Dosing considerations for preterm neonates: from pharmacometrics to clinical practice

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Citation

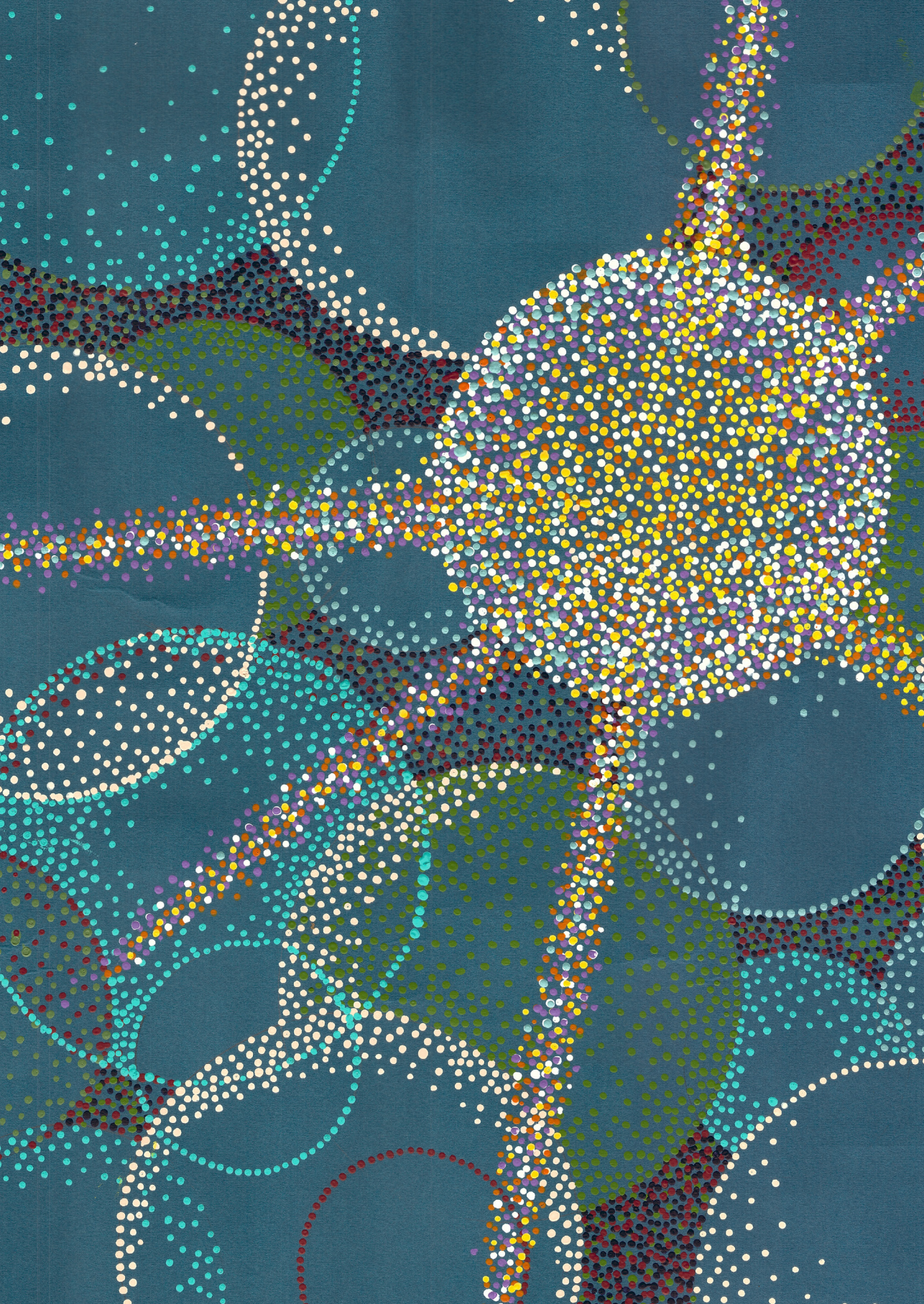Engbers, A. G. J. (2023, December 19). *Dosing considerations for preterm neonates: from pharmacometrics to clinical practice*. Retrieved from https://hdl.handle.net/1887/3674074

SECTION II.

Caffeine and doxapram for the treatment of apnea of prematurity

The pharmacokinetics of caffeine in preterm newborns: no influence of doxapram but important maturation with age

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ABSTRACT

Background

Apnea of prematurity can persist despite caffeine therapy in preterm infants. Doxapram may additionally support breathing. Although multiple small studies have reported the efficacy of doxapram, the structural co-treatment with caffeine impedes to ascribe the efficacy to doxapram itself or to a pharmacokinetic interaction where doxapram increases the exposure to caffeine. We examined whether there is a pharmacokinetic drug-drug interaction between doxapram and caffeine by developing a pharmacokinetic model for caffeine including infants with and without doxapram treatment.

Methods

In preterm neonates receiving caffeine, we determined caffeine plasma concentrations before, during and directly after doxapram co-treatment and used these to develop a population pharmacokinetic model in NONMEM 7.3. Patient characteristics and concomitant doxapram administration were tested as covariates.

Results

166 plasma samples were collected from 39 preterm neonates receiving caffeine (median gestational age 25.6 (range 24.0-28.0) weeks) of which 65 samples were taken during co-treatment with doxapram (39%, from 32/39 infants). Clearance of caffeine was 9.99 mL/h for a typical preterm neonate with a birth weight of 0.8 kg and 23 days postnatal age and increased with birth weight and postnatal age, resulting in a 4-fold increase in clearance during the first month of life. No pharmacokinetic interaction between caffeine and doxapram was identified.

Discussion

Caffeine clearance is not affected by concomitant doxapram therapy, but shows a rapid maturation with postnatal age. As current guidelines do not adjust the caffeine dose with postnatal age, decreased exposure to caffeine might partly explain the need for doxapram therapy after the first week of life.

INTRODUCTION

Neurological and respiratory immaturity in preterm infants is thought to contribute to apnea of prematurity. Apnea related hypoxic episodes are harmful to the infant's neurodevelopment.[1] Caffeine is standard of care to support breathing after preterm birth, due to its beneficial effect on short and long term outcome.[2,3] Caffeine reduces the number of apneic events and the duration of mechanical ventilation.[2,4]

If apnea persists despite optimal non-invasive ventilatory support and caffeine treatment, co-administration of doxapram may be considered. This off-label respiratory stimulant has been associated with a reduced rate of hypoxic events and duration of mechanical ventilation as well as less bronchopulmonary dysplasia.[5–8] A reduction in oxygen requirements has also been shown, but is limited by the small number of studies.[7–10] Ten Hove et al. suggested that doxapram is associated with an improved neurodevelopmental outcome at the age of 2 years.[11]

The limited evidence on doxapram efficacy, together with the structural co-treatment with caffeine, calls for an investigation whether the observed effects upon start of doxapram treatment can be attributed to doxapram itself. In the past, when therapeutic drug monitoring caffeine was still part of routine care, occasionally very high caffeine concentrations were observed when doxapram therapy was co-administered (unpublished data). Before doxapram can become a structural part of the apnea of prematurity treatment plan it is essential to exclude the existence of a pharmacokinetic (PK) interaction between caffeine and doxapram. Therefore, the current study aimed to investigate if doxapram co-treatment affects caffeine pharmacokinetics in preterm infants as a result of a PK interaction. To this end, a population PK modelling approach was applied, as this approach allows for the analysis of clinically obtained (sparse) data and can provide knowledge on the PK of a drug in clinical practice.[12,13] For our research question, caffeine concentration data from individuals before, during or after co-treatment with doxapram together with data from individuals that received caffeine treatment only, that were all obtained during opportunistic sampling as part of the Drug dosage Improvement in NeOnates (DINO) study, were analyzed together. The results were used to develop a population PK model for caffeine in preterm infants to examine the existence of a one-way drug-drug interaction between doxapram use and caffeine pharmacokinetics. Additionally, the population PK model was used to evaluate the exposure to caffeine upon the use of different dosing strategies.

METHODS

Patients and treatment

Patients were admitted at the neonatal intensive care unit of Erasmus Medical Centre and were enrolled in the DINO study, in which preterm neonates born before 32 weeks of gestation were included. The local ethics committee approved the protocol and written informed consent from parents/legal guardians was obtained (MEC-2014-067, NCT02421068). Patients were treated with caffeine (as base, 10 mg/ml, Pharmacy A15, Gorinchem, the Netherlands) starting with a loading dose of 10 mg/kg, followed by one daily maintenance dose of 5 mg/kg. Additional caffeine doses were allowed and the maintenance dose could be increased up to 8 mg/kg. Doxapram administration (as hydrochloride, Dopram®, Eumedica, Manage, Belgium) was initiated if the attending physician judged that apnoea or bradycardia persisted despite caffeine therapy and non-invasive ventilatory support. A doxapram loading dose of 2.5 mg/kg was administered intravenously over 15 minutes at discretion of the attending physician, followed by a maintenance dose of 2.0 mg/kg/h via continuous intravenous infusion or gastro enteral administration. In case of clinical improvement, the doxapram dose could be decreased step-wise. Doxapram was stopped upon need for endotracheal intubation or upon disappearance of apnoea, regarded as treatment success. Both caffeine and doxapram were allowed to be switched to gastro enteral administration once enteral feeds were well tolerated.

Blood samples

Blood samples of 0.2 mL were collected in EDTA-tubes and withdrawn from an indwelling arterial catheter or with routinely scheduled samples for clinical purposes. Samples were collected during caffeine and caffeine plus doxapram treatment period. Opportunistic sampling did not exceed 1% of the total blood volume per day, and 3% of the total blood volume per 4 weeks. Directly after collection samples were stored at 2-8°C. Within 24 hours the sample was centrifuged, and plasma was stored at -80°C until quantification.

Bioanalytical analysis

Caffeine plasma concentrations were measured using ultra-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UPLC-ESI-MS/MS) at the Pharmacy Department of the Erasmus Medical Centre, Rotterdam, the Netherlands. The assay was validated according to FDA guidelines, required 50 μL plasma volume and was linear over a caffeine concentration range of 0.75-50 mg/L (coefficient of variation (CV) intra-assay: 2.4%, CV inter-assay: 3.5%). The lower limit of the range represents the lower limits of quantification, and the limit of detection was 0.46 mg/L. Concentrations below the lower limit of quantification (0% of caffeine concentrations) and above the upper limit of quantification (4%) were reported by the laboratory and were used in the analysis.

Model development

A population PK model was developed in NONMEM V7.3 (ICON Development Solutions, Ellicott City, MD, USA). R version 3.5.1 was used in R-studio version 1.1.463 to build the dataset and visualize the data and model output.

Population PK model development was based on change in objective function value (dOFV), evaluation of goodness of fit (observed concentrations versus population and individual predicted concentrations, conditional weighted residuals (CWRES) vs population predicted concentration and time after last caffeine dose) plots, and numerical performance (relative standard error (RSE) below 30%). Due to limited plasma caffeine samples in the absorption phase during oral administration, we fixed the absorption rate to 4.0 h^{-1} and bioavailability to 100%.[14]

A covariate analysis was performed testing the available patient characteristics and doxapram use as potential covariates. Birth weight, current weight, postnatal age (PNA), gestational age (GA), gender, small for gestational age were plotted against inter-individual variability (IIV) of clearance and volume of distribution to select covariates to test on the structural model. The effect of doxapram therapy was tested on caffeine clearance as doxapram naivety (clearance before doxapram therapy versus clearance during and after doxapram administration) and as concomitant doxapram therapy (clearance before- versus during- versus after doxapram administration). To prevent missing an interaction as a result of a slower offset effect of doxapram on caffeine clearance, samples taken up to 24, 48 or 72 hours after stopping doxapram administration were included in the during-doxapram administration group in a sensitivity analysis. Covariates were included if dOFV was less than -6.6 (p<0.01). A backwards elimination procedure with a minimal dOFV of 10.8 (p<0.001) was initiated when inclusion of covariates did not further improve the model. The final model was validated by performing a bootstrap, a normalized prediction distribution error (NPDE) analysis and a prediction corrected visual predictive check, each based on 1000 simulations.

Dose evaluation

Based on the final model that was developed in this study, exposure to caffeine was illustrated for a median preterm infant with a GA of 26 weeks and a birthweight of 0.83 kg. Postnatal weight loss- and gain was based on predictions by https://www.growthcalculator.org/. According to clinical practice, during the first 14 days of life, the caffeine dose was based on birthweight, and above 14 days the absolute dose was based on current weight. Three different dosing regimens were evaluated, all starting with a loading dose of 10 mg/kg caffeine base. The maintenance dosages were either

2.5 mg/kg/day, 5 mg/kg/day or as proposed by Koch et al., i.e. 2.5 mg/kg/day during the first week, 3 mg/kg/day during the second week, 3.5 mg/kg/day during week 3 and 4, and 4 mg/kg/day from week 5 to 8.[15] Median caffeine concentrations were calculated from 1000 simulations.

RESULTS

Patients and samples

In 39 patients, 166 plasma caffeine samples were collected. Doxapram therapy was initiated in 32 patients during the study period. Sixty-three samples (38%) were taken before doxapram therapy was initiated, 65 (39%) during doxapram administration and 38 (23%) samples after stopping doxapram. Of the latter 38 samples, 10 samples were taken within 24 hours after stopping doxapram administration, 11 within 24-48 h and 2 (1%) within 48-72 h after stopping doxapram. Patient characteristics as well as dosing information are presented in Table 1. Observed caffeine plasma concentrations are presented in Figure 1.
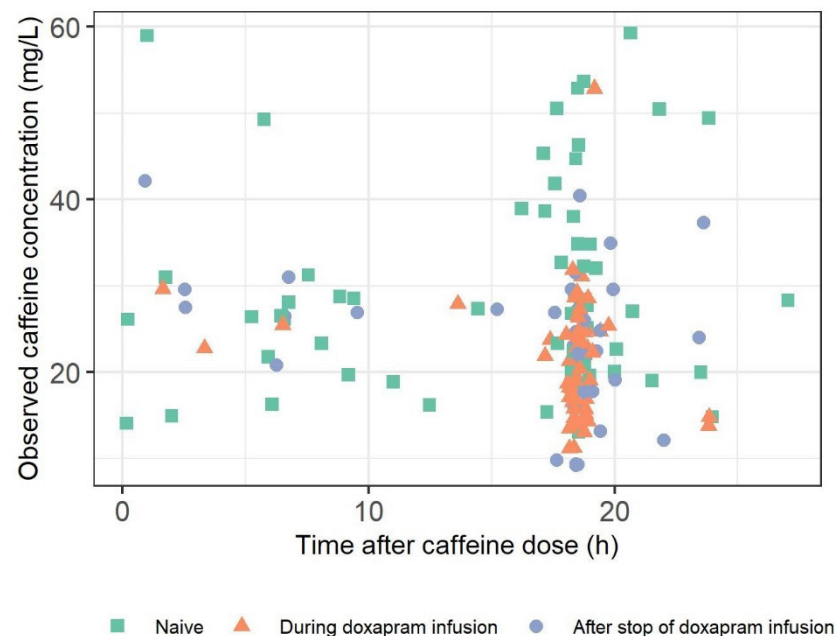

Figure 1. Observed caffeine plasma concentrations versus time after last dose.

Table 1. *Patient characteristics. Of time-changing characteristics the median numbers of individual median throughout the treatment period are presented.*

	Median (range)
Patient characteristics	
Number of patients (n)[%male]	39 [62%]
Birthweight (g)	800 (485 – 1290)
Gestational age (weeks)	25.6 (24.0 – 28.0)
Small for gestational age	9 (23%)
Postnatal age during caffeine treatment (days)*	23 (0 – 61)
Current bodyweight during caffeine treatment (g)*	990 (450 – 2160)
Patients receiving doxapram (n, %))	32 (82%)
Postnatal age at doxapram initiation (days)*	21 (5 – 40)
Postnatal age during doxapram treatment (days)*	32 (5 – 61)
Current bodyweight during doxapram treatment (g)*	1160 (700 – 2160)
Caffeine and Doxapram treatment and dosing	
Caffeine treatment duration (days)	38 (3 – 61)
Caffeine loading dose (mg/kg) [% I.V. doses]	10 (5 – 11) [100%]
Caffeine maintenance dose (mg/kg/24h) (median of median per patient)	5 (3-10)
Number of caffeine maintenance doses per patient during study [% I.V. doses]	35 (1 – 60) [41%]
Additional caffeine doses (mg/kg)	5 (3 -9)
Number of additional caffeine doses per patient (n) [% I.V. doses]	5 (1 – 52)[45%]
Doxapram	
Doxapram treatment duration (days)	14 (1 – 49)
Number of doxapram administrations per patient (n) [% I.V. doses]	7 (2 – 23) [46%]
Total doxapram dose per patient (mg/kg)	349 (25 – 1463)
Doxapram dose per patient per day (mg/kg/day)	22.8 (1.0 – 68.6)
First doxapram loading dose (mg/kg/15 minutes) [% I.V. doses]	2.4 (1.0 – 2.7) [81%]
First doxapram maintenance dose (mg/kg/h) [% I.V. doses]	2.0 (0.9 – 2.9) [71%]

Population Pharmacokinetic Model

A one-compartment model with a proportional residual error model described the data best. IIV was identified on clearance, but could not be identified on volume of distribution. Addition of a power-relationship between clearance and PNA to the base model resulted in a dOFV of -134.0 (p<0.001), and explained 8.3% of the IIV on clearance. Addition of a power-relationship between clearance and birth weight further decreased the OFV with 15.5 points (p<0.001) and explained another 5% of the IIV on clearance.

Comparison of doxapram naïve versus doxapram treated caffeine clearance suggested a 17% higher caffeine clearance in doxapram treated patients, but this effect did not meet the significance and precision criteria (dOFV -3.5 (p>0.05) and RSE 99%). In the sensitivity analysis, dOFV ranged from -4.7 when concomitant doxapram use was defined for samples taken during doxapram infusion, to -3.6 when samples taken up to 72h after stopping doxapram infusion were considered as concomitant doxapram

use as well (p>0.05). Based on these results doxapram therapy was not included as a covariate and did not significantly affect the clearance of caffeine.

As no other significant covariates were identified, backwards elimination analysis was performed in which both covariates, i.e. birth weight and PNA on clearance, remained significant (dOFV +15 and +145, respectively). Final model parameters and bootstrap estimates are presented in Table 2. The estimated maturation of clearance is visualized in Figure 2, and compared with previously reported maturation profiles in Figure 3. Goodness of fit plots of the final model are presented in Supplementary Figures 1 and 2, remaining IIV on CL is presented in Supplementary Figure 3, results of the NPDE analysis are presented in Supplementary Figure 4 and a pcVPC is presented in Supplementary Figure 5.

Figure 3. *Predicted maturation of caffeine clearance (lines) for preterm neonates with a birth weight of 0.5 (light orange), 0.875 (orange) or 1.25 kg (dark orange). Individual posthoc clearance estimates are presented as dots, with colour intensity increasing with birth weight.*

Table 2. *Parameter and bootstrap estimates of the final population PK model.*

	Final model estimate (RSE %) [shrinkage %]	Bootstrap estimate (95% CI)
$CL_{ind} = CL_{pop} * (PNA_{ind}/23\ days)^{\Theta PNA} * (WT_{B,ind}/0.8\ kg)^{\Theta WTB}$		
CL_{pop} (mL/h)	9.99 (4)	9.93 (9.20– 10.7)
ΘPNA	0.505 (16)	0.519 (0.401 – 0.815)
ΘWTB	0.707 (20)	0.732 (0.438 – 1.049)
$V_{ind} = V_{pop}$		
V_{pop} (mL)	513 (16)	528 (414 – 896)
Interindividual variability		
IIV on clearance (%)	20.5 (11)[11]	19.6 (14.9 – 23.9)
Residual unexplained variability		
Proportional error	0.0462 (20)[9]	0.0435 (0.0246 – 0.0628)

CL_{ind}: individual caffeine clearance in mL/h ,CL_{pop}: population caffeine clearance in mL/h for a typical individual with a postnatal age of 23 days and a birthweight of 0.8 kg, PNA_{ind}: individual postnatal age in days, $WT_{B,ind}$: individual birth weight in kg, V_{ind}: individual volume of distribution in mL, V_{pop}: population volume of distribution in mL for a typical individual with a postnatal age of 23 days and a birthweight of 0.8 kg, IIV: interindividual variability.

Dose evaluation

In Figure 4 the exposure to caffeine following different dosing strategies is presented. A constant maintenance dose of either 2.5 or 5 mg/kg/day results in relatively high trough concentrations during the first week of life (maximal concentration of 17.6 and 28.3 mg/L, respectively). During the second and third week the trough concentrations decrease until a minimum is reached during the fourth week (8.2 and 16.4 mg/L, respectively), from where they remain stable. The maintenance dose adjustments to PNA, as suggested by Koch et al.[15], prevent the large differences between trough concentrations throughout the treatment period, but still lead to a decrease in trough concentrations after the first week of life (from 17.6 in week 1 to 11.5 mg/L in week 4).
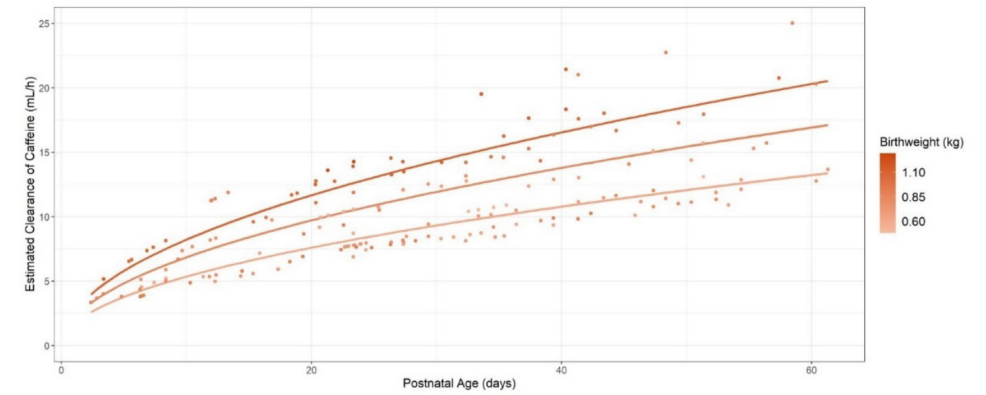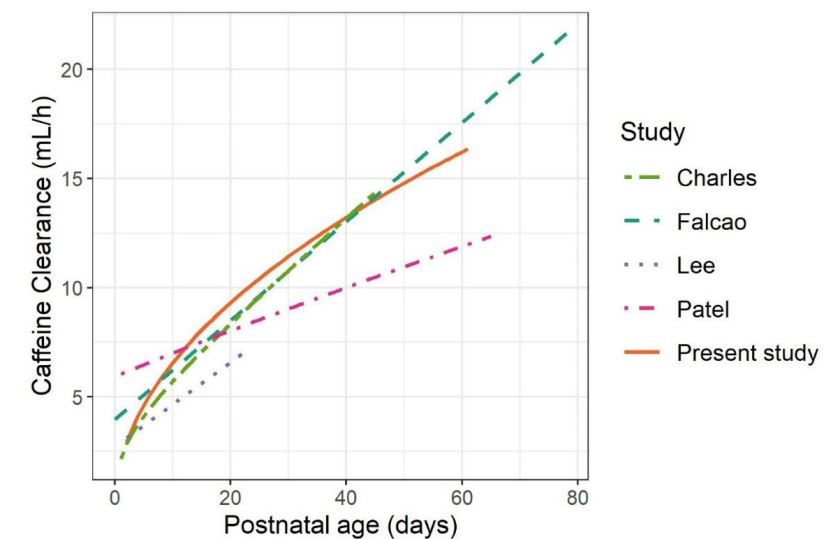

Figure 4. *Caffeine clearance as described in literature (14,23–25) (dashed lines). For the present study, population clearance versus postnatal age is given for the median birthweight of 0.8 kg. For other studies weight was predicted by a linear regression model based on observed weights in the study population. For each study, the predicted maturation is presented only for the range in postnatal age.*
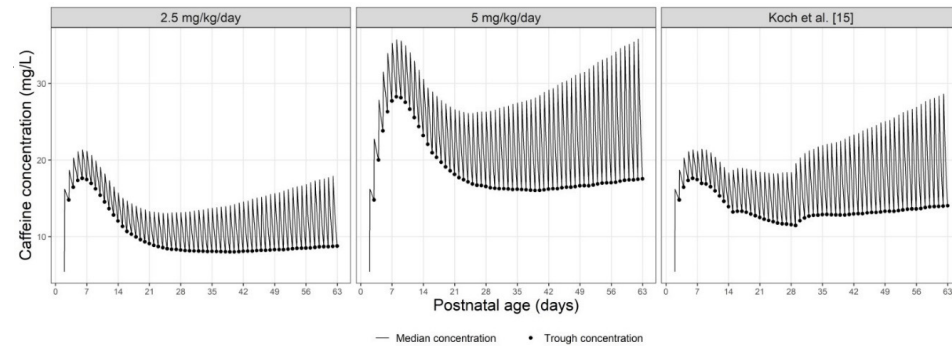
Figure 5. *Simulated caffeine concentrations in a median preterm infant with a gestational age of 26 weeks and birthweight of 0.83 kg. In all three scenarios a loading dose of 10 mg/kg was given. For the left scenario a maintenance dose of 2.5 mg/kg/day was given, while for the middle scenario the maintenance dose was 5 mg/kg/day. For the right scenario, based on Koch et al.[15] the maintenance was 2.5 mg/kg/ day during the first week, 3 mg/kg/day during the second week, 3.5 mg/kg/day during the third and fourth week and 4 mg/kg/day from the fifth week and up. Solid lines represent the median concentration and dots represent a trough concentration, both based on 1000 simulations.*

DISCUSSION

We studied the PK of caffeine in preterm newborns before, during and after doxapram therapy, to investigate whether there is an interaction between doxapram and caffeine PK. In the current study, such a PK interaction was not identified.

For our study we had access to data representative of the clinical setting that was collected without causing any burden to the patient. The population PK approach used in this study allowed the identification of the PK of caffeine based on sparse data, and has proven its worth before for similar datasets of preterm infants.[16,17] Concomitant doxapram therapy was a covariate of special interest due to its structural co-treatment to caffeine. The covariate analysis did not identify doxapram treatment naivety or concomitant doxapram treatment as significant predictor of caffeine clearance. Even when the concomitant doxapram therapy definition was extended to 24, 48 or 72 hours after stopping doxapram the effect remained insignificant, which excludes the presence of a PK interaction between doxapram and caffeine. A drug-drug interaction can also be of a pharmacodynamic (PD) nature. A synergistic PD interaction between caffeine and doxapram is not expected because they act via different mechanisms, but based on our study this cannot be excluded. Recently, novel methods have been identified to quantify the amount of apnea using monitor data that might be useful for the investigation of a PD interaction between doxapram and caffeine.[18,19] Based on the present results we can conclude that the previously reported effects of doxapram on apnoea in preterm infants cannot be attributed to increased caffeine concentrations. [5–7]

In our analysis, we observed an important maturation of caffeine clearance with PNA. Next to the important effect of PNA we also found that clearance is predicted by birth weight which was independent of PNA, and for which a cut-off value of PNA for the effect of birthweight could not be identified. The PK of caffeine has been described previously, with clearance of caffeine predicted by PNA and current body weight [14,20–23]. In Figure 3 the reported increase in clearance with PNA is presented for the current and previous studies, which shows that the predicted effect of PNA on caffeine clearance is in line with previously reported maturation profiles. [14,20–23] Figure 4, left and middle panel, shows how exposure to caffeine changes throughout the treatment period when the 2.5 or 5.0 mg/kg maintenance dose is not adjusted for PNA. The decreasing trough concentrations after the first week of treatment are a result of the rapid increase in clearance. After the fourth week of treatment a slight increase in trough concentrations is observed, which is likely to be an effect of the rapid increase in body weight but a less rapid increase in clearance. In other words, bodyweight, and therefore absolute dose, increases more rapidly than clearance at higher PNAs. From these results, we can even speculate that the lower caffeine concentrations in our population might have contributed to the decision to start concomitant doxapram therapy that was initiated at a median PNA of 21 days in our population. A stepwise increase in absolute dose with increasing PNA, as suggested by Koch et al. (Figure 4, right panel), results in a smaller difference in trough concentrations after the first week of life. Therefore, clinicians should be aware that patients might require a higher caffeine dose in mg/kg after the first week of life.

The opportunistic sampling method allowed us to collect samples from a vulnerable population, with minimal burden for the patients. Because of this approach most samples were obtained from routine blood sampling for clinical purposes, which was mostly scheduled around 8:00 a.m. As patients were scheduled to receive their caffeine maintenance dose at 2:00 p.m., most samples were taken around 18 hours after the last caffeine dose (Figure 1). Although our developed caffeine PK model was suitable to detect a potential interaction with doxapram, the small variation in time after dose limits the complete characterization of caffeine PK in preterm infants, especially for volume of distribution. Even though the population PK approach we used resulted in a population PK model whose estimated parameters are well in line with previously reported studies, caution is requested upon interpretation of the peak plasma concentrations presented in Figure 4. [14,20–23].Because we could not identify an influence of weight on volume of distribution in our data, in figure 4 the peak plasma concentrations increase with an increase in dose, which may not be realistic and therefore this model is less suitable to evaluate potential toxicity. Since clearance was well identified in the model the predicted trough concentrations are likely to be reflective of reality.

In our analysis, doxapram therapy was tested as a categorical covariate yes/no. As doxapram metabolism is reported to increase with PNA and GA [24], neonates may have been exposed to varying concentrations of doxapram. If our results would have suggested the presence of an interaction between doxapram and caffeine, doxapram concentrations would have provided a more precise investigation. Since we did not observe any signs for the presence of this interaction upon the maximum described doxapram dose administered, we do not expect that this interaction will arise when doxapram concentrations are studied in the model.

CONCLUSION

Caffeine clearance is not affected by doxapram therapy, but it does show a rapid maturation with postnatal age. The potential therapeutic effect of doxapram can therefore not be attributed to increased caffeine concentrations. The decreased exposure to caffeine upon increasing PNA might party explain the need for doxapram therapy after the first week of life.

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SUPPLEMENTAL MATERIALS
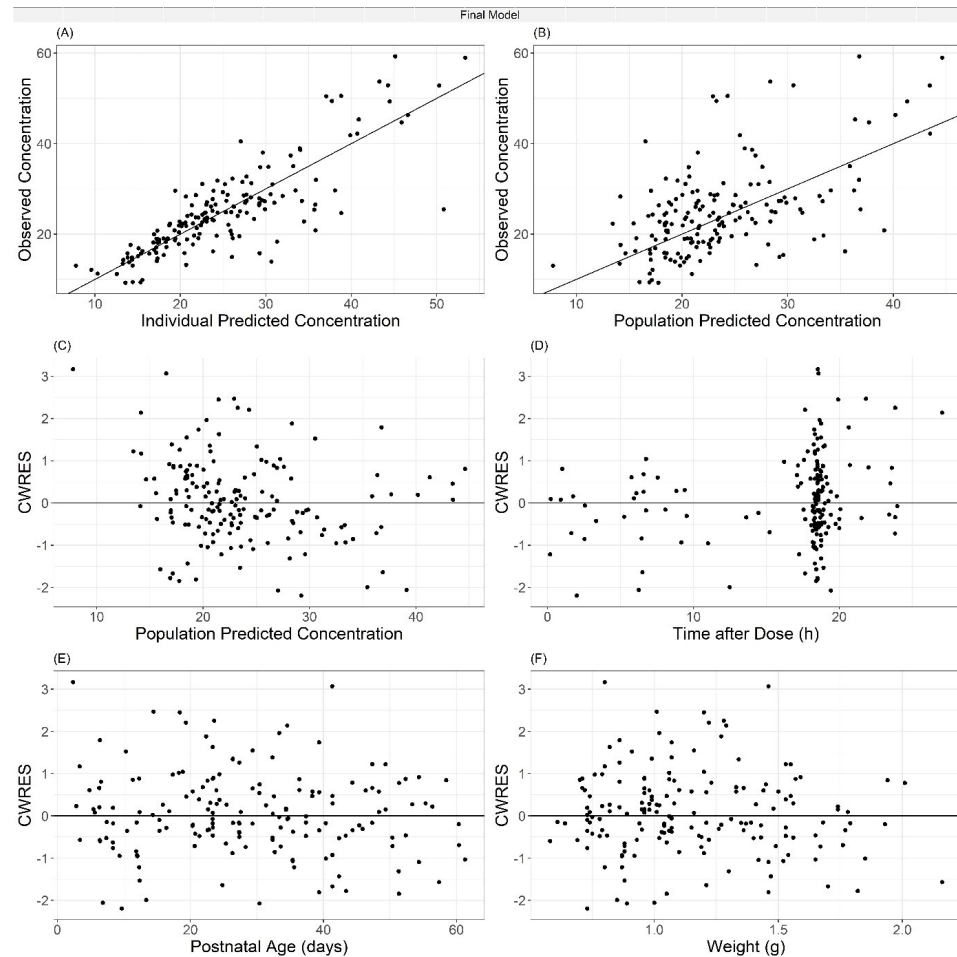
Supplementary Figure 1. *Goodness of fit plots of the final pharmacokinetic model. A:Observed concentration versus individual predicted concentrations, B: observed concentrations versus population predicted concentrations, C: conditional weighted residuals (CWRES) versus population predicted concentrations, D: CWRES versus time after last caffeine dose, E: CWRES versus postnatal age, F: CWRES versus current body weight.*
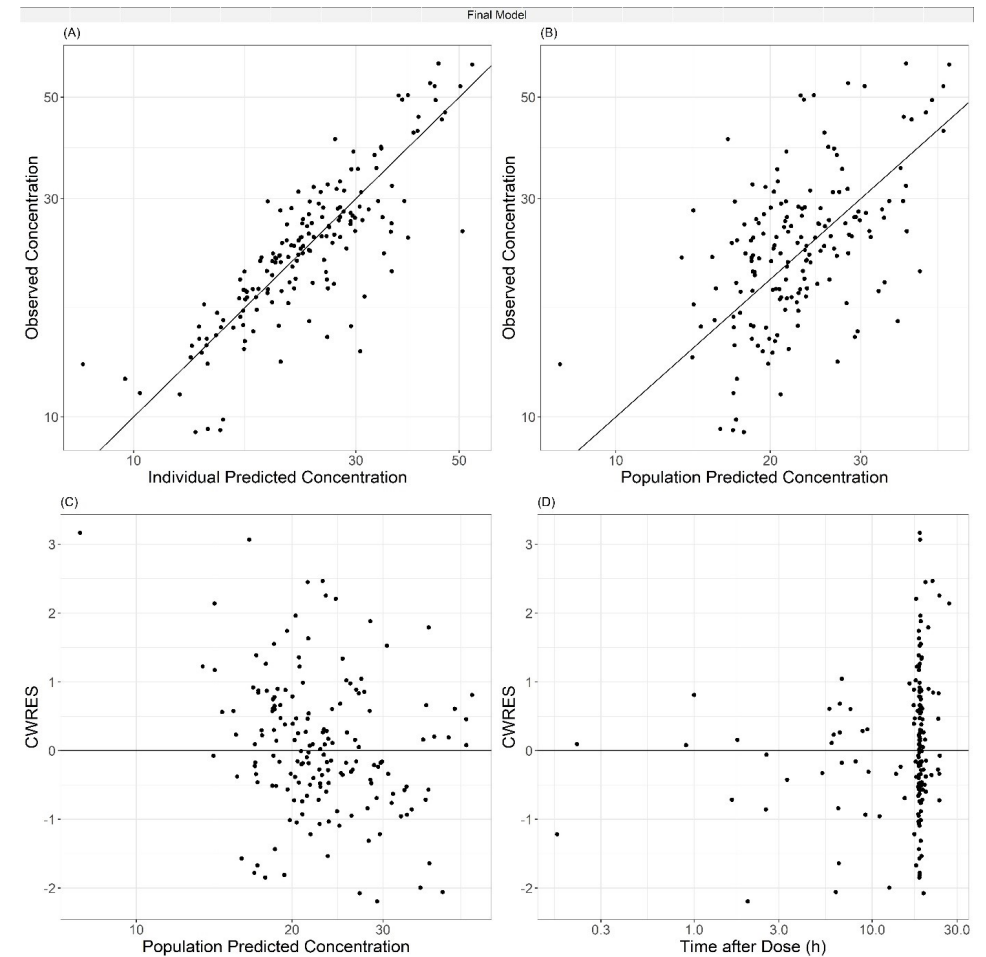

Supplementary Figure 2. *Goodness of fit plots of the final pharmacokinetic model on a log-scale. A:Observed concentration versus individual predicted concentrations, B: observed concentrations versus population predicted concentrations, C: conditional weighted residuals (CWRES) versus population predicted concentrations, D: CWRES versus time after last caffeine dose.*
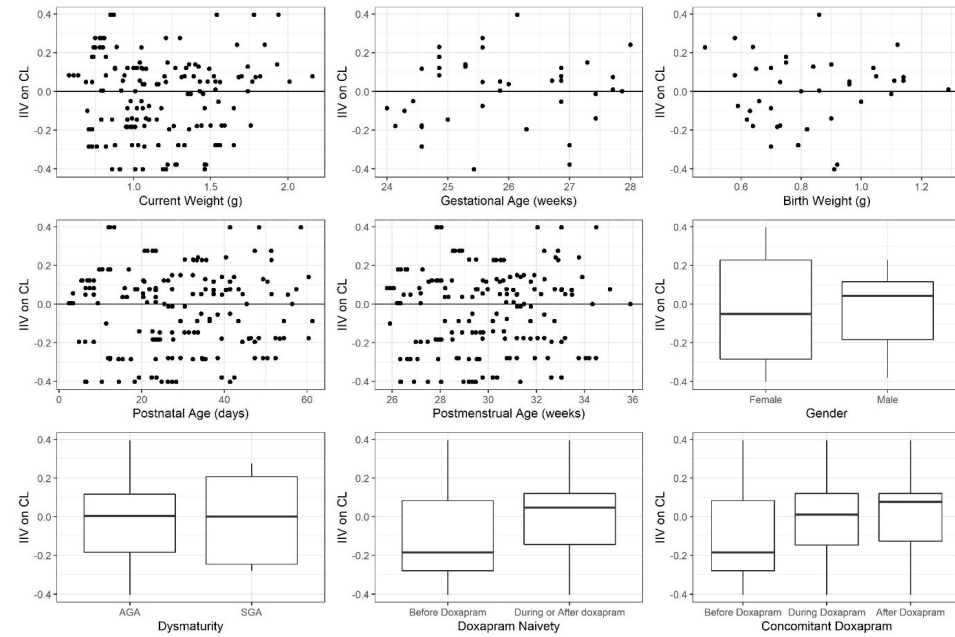
Supplementary Figure 3. *Interindividual variability plots versus available covariates of the final population pharmacokinetic model.*
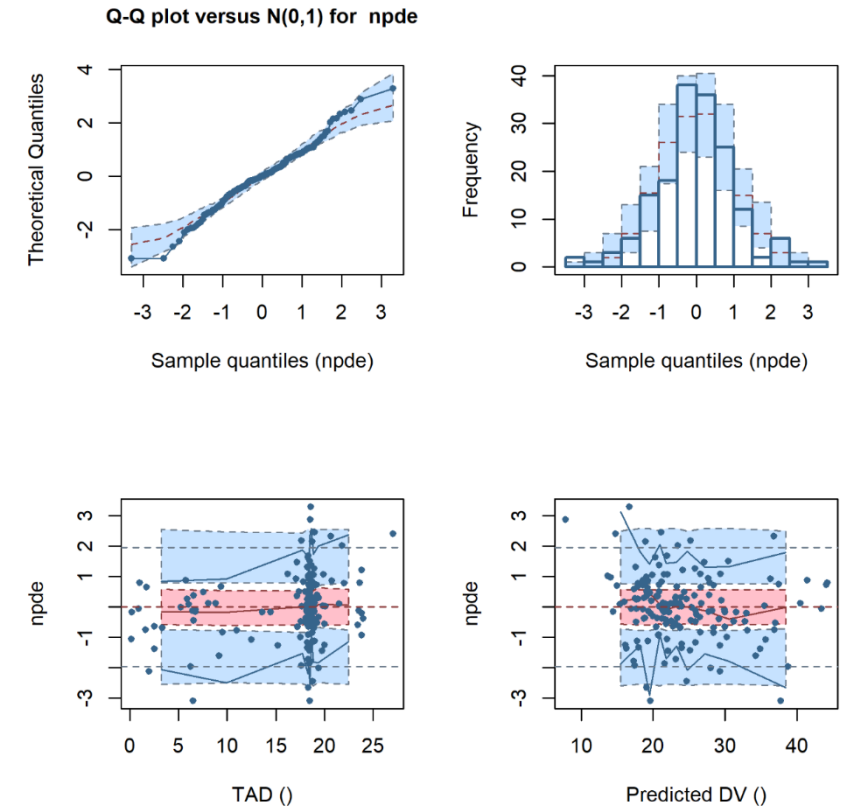
Supplementary Figure 4. *Results of the normalized prediction distribution errors (npde), based on 1000 simulations of the final population pharmacokinetic model. Top left: quantile-quantile plot, top right: npde quantiles with a normal distribution overlay, bottom left: npde versus time after dose in hours, bottom right: npde versus and predicted concentrations in mg/L.*
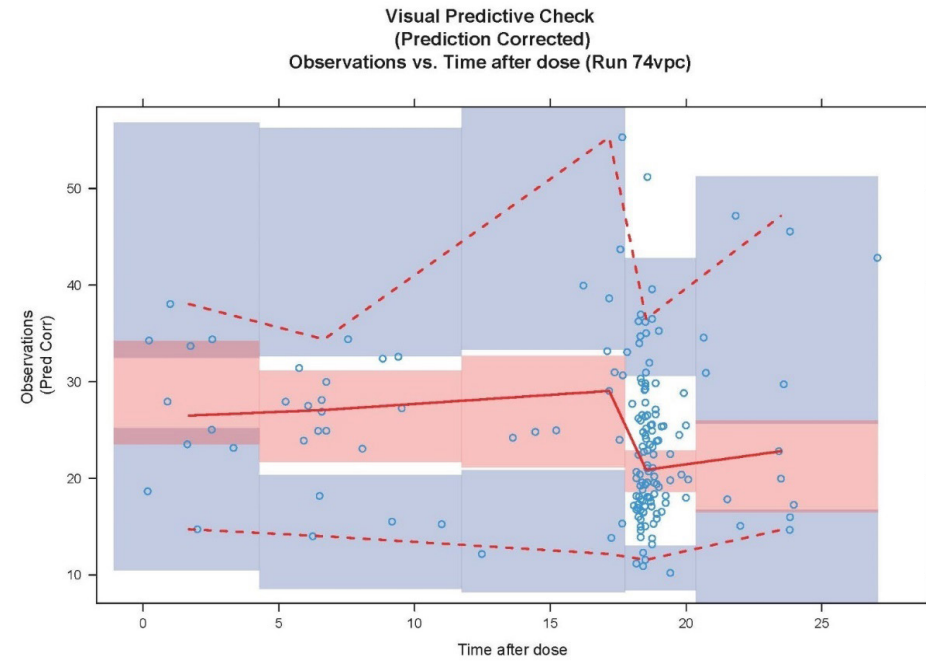
Supplementary Figure 5. *Prediction corrected visual predictive check of the final model, based on 1000 simulations.*