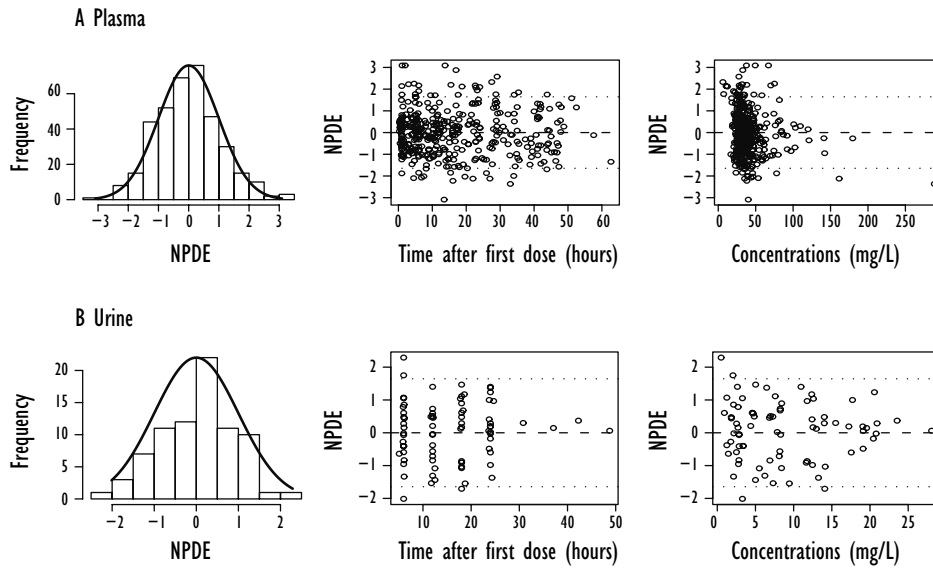
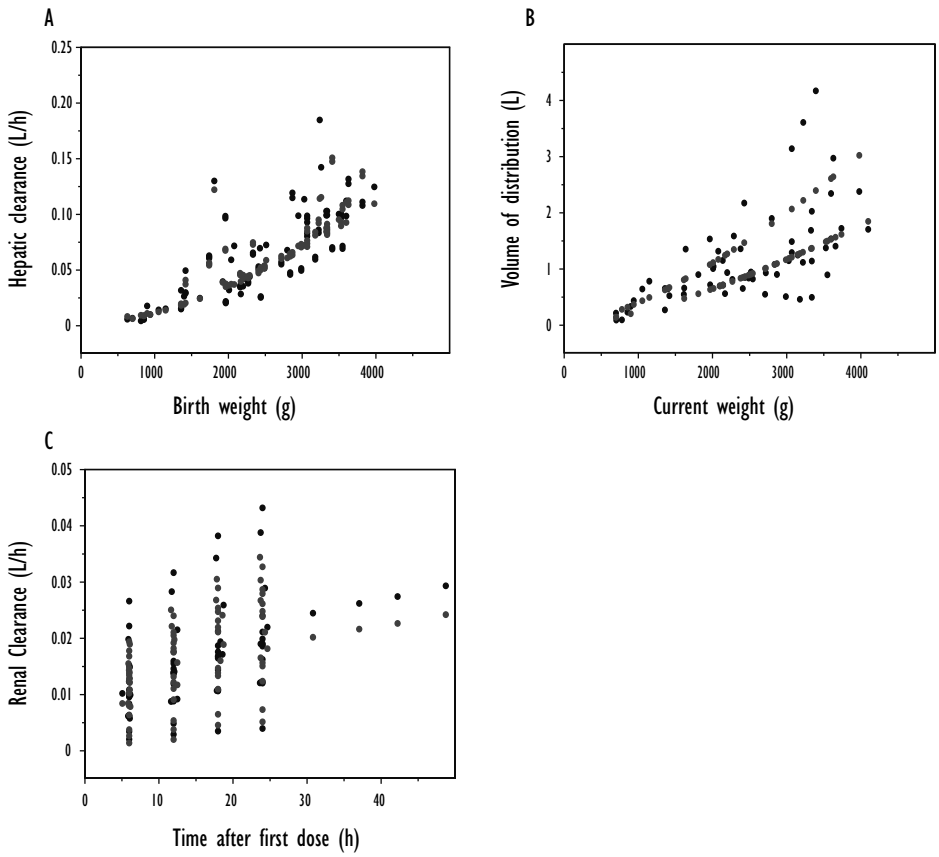



Figure 6: NPDE results for plasma and urine observations of the final model for propylene glycol. The histograms show the NPDE distribution for propylene glycol in plasma (upper panel) and urine (lower panel) with solid lines indicating a normal distribution. The distribution of the NPDE *versus* time after the first dose of propylene glycol and the NPDE *versus* the propylene glycol concentrations are also illustrated.

effects of propylene glycol leading to higher volumes of urine when more propylene glycol is excreted by the renal route. Subsequently, to evaluate whether this time dependent increase in renal elimination of propylene glycol is due to renal maturation or specifically caused by propylene glycol, the amount of creatinine was determined in urine (model V). No increase in renal elimination of creatinine was seen over time implicating that other factors are causing this trend. A potential explanation for these findings is an auto-induced increase in renal clearance of propylene glycol, including either glomerular filtration, active tubular secretion or both. Another explanation may be found in failure of the tubular reabsorption upon propylene glycol use, causing this time-dependent increase of propylene glycol in urine. Finally, the model using a hyperbolic function based on time after first dose (model IV) was identified as the best model. In this model, it was taken into account that the increase in renal clearance of propylene glycol will level of at a certain bodyweight or age as seen in adults for which renal clearance of propylene glycol is estimated to be around 45% compared to hepatic clearance which was estimated to be 55% [8, 12, 13]. As a result, in model IV renal elimination of propylene glycol was estimated as a fraction of hepatic elimination, which also indicates that besides the increase over time after the first dose, renal elimination of propylene glycol increases in a similar manner




Supplement figure 1: Individual predicted (black dot) and population predicted (grey dot) parameter estimates for hepatic clearance (a), volume of distribution (b) and renal clearance (c) *versus* the most predictive covariate birth weight, current weight and time after first dose.

as hepatic clearance with birth weight and postnatal age. The time at which 50% of the maximum renal clearance is reached, was estimated to be 42.2 hours. This value should however be considered with caution since it is based on limited data. To evaluate this time-dependent increase in renal elimination of propylene glycol, which has not been described before in any age group, further research is needed, particularly in preterm neonates who are exposed for several days to drugs containing high concentrations of propylene glycol (e.g. lorazepam).

The hepatic clearance of propylene glycol in preterm and term neonates was best described using birth weight and postnatal age as covariates. Birth weight,

representing antenatal maturation of hepatic clearance was implemented using a power function. Maturation after birth of hepatic clearance was quantified by postnatal age, implemented using a linear function. The identification of these covariates confirmed the results of a previous analysis where only plasma data of propylene glycol were available [15]. The influence of both covariates on hepatic clearance is illustrated in figure 4 and figure 5. Both figures illustrate clearly how hepatic clearance of propylene glycol is increasing with birth weight and postnatal age and indicate that caution is needed when propylene glycol is administered to preterm neonates at the first days of life. The sum of hepatic and renal clearance of propylene glycol as illustrated in figure 5 correspond well with the total clearance of propylene glycol previously found in preterm and term neonates using plasma samples [15].

Finally, the amount of propylene glycol given in this study following the administration of paracetamol or phenobarbital varied between 16 and 70 mg/kg/day. Although for some of the patients the daily dose of propylene glycol was higher than the maximum daily dose suggested by the FDA (25 mg/kg/day), it was much lower than the maximum daily intake proposed by the EMA. These guidelines should however be considered with caution since the guideline proposed by the FDA is based on the administration of propylene glycol as a food additive and it has not been revised since 1974. Moreover both guidelines are to our knowledge not based on observational data.

## 8.5. Conclusion

Based on the current analysis of propylene glycol data in plasma and urine in preterm and term neonates, renal and hepatic elimination rates of propylene glycol were determined. Hepatic elimination of propylene glycol proved to be the most important elimination route in (pre)term neonates. Renal elimination of propylene glycol increased over time after first dose and proved to be 15, 20, 23 and 25% of the total clearance at 6, 12, 18 and 24 hours after administration of the first dose, respectively. To evaluate whether this increase indicates an auto-induced increase in renal secretion or failure of tubular reabsorption of propylene glycol, further studies are needed.

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