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PHARMACOKINETICS AND DISPOSITION

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Population pharmacokinetics of caffeine in premature neonates

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Abstract *Objective*: To determine population pharmacokinetic parameters of caffeine in premature neonates. *Methods*: This population analysis was done using 145 serum concentration measurements gathered from 75 hospitalized patients during their routine clinical care. The data were analysed by use of NONMEM (mixed effects modelling) according to a one-compartment open model with either zero or first-order absorption and first-order elimination. The effect of a variety of developmental, demographic and clinical factors (gender, birth weight, current weight, gestational age, postnatal age, postconceptional age and concurrent treatment with phenobarbital and parenteral nutrition) on clearance and volume of distribution was investigated. Forward selection and backward elimination regression identified significant covariates.
Results: The final pharmacostatistical model with influential covariates were as follows: clearance ($ml \cdot h^{-1}$) = 5.81 · current weight (kg) + 1.22 · postnatal age (weeks), multiplied by 0.757 if gestational age ≤ 28 weeks and 0.836 if the current primary source of patients' nutrition is parenteral nutrition, and volume of distribution (ml) = 911 · current weight (kg). The interindividual variability in clearance and the residual variability, expressed as coefficients of variation, were 14.87% and 18.44%, respectively. Due to the lack of information on the data set we were unable to characterize the interindividual variability for volume of distribution.
Conclusion: In this study, which involved on average only two serum concentrations of caffeine per patient, the use of NONMEM gave us significant and consistent information about the pharmacokinetic profile of caffeine when compared with available bibliographic information. Additionally, parenteral nutrition and low gestational age (≤ 28 weeks) may even come to be considered as risk factors, and their presence may serve as an indicator of the need for periodic monitoring of caffeine concentrations in premature infants.

Key words Caffeine, Apnoea of prematurity; neonatology, paediatrics, population pharmacokinetics

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Introduction

Caffeine (1,3,7-trimethylxanthine) is an alkaloid that is currently used for the treatment of idiopathic apnoea associated with prematurity [1]. The first report of the chemical use of caffeine in premature infants was done by Aranda et al. [2], and since then numerous other studies have confirmed its efficacy in counteracting respiratory problems in neonatology [3–6]. There are few data on caffeine pharmacokinetic parameters and dosage schedules in premature infants [7–12], because ethical and logistic issues have limited the scope of the available studies done with traditional methodology [13, 14].

The population approach allows pooling of data and the estimation of pharmacokinetic parameters and interindividual variability with a limited number of samples per individual. With this approach one is able to estimate the pharmacokinetic parameters of a population by using sparse data collected during routine clinical care rather than data collected through intensive blood sampling [15, 16]. The non-linear mixed-effects model (NONMEM) population pharmacokinetic program was used to assess information regarding the pharmacokinetic profile of caffeine in this fragile population, which could be considered the clinical prototype for the application of this kind of data analysis [17].

The purpose of this study was to determine population pharmacokinetic parameters for neonatal patients, specifically those of very low birth weight, to pinpoint

the patterns of variability of the disposition of caffeine in this kind of patient and to identify characteristics associated with interindividual variability.

Methods

Patients

Data were obtained retrospectively from medical records and routine caffeine monitoring of 75 hospitalized patients (33 female and 42 male) at the University Hospitals of Salamanca (Spain) and Coimbra (Portugal), during the period from 1988 to 1994, with a total of 145 caffeine measurements. The covariate data collected on each patient included gender, birth weigth (BW), current weight (WT), gestational age (GA), postnatal age (PNA), postconceptional age (PCA) and concurrent treatment with phenobarbital and parenteral nutrition. The frequency of distribution of weight and age of the 75 neonates is shown in Fig. 1. The percentage of caffeine concentration measurements for which the discrete variables female sex (SEX), concurrent treatment with phenobarbital (PB) and parenteral nutrition (PN) were present were 44%, 18.7% and 36%, respectively.

Accurate dosing history, including date, dose and route of administration was collected. Typical loading and maintenance doses (caffeine citrate), administered by oral (syrup) or intravenous (short infusion) routes, were 20 and 5 $mg \cdot kg^{-1}$ once a day, respectively. However, due to several factors (e.g. rounding up or down, weight inconstancy, etc.), the loading dose ranged from 17.4 to 21.3 $mg \cdot kg^{-1}$ and the maintenance dose ranged from 2.14 to 9.47 $mg \cdot kg^{-1}$ once a day.

Serum sampling and drug analysis

Serum sampling times and corresponding concentrations were recorded (Fig. 2). The available caffeine serum levels ranged from 4.75 to 26.1 $\mu g \cdot ml^{-1}$, with a mean (SD) of 11.8 (4.22) $\mu g \cdot ml^{-1}$. For the whole data set, the number of caffeine concentrations per patient ranged from 1 to 6, with an average of 1.93 per patient. All caffeine measurements were carried out on a routine basis using an enzyme immunoassay (EMIT; Syva Co., Palo Alto, CA, USA). The coefficient of variation reported for the EMIT assay was less than 10% over the range of caffeine concentrations observed in this study (1–30 $\mu g \cdot ml^{-1}$), demonstrating that it is sufficiently accurate and practical for the therapeutic drug monitoring of caffeine in clinical practice [18–20].

Pharmacokinetic model

The available bibliographic information supports the idea that the one-compartment open model could be a mathematically reasonable approach for the explanation of the caffeine kinetic profile over time [7–12, 21, 22]. Additionally, a preliminary study revealed that the data contained no information on the absorption process and there was no evidence of biexponential elimination. So, the concentration time course of caffeine was described using a one-compartment model with either zero and first-order (infusion vs syrup) absorption and first-order elimination, assuming a permanent non-steady-state condition. Bioavailability was assumed to be complete ($F = 1$) for orally caffeine administration with an absorption rate fixed at 4.4 h^{-1} [23].

Statistical model

Initially, intersubject variability in clearance (CL) and volume of distribution (V), as well as residual intrasubject error, were modelled with proportional (constant CV) error models:

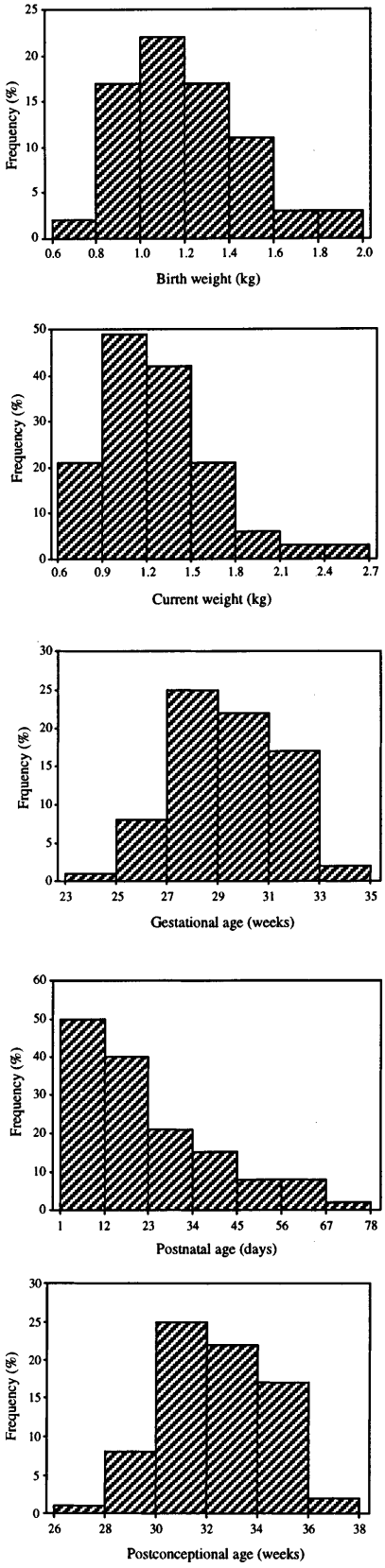

Fig. 1 Frequency of distribution of birth weight (BW), current weight (WT), gestational age (GA), postnatal age (PNA) and postconceptional age (PCA) in the study population

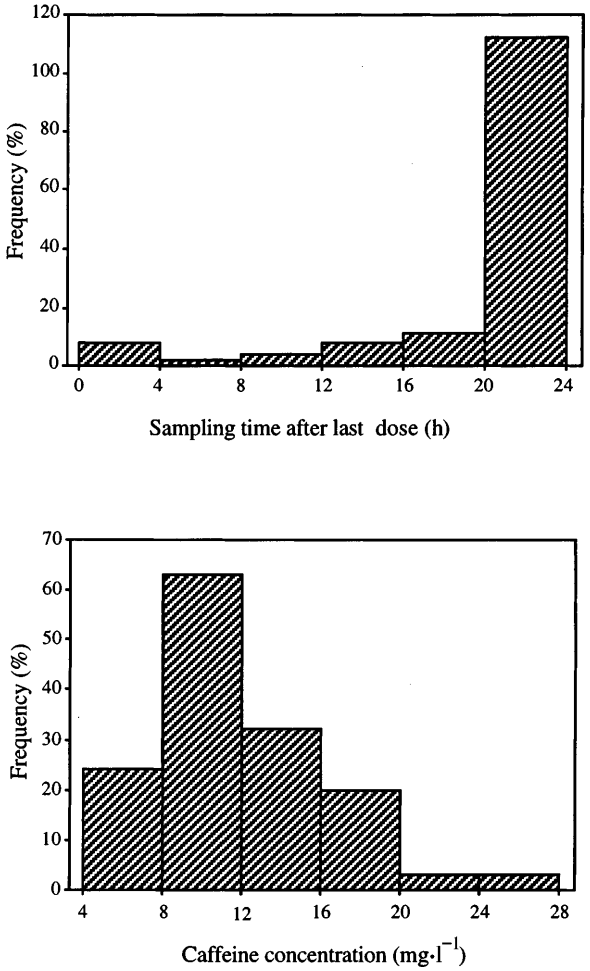

Fig. 2 Frequency of distribution of the sampling time and observed concentration of the 145 measurements

$$CL_j = CL \times (1 + \eta^{CL_j})$$

$$V_j = V \times (1 + \eta^{V_j})$$

$$C_{ij} = C^*_{ij} \times (1 + \varepsilon_{ij})$$

in which η^{CL_j} and η^{V_j} denote the difference between the true parameters (CL_j and V_j) for the j^{th} individual and the typical value for the population (CL and V). C_{ij} and C^*_{ij} are, in this order, the i^{th} measured and model predicted concentrations for the same individual. Moreover, the η^{CL_j}, η^{V_j} and ε_{ij} are zero mean random variables with variances ϖ^2_{CL}, ϖ^2_V and $\sigma^2_{\varepsilon ij}$, respectively.

Data analysis

All data from all subjects were fitted simultaneously with the version IV (level 2.0, double precision) of NONMEM, using the ADVAN2, TRANS2 and SSS0 subroutines from PREDPP to define the pharmacokinetic model. The regression model was developed by use of the forward inclusion, backward elimination method. In the construction of the regression model for fixed effects, the change in the minimum objective function produced by the addition of a new factor is termed the log likelihood difference (LLD), and is asymptotically distributed as χ^2 with one degree of freedom. The LLD was applied when the test models fulfilled the full/reduced model definition [24]. During forward inclusion the regression model was built by testing each characteristic, one at a time, using an LLD of 6.6, which is associated with a P value of 0.01. The elaboration of the final model was made by removing covariates from the full model (backward elimination). To partially compensate for the multiple comparisons, a P value of 0.005 was used. Thus, an LLD of 7.8 was necessary to show statistical significance between each proposed restricted model and the full model when two models differed by one parameter. If the test models did not meet the above definition (full/reduced pair with at least one degree of freedom), the Akaike Information Criterion (AIC) was applied [25]. In addition, the following diagnostic tools were considered when choosing between models: graphical analysis, standard error and correlation matrix of parameter estimates, and variance of the random effects (η_j and ε_{ij}).

Model-building process

With the above-mentioned diagnostic tools, we proceeded step by step from the basic model, which involves the simplest deterministic model likely to fit the data, and the simplest possible structural pharmacokinetic parameter model: each parameter is simply identified with a separate element of theta (θ). At this stage, the statistical model adopted for the random effect parameters was the proportional one. The process finished when the judgement tools indicated no improvement with any of the additions suggested by the diagnostic tools, or when the diagnostic tools failed to suggest any more additions. In practice, the model-building process was performed in four main steps:

Step 1. Construction of the intermediate model by testing the incorporation of continuous variables (BW, WT, GA, PNA and PCA) in the basic model through a linear and non-linear way, thus:

$$P_0 = \theta_1 + \theta_2 * COV + \theta_3 * COV^{\theta_4}$$

where P_0 is the base value of a pharmacokinetic parameter P and COV denotes the general continuous covariates.

Step 2. Construction of the full model by testing the incorporation of categorical variables in the intermediate model. Morever, in order to investigate a possible influence of discrete values of WT and GA, these were modelled as proportional factors for the following conditions: WT ≤ 1 and ≤1.2 kg, and GA ≤ 28, 29 and 30 weeks. Statistically significant factors were added to the description of the pharmacokinetic parameters as follows:

$$P = P_0 \Pi \theta_{CV}$$

where P is the final pharmacokinetic parameter value and CV denotes general categorical variables.

Step 3. Selection of the statistical model, where the random effects (the interindividual and residual components) were evaluated with the best model found for the fixed effects (pharmacokinetic parameter and covariates). Several combinations (additive and proportional error models) were proved. Additionally, the eventual difference between Portuguese and Spanish sources of residual error were equally tested.

Step 4. Refinement of the full pharmacostatistical model in order to obtain a final model which would be as parsimonious as reasonable. The diagnostic tools involved in this step included: standard errors (SE) of the estimates and 95% confidence intervals (CI).

Additionally, after the final model was found, each covariate was in turn deleted from the final model, and the reduced model was tested against the full model, as a final check.

Results

Tables 1 and 2 show the effect of a variety of demographic, developmental and clinical factors on clearance (CL) and volume of distribution (V), investigated in a

stepwise fashion as explained before. The final pharmacostatistical model included only those parameters and covariates which really improve its predictive capacity (see Table 1). The final parameter estimates and the corresponding standard errors (%) and 95% confidence intervals are shown in Table 3. Table 4 illustrates the evolution suffered by the basic model and demonstrated by the diagnostic tools, particularly with regards to objective function and size of the random variables related to the regression model for CL. This gives some assurance to the final result. Table 5 shows the results of simulation studies in which the final pharmacostatistical model derived in NONMEM was used to calculate once a day maintenance doses of caffeine citrate required to achieve an average steady-state serum caffeine concentration of 12 $\mu g \cdot ml^{-1}$ (mean value observed in our population) in premature infants of various weights and postnatal ages.

Discussion

Population pharmacokinetics provides a quantitative view of the influence of several physiopathological and/or clinical covariates on the pharmacokinetic profile of the drugs. Mean values for the parameters in individuals presenting those variables and an estimate of the previsible variability in terms of interindividual and residual errors are obtained. The use of routine clinical data in such a population analysis heralded a new era in which a kinetic profile of drugs is assessed in key populations, as occurs with neonatal patients.

In the present work, to consider time-dependent physiological characteristics that may influence drug disposition in neonates, several covariates associated with the maturation process were analysed: birth weight (BW), current weight (WT), gestational age (GA), postnatal age (PNA) and postconceptional age (PCA). The eventual influence of some categorical variables on basic pharmacokinetic parameters was assessed and include sex (SEX), parenteral nutrition (PN), the presence of phenobarbital (PB), low birth weight (LBW) and low gestational age (LGA).

Caffeine is mainly eliminated by renal excretion in the first weeks of life [26, 27]. Therefore, physiological variables most closely related to the development of renal function would have some influence upon caffeine clearance in this age range [28]. Accordingly, the inclusion of age (postnatal, gestational or postconceptional) in the structural model for clearance should not be thought strange, thus allowing patients' capacity for elimination to be discriminated in accordance with their renal function [29, 30]. In the final structural model for clearance, apart from current weight, the remaining continual variable that gave rise to the best adjustment of data was postnatal age. A similar result was recently obtained by Thomson et al. [22], for whom the clearance was modelled as a simple function of current weight and postnatal age without the effect of any other covariate.

The influence of postnatal age on clearance excludes the simultaneous inclusion of postconceptional age as a continual variable. However, gestational age as categorical variable improved the goodness of fit. This result is in accordance with previous studies showing postconceptional age as the most reliable indicator of ma-

Table 1 Structural evolution related with the model-building process

Model	Pharmacokinetic parameters	Stage
Basic	$CL = \theta_1$ $V = \theta_2$	Initial status
Intermediate	$CL = \theta_1 * WT^{\theta_2} + \theta_3 * PNA$ $V = \theta_4 * WT$	After step 1
Full	$CL = (\theta_1 * WT^{\theta_2} + \theta_3 * PNA) * \theta_{PN} * \theta_{LGA}$ $V = \theta_4 * WT$	After step 2
Final	$CL = (\theta_1 * WT + \theta_2 * PNA) * \theta_{PN} * \theta_{LGA}$ $V = \theta_3 * WT$	After step 4

WT is current weight (kg); PNA is the postnatal age (weeks); PN and LGA denote parenteral nutrition and low gestational age (≤ 28 weeks), respectively

Table 2 Results of hypothesis testing of full model

Hypothesis	LLD	*df*	*P* value	Decision
Does weight influence CL?	55.1	2	< 0.005	Yes
Does weight influence CL in a linear relationship?	42.5	1	< 0.005	Yes
Does weight influence CL in an exponential power relationship?	0.12	1	NS	No
Does postnatal age influence CL?	25.2	1	< 0.005	Yes
Does parenteral nutrition influence CL?	8.6	1	< 0.005	Yes
Does low gestational age (≤ 28 weeks influence CL?	12.9	1	< 0.005	Yes
Is a model without weight on V as good as a model which uses weight?	31.2	0	–	Probably not

Table 3 Final parameter estimates

Parameters	Estimate (units)	SE(%)	95% CI
θ_1	5.81 ($ml \cdot h^{-1} \cdot kg^{-1}$)	9.24%	4.74–6.88
θ_2	1.22 ($ml \cdot h^{-1} \cdot week^{-1}$)	20.33%	0.72–1.72
θ_3	911 ($ml \cdot kg^{-1}$)	4.02%	837.8–984.2
θ_{PN}	0.836 (fractional decrease)	6.22%	0.732–0.940
θ_{LGA}	0.757 (fractional decrease)	6.10%	0.665–0.849
ω_{CL}	14.87%	36.02%	7.86%–19.49%
σ_ε	18.44%	15.35%	15.36%–21.07%

SE (%) percentage relative standard error, *95% CI* 95% confidence intervals

turity with respect to the capacity for caffeine elimination [10, 21]; however, the inconvenience of PCA for dosage schedules in clinical practice was recognized. Therefore, our model, which was developed by considering the components making up the PCA separately (GA and PNA), gives a more practical result whilst indirectly maintaining the underlying influence of the PCA. With the entry of low gestational age (LGA ≤ 28 weeks), another categorical variable was immediately discarded, namely low birth weight (LBW ≤ 1 kg), due to the fact that LGA in isolation proved to be better than the LBW and the possibility of simultaneous use was rejected, owing to the strong correlation existing between these two covariates (Pearson's correlation coefficient equals 0.794 for our population).

Parenteral nutrition was found to be an influencing factor diminishing caffeine clearance to the order of 16.5% in neonates. Moore et al. [31] detected a similar degree of influence of parenteral nutrition upon theophylline clearance in newborns, as occurred in our pharmacostatistical model, which confirms that metabolism and/or excretion of methylxanthnines in this patient population may be affected by the feeding method used. Although the inductive capacity of phenobarbital and its interaction with methylxanthines has been previously confirmed [32, 33], we were unable to demonstrate such influence on caffeine clearance, as only 14 of our patients had this association, representing about 18% of caffeine serum concentration data. Even so, the estimated caffeine clearance in this subgroup of patients was slightly increased (12%), suggesting a positive influence which may warrant further study.

Individual estimates of clearance were obtained using the population estimates and a post hoc Bayesian analysis of the individual concentration measurements. The mean (SD) clearance estimates obtained by us from this analysis were 7.6 (1.5) $ml \cdot h^{-1} \cdot kg^{-1}$ and are consistent with the average clearance values of 7.9 (1.9) $ml \cdot h^{-1} \cdot kg^{-1}$, 8.9 (1.5) $ml \cdot h^{-1} \cdot kg^{-1}$ and 8.5 (0.4) $ml \cdot h^{-1} \cdot kg^{-1}$ reported by Thomson et al. [22], Aranda et al. [8] and Gorodischer et al. [9], respectively.

The final model for the volume of distribution is extremely simple, since only the influence of current weight is considered. The independence of this parameter in relation to clinical factors has already been described [21]. The lack of earliest blood samples after administration (Fig. 2) and, especially, the low percentage of

Table 4 Effect of modelling clearance on objective function and random effects variables

Clearance model	OBJ	DOBJ	ω_{CL}	σ_ε
$CL = \theta_1$	589.435	–	31.9%	26.6%
$CL = \theta_1 * WT$	469.526	119.909	20.5%	19.7%
$CL = \theta_1 * WT + \theta_2 * PNA$	443.331	26.195	20.5%	19.7%
$CL = (\theta_1 * WT + \theta_2 * PNA) * \theta_{PN}$	414.578	28.753	17.3%	18.9%
$CL = (\theta_1 * WT + \theta_2 * PNA) * \theta_{PN} * \theta_{LGA}$	399.330	15.248	14.9%	18.4%

OBJ value of objective function in each NONMEM run, *DOBJ* difference in OBJ between two models

Table 5 Daily doses of caffeine citrate (mg) calculated[a] to achieve an average steady-state concentration of 12 $\mu g \cdot ml^{-1}$ in premature infants of various weights and postnatal ages

Current weight (kg)	Postnatal age (weeks)									
	1	2	3	4	5	6	7	8	9	10
0.6	2.7	3.4	4.1	4.8	5.5	6.2	6.9	7.6	8.3	9.0
0.8	3.4	4.1	4.8	5.5	6.2	6.9	7.6	8.3	9.0	9.7
1.0	4.1	4.7	5.5	6.2	6.8	7.5	8.3	9.0	9.7	10.4
1.2	4.7	5.4	6.1	6.8	7.5	8.2	8.9	9.6	10.3	11.0
1.4	5.4	6.1	6.8	7.5	8.2	8.9	9.6	10.3	11.0	11.7
1.6	6.1	6.7	7.5	8.2	8.9	9.6	10.3	11.0	11.7	12.4
1.8	6.7	7.4	8.1	8.8	9.5	10.2	10.9	11.6	12.4	13.1
2.0	7.4	8.1	8.8	9.5	10.2	10.9	11.6	12.3	13.0	13.7

[a] Calculated from $C_{av,ss} = D \cdot F \cdot S / CL.\tau$, where $C_{av,ss}$ is the average steady-state concentration, D is the administered dose, F is the bioavailability (equal to one for caffeine citrate), S denotes the salt factor (0.5 for caffeine citrate), τ is the posological interval (24 h) and CL represents the clearance (from NONMEM); thus CL = 5.81 * current weight (kg) + 1.22 * postnatal age (weeks)

concentrations determined after the loading dose (5.5%) make it difficult both to detect the influence of covariates and to estimate interindividual variability for the volume of distribution in our population. However, the estimate of the population mean volume of distribution of caffeine (911 $ml \cdot kg^{-1}$) is similar to the range values found by others [7–9, 21, 23] and in a certain way with the value obtained by Thomson et al. [22], for whom the volume of distribution is a fixed value (0.82 l), independent of any covariate (including the current weight).

Using the proportional error model for the random effects parameters, the interindividual variability of clearance was determined to be 14.87% and the residual variability presented a value of 18.44%. Moreover, the estimated values for the final parameters presented a typical pattern with a degree of precision within acceptable limits for both the fixed effects parameters ($< 20\%$) and the random effects parameters ($< 50\%$) [34].

The present work identified some scope for refining caffeine usage in premature neonates. In accordance with the available information obtained from traditional studies, most clinicians prescribe caffeine doses based solely on current weight, but in this study it was established that caffeine clearance was significantly influenced in a linear way by two factors, current weight and postnatal age. Additionally, in contrast to a previous populational analysis done by Thomson et al. [22], we identified the low gestational age (≤ 28 weeks) and concurrent treatment with parenteral nutrition as categorical variables related to a decreased capacity on the elimination profile of caffeine in this kind of population. However, it must be emphasized that doses shown in Table 5 are only intended as a guide and do not alleviate the need for routine caffeine monitoring. In fact, we observed a slight underprediction for concentrations above 18 $\mu g \cdot ml^{-1}$, which could be related with an eventual non-linearity (unrecognized routes of drug entry, altered protein binding, blood pH variations, etc.) or which could be due to the lack of information of our data set concerning these concentrations (Fig. 2).

The close agreement between the results of previous more traditional studies and those provided by NONMEM analysis underlines the potential of mixed effects models for population analysis in this kind of population. This is due not only to its consistency but also because the results obtained confer a dynamic characteristic upon pharmacokinetic parameters. Thus, the influence that variables such as current weight, postnatal age, parenteral nutrition and low gestational age may have upon caffeine kinetic profile in neonates has been proved by means of a structural model capable of conferring a dynamic character to basic pharmacokinetic parameters. The introduction of this pharmacostatistical model in computer programs will permit individual pharmacokinetic parameter determination through Bayesian estimation, which will probably increase the predictive accuracy of dosage readjustments. Additionally, parenteral nutrition and low gestational age may even come to be considered as risk factors, suggesting the need for periodic monitoring. However, caution must be exercised in extrapolating this information to patients in other settings, owing to implicit differences in the covariates involved.

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