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A Population and Developmental Pharmacokinetic Analysis To Evaluate and Optimize Cefotaxime Dosing Regimen in Neonates and Young Infants

Stéphanie Leroux,[a,b,c] Jean-Michel Roué,[d] Jean-Bernard Gouyon,[e] Valérie Biran,[f] Hao Zheng,[a] Wei Zhao,[a,b,g] Evelyne Jacqz-Aigrain[a,b,g]

Department of Pediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, APHP, Paris, France[a]; EA7323, Université Paris Diderot-Université Paris Descartes, Paris, France[b]; Neonatal Intensive Care Unit, CHU de Rennes, Rennes, France[c]; Neonatal Intensive Care Unit, CHU de Brest, Brest, France[d]; Neonatal Intensive Care Unit, Centre d'Etudes Périnatales de l'Océan Indien (EA7388), CHU de la Réunion, Réunion, France[e]; Neonatal Intensive Care Unit, Hôpital Robert Debré, APHP, Paris, France[f]; Clinical Investigation Center CIC1426, INSERM, Paris, France[g]

Cefotaxime is one of the most frequently prescribed antibiotics for the treatment of Gram-negative bacterial sepsis in neonates. However, the dosing regimens routinely used in clinical practice vary considerably. The objective of the present study was to conduct a population pharmacokinetic study of cefotaxime in neonates and young infants in order to evaluate and optimize the dosing regimen. An opportunistic sampling strategy combined with population pharmacokinetic analysis using NONMEM software was performed. Cefotaxime concentrations were measured by high-performance liquid chromatography-tandem mass spectrometry. Developmental pharmacokinetics-pharmacodynamics, the microbiological pathogens, and safety aspects were taken into account to optimize the dose. The pharmacokinetic data from 100 neonates (gestational age [GA] range, 23 to 42 weeks) were modeled with an allometric two-compartment model with first-order elimination. The median values for clearance and the volume of distribution at steady state were 0.12 liter/h/kg of body weight and 0.64 liter/kg, respectively. The covariate analysis showed that current weight, GA, and postnatal age (PNA) had significant impacts on cefotaxime pharmacokinetics. Monte Carlo simulations demonstrated that the current dose recommendations underdosed older newborns. A model-based dosing regimen of 50 mg/kg twice a day to four times a day, according to GA and PNA, was established. The associated risk of overdose for the proposed dosing regimen was 0.01%. We determined the population pharmacokinetics of cefotaxime and established a model-based dosing regimen to optimize treatment for neonates and young infants.

Cefotaxime is one of the most frequently prescribed antibiotics in neonates (1). This third-generation cephalosporin is mainly used in the treatment of neonatal sepsis (2) and meningitis caused by Gram-negative bacteria. Because of the high rates of morbidity and mortality (3), the optimal use of cefotaxime is essential in neonatal infection management. However, the dosing regimens routinely used in clinical care vary considerably. As reported in our previous study, 25 different dosage regimens of cefotaxime were identified in the French neonatal intensive care unit (NICU) network, with median daily doses varying from 75 mg/kg of body weight/day to 180 mg/kg/day among NICUs (4). This huge variation can be partly explained by the different dosage recommendations available in reference textbooks and published guidelines (1). It also highlights the need for powerful pharmacokinetic (PK) data for neonates. As recently reviewed by Pacifici et al. (5), the pharmacokinetics of cefotaxime in neonates were mainly studied in the 1980s with a limited number of patients. The study design and analysis method limited the power to determine a precise dose of cefotaxime derived from pharmacokinetic data, as the quantitative impacts of covariates (i.e., maturation, organ function) on dose were not fully assessed. The simplification of the impacts of covariates could lead to significant imprecision in dose recommendations for a subgroup of patients, in particular, for neonates.

Pharmacometric approaches are now highly recommended to personalize the dose of antimicrobial therapy in neonates (6); thereby, the objective of the present study was to conduct a population pharmacokinetic study of cefotaxime in neonates in order to evaluate and optimize the dose regimen in neonates.

MATERIALS AND METHODS

Study design and pharmacokinetic sampling. This open-label population pharmacokinetic study of cefotaxime was conducted in three French neonatal intensive care units (NICUs) (Robert Debré [Paris], Brest, and Saint Pierre de la Réunion University Hospitals). Neonates and young infants (postmenstrual age [PMA], ≤44 weeks) receiving intravenous cefotaxime as part of their routine clinical care (for suspected or proven neonatal sepsis) were enrolled. This noninterventional study was approved by the ethics committee of Robert Debré University Hospital.

Cefotaxime dosing followed the local guidelines routinely used in each NICU (Table 1). An opportunistic pharmacokinetic sampling approach was followed (7): samples for PK analysis were exclusively collected from blood remaining after routine biochemical tests (determination of C-reactive protein and serum electrolyte levels) and pharmacological tests (vancomycin therapeutic drug monitoring) performed as part of patient

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Address correspondence to Evelyne Jacqz-Aigrain, evelyne.jacqz-aigrain@rdb.aphp.fr.

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TABLE 1 Dosing regimens for cefotaxime in neonates from reference textbooks and current study guidelines[a]

Source (reference)	GA (wk)	BW (kg)	PMA (wk)	PNA (days)	Unit dose (mg/kg/dose)	Dose interval (h)
Reference textbooks						
Blue Book (17)				<7	25[b]	12
				7–21	25[b]	8
				21–28	25[b]	6
NeoFax (18)			≤29	≤28	50	12
			≤29	>28	50	8
			30–36	≤14	50	12
			30–36	>14	50	8
			37–44	≤7	50	12
			37–44	>7	50	8
			≥45	All	50	6
PDH (48)		<1		≤14	50	12
		<1		15–28	50	8–12
		1–2		≤7	50	12
		1–2		8–28	50	8–12
		>2		≤7	50	12
		>2		8–28	50	6–8
Current study[c]						
Hospital 1				≤7	50–100	12
				>7	50–100	8
Hospital 2	<37				25[b]	12
	≥37				20	8

[a] GA, gestational age; BW, birth weight; PMA, postmenstrual age; PNA, postnatal age; PDH, *Pediatric and Neonatal Dosage Handbook*.
[b] Doses may be doubled in patients with severe infection.
[c] Hospital 3 used the NeoFax (18) guidelines.

clinical care. No additional blood volume was taken for these samples. Each sample was centrifuged and then stored at −80°C (a maximal 48-h period at ambient temperature was allowed before the samples were frozen). The samples were shipped on dry ice to the Department of Pediatric Pharmacology, Robert Debré University Hospital, where they were stored at −80°C prior to analysis but were stored for a period not exceeding 12 months from the time of collection.

The following clinical data were collected and evaluated as covariates with a potential influence on cefotaxime pharmacokinetics: gestational age (GA); postnatal age (PNA); PMA (defined as the sum of gestational and postnatal age [8]); birth weight; current weight; sex; serum concentrations of total protein, albumin, liver enzymes (aspartate and alanine aminotransferases), C-reactive protein, and creatinine; coadministered drugs (inotropes, ibuprofen, and aminoglycosides); and ventilation. The precise sampling time and drug administration history (including dosing and infusion time) were recorded by the clinical team using dedicated documentation and were later transcribed to the case report form. Samples with missing pharmacokinetic information were excluded from analysis.

Method of cefotaxime analysis. A multiplex high-performance liquid chromatography-tandem mass spectrometry assay for 8 antibiotics, including cefotaxime, was developed and validated. Briefly, cefotaxime concentrations were determined by use of a microvolume (50 μl). The calibration curve ranged from 0.05 mg/liter to 150 mg/liter. The lower limit of quantification was 0.05 mg/liter. The intraday and interday coefficients of variation for the controls were 7.7% and 7.3%, respectively. The short-term stability (at ambient temperature) and long-term stability (−80°C) of cefotaxime in plasma and serum were documented for at least 48 h and 12 months, respectively. For all samples, sample handling and storage duration respected the known cefotaxime stability conditions.

Population pharmacokinetic modeling. The concentration-time data for cefotaxime were modeled by first-order conditional estimation with interaction (FOCE-I), using the nonlinear mixed effects modeling program NONMEM (v7.2).

(i) Step 1: model building. An initial analysis was first conducted to estimate the pharmacokinetic parameters for a basic model (i.e., a model without covariates). Both one- and two-compartment structural models were tested. The interindividual variability (IIV) of the pharmacokinetic parameters was estimated according to an exponential model and could be expressed as follows: $\theta_i = \theta_{pop} \cdot \exp^{\eta i}$, where θ_i is the estimated parameter value (e.g., clearance [CL] or volume of distribution [V]) for the ith subject; θ_{pop} is the mean population value of the parameter; and ηi is the interindividual variability, which is assumed to follow a normal distribution with a mean of 0.

Covariate analysis was then performed by following a forward and backward selection method (9). The likelihood ratio test was used to test the influence of each variable on the model parameters. During the first step of covariate model building, inclusion of a covariate required a significant ($P < 0.05$, χ^2 distribution with 1 degree of freedom) decrease (reduction, >3.84) in the objective function value (OFV) and a concomitant reduction in the variability of the pharmacokinetic parameter. An intermediate full model including all significant covariates was then obtained. Second, each covariate was independently removed from the full model. At this step, a significant ($P < 0.01$, χ^2 distribution) increase (more than 6.635) of the OFV was required to finally retain the covariate in the final model.

(ii) Step 2: model validation. The validation of the final model was based on graphic inspection and statistical analysis. The performance of the model was assessed by visual inspection of goodness-of-fit plots. The accuracy and robustness were evaluated using a nonparametric bootstrap analysis (10) with resampling and replacement (500 times); the parameters estimated by bootstrap analysis (median and percentile 95% intervals) were compared to the respective values estimated from the original data set. We also evaluated the final model by the use of normalized prediction distribution errors (NPDE). One thousand data sets were simulated using the final population model parameters. NPDE results were summarized graphically by use of the NPDE R package (11). The NPDE

TABLE 2 Baseline characteristics[a] of neonatal study population

Characteristic	No. of neonates	Mean (SD)	Median (range)
Patients	100		
Demographic data			
Gender (female/male)	60/40		
Gestational age (wk)		31.4 (5.0)	31.5 (23.0–42.0)
Postnatal age (days)		13.3 (13.1)	9.0 (0.0–69.0)
Postmenstrual age (wk)		33.3 (4.9)	33.0 (25.0–44.0)
Birth wt (g)		1,658.3 (904.9)	1,415.0 (512.0–3,990.0)
Current wt (g)		1,815.2 (875.3)	1,647.5 (530.0–4,200.0)
Clinical data			
Proven infection	25		
Invasive ventilation	53		
Drug coadministration			
Vasopressive agent	21		
Aminoglycoside	74		
Ibuprofen	3		
Biological data[b]			
Serum creatinine concn (μmol/liter)		51.7 (29.3)	44.0 (13.0–226.0)
Total protein concn (g/liter)		46.8 (8.6)	47.0 (20.0–65.0)
Albumin concn (g/liter)		26.9 (5.6)	27.0 (17.0–38.0)
Aspartate aminotransferase concn (IU/liter)		40.4 (20.5)	35.0 (17.0–85.0)
Alanine aminotransferase concn (IU/liter)		22.7 (16.6)	14.0 (6.0–77.0)
C-reactive protein concn (mg/liter)		46.6 (60.5)	18.3 (0.3–255.0)
Pharmacokinetic data			
No. of samples per patient		1.8 (1.2)	1.0 (1.0–6.0)
Time of sampling[c] (h)		6.0 (5.5)	5.0 (0.1–51.7)
Cefotaxime concn (mg/liter)		39.2 (31.5)	29.1 (0.1–149.6)

[a] At time of first dosing.
[b] Within 48 h before dosing.
[c] Since administration of the previous dose.

distribution was expected to follow a normal distribution (mean, 0; variance, 1) [N (0, 1) distribution].

Dosing regimen optimization. For cefotaxime, which has time-dependent bacterial killing (12), the following pharmacokinetic-pharmacodynamic target was selected: 90% of the simulated patients were to achieve an unbound cefotaxime concentration (50% of the total concentration in the worst case [13]) higher than the MIC for 75% of the dosing interval at steady state. This percentage of the dosing interval that the concentration is above the MIC (time above the MIC [T_{MIC}]) target of 75% was selected due to the known immunocompromised status of neonates (14, 15). The distribution of common pathogens causing early-onset sepsis (EOS) and late-onset sepsis (LOS) (13) and the MIC values reported by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were also considered for dose optimization (16). The standard MIC susceptibility breakpoints of 2 mg/liter and 4 mg/liter were used for early-onset sepsis (PNA, <7 days) and late-onset sepsis (PNA, ≥7 days), respectively.

According to pharmacokinetic-pharmacodynamic and microbiological criteria, 1,000 Monte Carlo simulations were first performed, using NONMEM, to assess target attainment rates in patients treated with cefotaxime according to the dosing recommendations obtained from the Blue Book (17) and NeoFax (18) (Table 1). The simulation cohort consisted of the 100 newborns from the original data set divided into different subgroups by age (16 newborns with a GA of <32 weeks and a PNA of <7 days, 21 newborns with a GA of ≥32 weeks and a PNA of <7 days, 34 newborns with a GA of <32 weeks and a PNA of ≥7 days, and 29 newborns with a GA of ≥32 weeks and a PNA of ≥7 days), representing a real distribution of patient characteristics in clinical practice.

Second, to optimize the dosing regimen, Monte Carlo simulations (n = 1,000) were used to generate cefotaxime pharmacokinetic profiles for different dosing regimens. The neonatal dose of cefotaxime was simulated on a milligram-per-kilogram basis for the different age groups. Various dosages (50 mg/kg one to four times a day) were simulated in each age group. To ensure comparable safety profiles, the area under the concentration-time curve (AUC) at steady state was also calculated for each simulated patient. The risk of overdose was defined as the percentage of simulated patients with an AUC above the maximal AUC value observed in the study population. The target attainment rate was then calculated for each dosing regimen to define the optimal dosing regimen in each neonatal group.

RESULTS

Patient characteristics. One hundred patients were analyzed after exclusion of 14 patients because of incomplete dosing information. Baseline patient characteristics are detailed in Table 2. The median gestational age and birth weight were 31.5 weeks (range, 23.0 to 42.0 weeks) and 1,415.0 g (range, 512.0 to 3,990.0 g), respectively. Newborns received cefotaxime as a direct injection or a 15- to 30-min infusion at a dose of 50 mg/kg (mean, 47.7 mg/kg; standard deviation, 8.2 mg/kg) two times a day (BID), three times a day (TID), or four times a day (QID). Among the 100 newborns treated with cefotaxime (alone or in association with other antibiotics), 25 had positive blood cultures (2 of the pathogens [1 *Streptococcus agalactiae* isolate and 1 *Escherichia coli* isolate] were isolated in patients within the first week of life; 23 others [19 co-

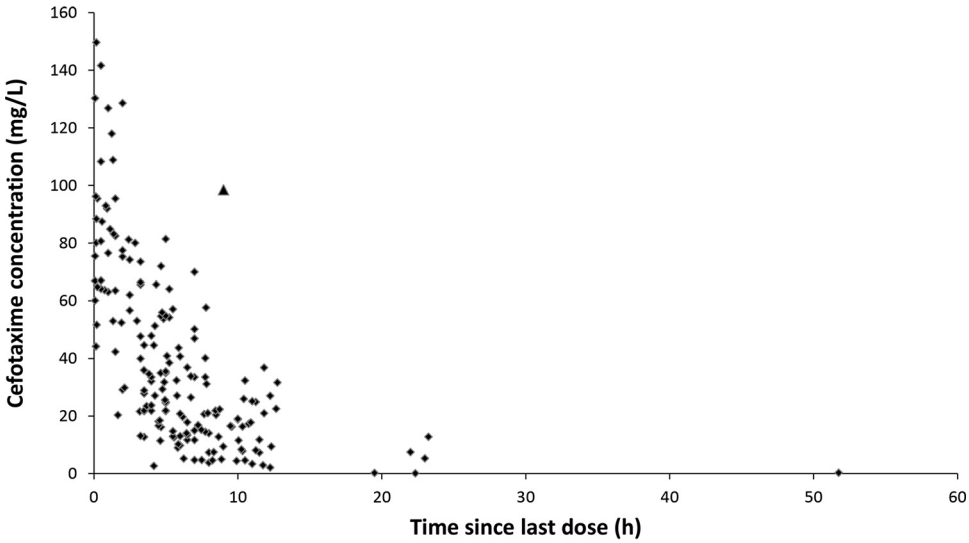

FIG 1 Cefotaxime concentrations versus time. One patient received a dose of 100 mg/kg; his concentration is represented with a triangle. All other newborns received cefotaxime at a dose of 50 mg/kg.

agulase-negative staphylococci, 2 *Staphylococcus aureus* isolates, and 2 *Escherichia coli* isolates] were identified later).

Population pharmacokinetic modeling. A total of 185 concentrations from 100 newborns were available for pharmacokinetic analysis. The concentration-versus-time profile is shown in Fig. 1.

Model building. Data were best fit by a two-compartment model with first-order elimination. The model was parameterized in terms of clearance (CL), central volume of distribution (V_1), peripheral volume of distribution (V_2), and intercompartmental clearance (Q). Interindividual variability was exponentially modeled and could be estimated only for CL. A proportional model best described the residual unexplained variability.

The allometric size approach, which consisted of *a priori* incorporation of the current weight into the basic model, allowed a significant drop in the OFV of 101.8 points. Allometric exponents of 0.75 and 1 were fixed for CL and V, respectively (19); their estimation by use of the model (resulting in allometric exponents of 0.73 and 0.8 for CL and V, respectively) did not significantly improve the fit of the data. Gestational age and postnatal age, incorporated together to reflect the impact of maturation, caused a further important decrease in the OFV of 121.8 points. Use of this association was superior to the use of postmenstrual age alone (change in OPV [ΔOFV], 68.4 points) and also to the use of birth weight and postnatal age together (ΔOFV, 107.4 points). After the integration of gestational age and postnatal age into the allometric basic model, the serum creatinine concentration caused a further significant drop in the OFV of 5.4 points in the forward selection process. However, it could not be retained in the final model after the backward selection process. All other covariates were rejected during the forward selection step: none of them showed a sufficient OFV decrease. Finally, size and maturation explained, respectively, 24.1% and 41.8% of the interindividual variability of cefotaxime clearance. Interoccasion variability could not be estimated. The η shrinkage was 25.6% for CL, and the ε shrinkage was 12.1%. The results of the covariate analysis are presented in Table 3.

The final estimates of the pharmacokinetic parameters and bootstrap results are summarized in Table 4. The volume of distribution at steady state (sum of V_1 and V_2) was 0.64 liters/kg. The median of CL and half-life were 0.12 liter/h/kg (range, 0.04 to 0.26 liter/h/kg) and 3.63 h (range, 1.67 to 10.35 h), respectively.

Model validation. Figure 2 shows the results of model evaluation using different diagnostic methods. No bias in the goodness-of-fit plots was observed (Fig. 2A to D). The NPDE distribution and histogram met the theoretical N (0, 1) distribution and density well, indicating a good fit of the model to the individual data (Fig. 2E and F). The mean and variance of the NPDE were 0.05 (Wilcoxon signed-rank test, $P = 0.52$) and 1.09 (Fisher variance test, $P = 0.37$), respectively. Moreover, the results of the bootstrap analysis demonstrated the reliability and stability of the final model. The median parameter estimates from the bootstrap procedure closely agreed with the respective values from the final population model (Table 4).

Dosing regimen optimization. Figure 3 presents the target attainment rates as a function of dose and age group for the standard MIC susceptibility breakpoints of 2 mg/liter (PNA $<$ 7 days) and 4 mg/liter (PNA $\geq$ 7 days). In the newborns with a PNA of $\geq$7 days and a GA of $\geq$32 weeks, the optimal dosing required to achieve a 90% probability of target attainment was 50 mg/kg QID. Figure 4 demonstrates that the current dose recommendations by the Blue Book (17) and NeoFax (18) underdosed these older newborns: the target was attained in only 68.0% and 52.9% of the simulated patients in this age group.

Dose optimization was performed to determine the percentage of newborns achieving predefined target concentrations (2 mg/liter for a PNA of $<$7 days and 4 mg/liter for a PNA of $\geq$7 days) for 75% of the cefotaxime dosing interval. The cutoff points of 32 weeks for GA and 7 days for PNA were selected to separate age groups on the basis of (i) visual inspection of the plots of cefotaxime clearance versus GA (see Fig. S1 in the supplemental material) and PNA (see Fig. S2), (ii) the targeted neonatal sepsis pathogens (which varied according to PNA) (13), and (iii) the

TABLE 3 Results of covariate analysis[e]

Characteristic[a]	Pharmacokinetic parameter(s)[b]	OFV[c]	IIV[d] of CL (%)	Residual variability (%)
Structural model		**1,338.6**	**61.7**	**44.4**
Current body wt (allometric model)	**CL, V_1, V_2, Q**	**1,236.8**	**46.8**	**38.0**
Impact of maturation				
BW		1,210.2	35.6	39.2
GA		1,204.9	34.3	39.1
PNA	**CL**	1,190.2	44.7	32.6
PMA		1,168.4	30.0	36.6
BW and PNA		1,129.4	25.1	34.5
GA and PNA		**1,115.0**	**21.0**	**35.1**
Impact of maturation and renal function (GA, PNA, and serum creatinine concn)	CL	1,109.6	18.3	35.8

[a] BW, birth weight (grams); GA, gestational age (weeks); PNA, postnatal age (days); PMA, postmenstrual age (weeks).
[b] CL, clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution; Q, intercompartmental clearance.
[c] OFV, objective function value.
[d] IIV, interindividual variability.
[e] The characteristics in boldface and their values were retained in the final population model.

current clinical practice in neonatal care. For newborns with a PNA of <7 days, the target was achieved in 99.0% of newborns with a GA of <32 weeks and 95.7% of newborns with a GA of ≥32 weeks when they were treated with 50 mg/kg BID. For newborns with a GA of <32 weeks and a PNA of >7 days, the target was achieved in 96.8% of newborns when they were treated with a dose of 50 mg/kg TID. For newborns with a GA of ≥32 weeks and a PNA of >7 days, the target was achieved in 93.5% of newborns when they were treated with a dose of 50 mg/kg QID. The risk of overdose (defined as an AUC over the maximal value of 1,545.5 mg · h/liter measured in the present study) associated with the new model-based dosing regimen was 0.01%.

DISCUSSION

To our knowledge, this is the first population pharmacokinetic study of cefotaxime conducted in a representative cohort of newborns. Using an opportunistic sampling strategy combined with population pharmacokinetic analysis (7), we determined the population pharmacokinetic parameters of cefotaxime in neonates and young infants, allowing description and prediction of the pharmacokinetics of cefotaxime under real clinical care conditions and investigation of the optimal dosing regimen for neonates.

The cefotaxime dosing regimen described in different guidelines and references varies (Table 1). Two dosing recommendations were previously published for neonates in the first week of life: 50 mg/kg BID (20–23) or 25 mg/kg/dose BID (24, 25). For neonates 7 to 28 days of age, three different dosages are available: 50 mg/kg TID (23), 25 mg/kg TID (24, 25), or 25 mg/kg QID (term neonates only) (25). As for many other antibiotics, the cefotaxime dosing regimens described in the prescription practices used in

TABLE 4 Final estimates of population pharmacokinetic parameters of cefotaxime and bootstrap analysis results[a]

	Final model		Bootstrap analysis (n = 500)	
Parameter	Mean estimate	RSE (%)	Median	95% CI
$CL = \theta1 \times (CW/1{,}665)^{0.75} \times FGA \times FPNA$				
Values for θ1	0.21	3.9	0.21	0.20–0.23
$FGA = (GA/30)^{\theta5}$				
Values for θ5	2.27	9.4	2.30	1.94–2.66
$FPNA = (PNA/12)^{\theta6}$				
Values for θ6	0.28	8.2	0.29	0.24–0.32
$V_1 = \theta2 \times (CW/1{,}665)$				
Values for θ2	0.71	12.7	0.70	0.36–0.90
$V_2 = \theta3 \times (CW/1{,}665)$				
Values for θ3	0.35	28.1	0.38	0.19–0.89
$Q = \theta4 \times (CW/1{,}665)^{0.75}$				
Values for θ4	0.27	38.5	0.26	0.10–3.75
Interindividual variability (%) for CL	21.0	27.7	20.0	14.6–25.9
Residual variability (%)	35.1	13.3	34.3	30.2–38.2

[a] CL, clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution; Q, intercompartmental clearance; CW, current weight (grams); GA, gestational age (weeks); PNA, postnatal age (days); RSE, relative standard error; CI, confidence interval. At the time of sampling (all samples together), 30 weeks, 12 days, and 1,665 g were the median gestational age, postnatal age, and current weight, respectively.

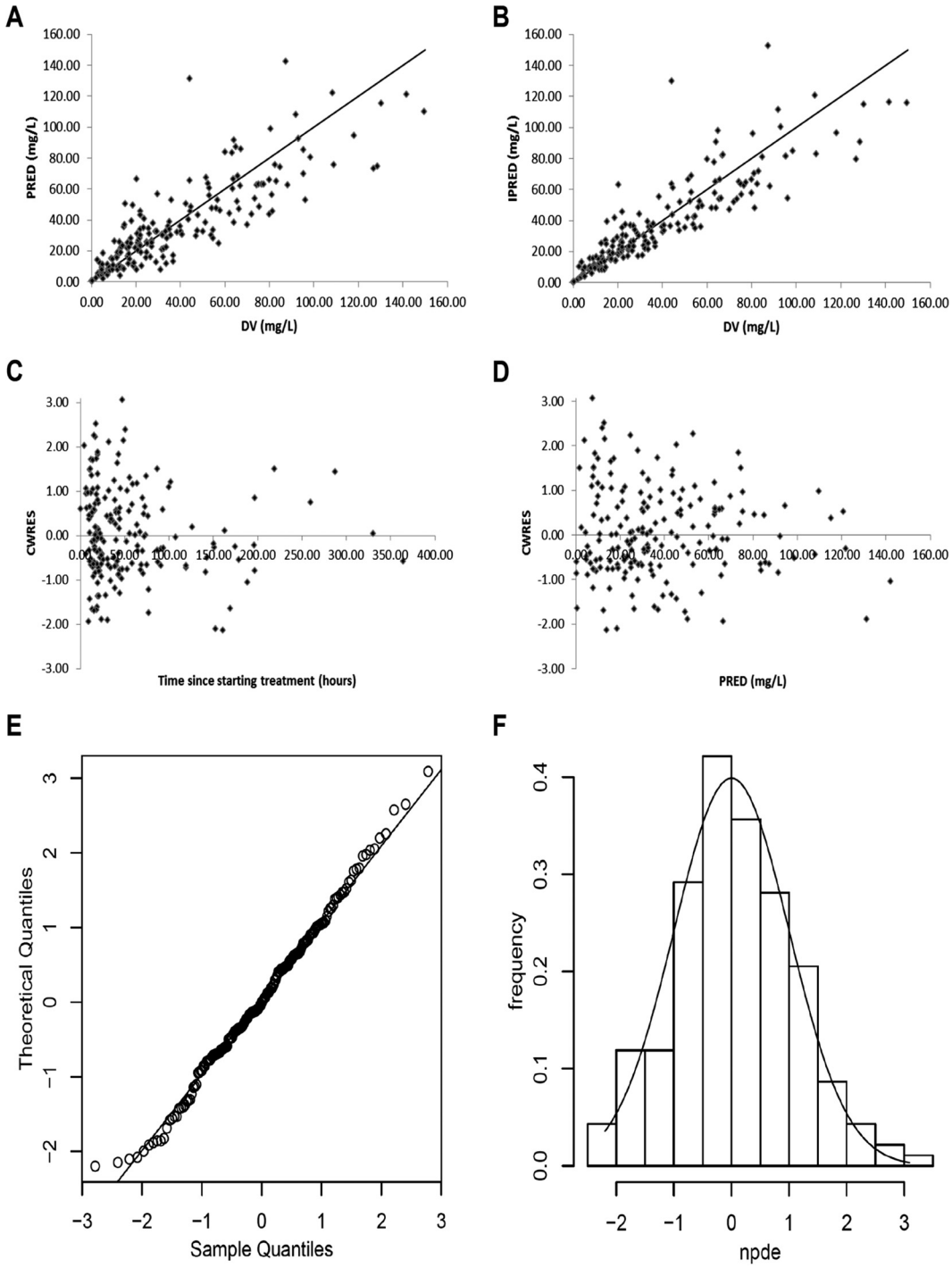

FIG 2 Model validation for cefotaxime. (A) Population predicted (PRED) versus observed concentrations (DV); (B) individual predicted (IPRED) versus observed concentrations (dependent variable [DV]); (C) conditional weighted residuals (CWRES) versus time; (D) conditional weighted residuals versus population predicted concentration; (E) quantile-quantile (QQ) plot of the distribution of the normalized prediction distribution errors (NPDE) versus the theoretical $N(0, 1)$ distribution; (F) histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution being overlaid (line).

France (4) and Europe (1) were also found to vary. All these observations of routine care highlight the urgent requirement for powerful pharmacokinetic data for this vulnerable population.

Previous studies assessing the pharmacokinetics of cefotaxime in neonates included a relatively small number of patients ($n \leq 37$) (18, 22–29) and did not precisely quantify the impact of maturation on the disposition of cefotaxime. Previous mean estimates of cefotaxime clearance in term neonates varied from 0.09 liter/h/kg to 0.14 liter/h/kg (5). The relevance and significance of the pharmacometric approach for quantitatively assessing factors that may explain the interindividual variability of drug disposition and, thereby, dose have been well demonstrated in recent years, in

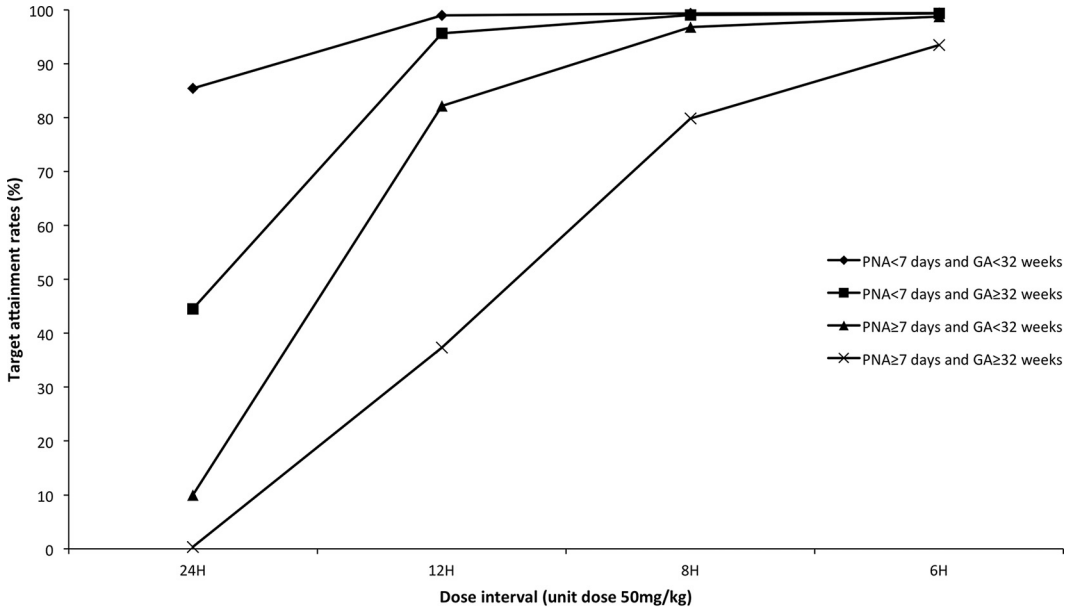

FIG 3 Target attainment rates for 1,000 simulated trials. The target attainment rates for the 1,000 simulated trials for MIC values of 2 mg/liter (PNA < 7 days) and 4 mg/liter (PNA ≥ 7 days) are presented as a function of the dose and age group. The time above the MIC target is 75% of the dosing interval.

particular, for neonates (30). Recently, the European Medicines Agency (EMA) highlighted its preference for a population pharmacokinetic approach due to the importance of finding covariates related to dose individualization for individuals and over time in the maturating individual (31).

Since cefotaxime is mainly eliminated by the kidney (70%) and to a lesser extent is hydrolyzed by hepatic esterases (2), renal maturation was expected to have a major impact on cefotaxime clearance and, thereby, dose in neonates. Moreover, while renal maturation is completed by about 1 year of age (32), the metabolic pathway responsible for the biotransformation of cefotaxime is already active at 27 to 28 weeks of GA (21). In agreement with

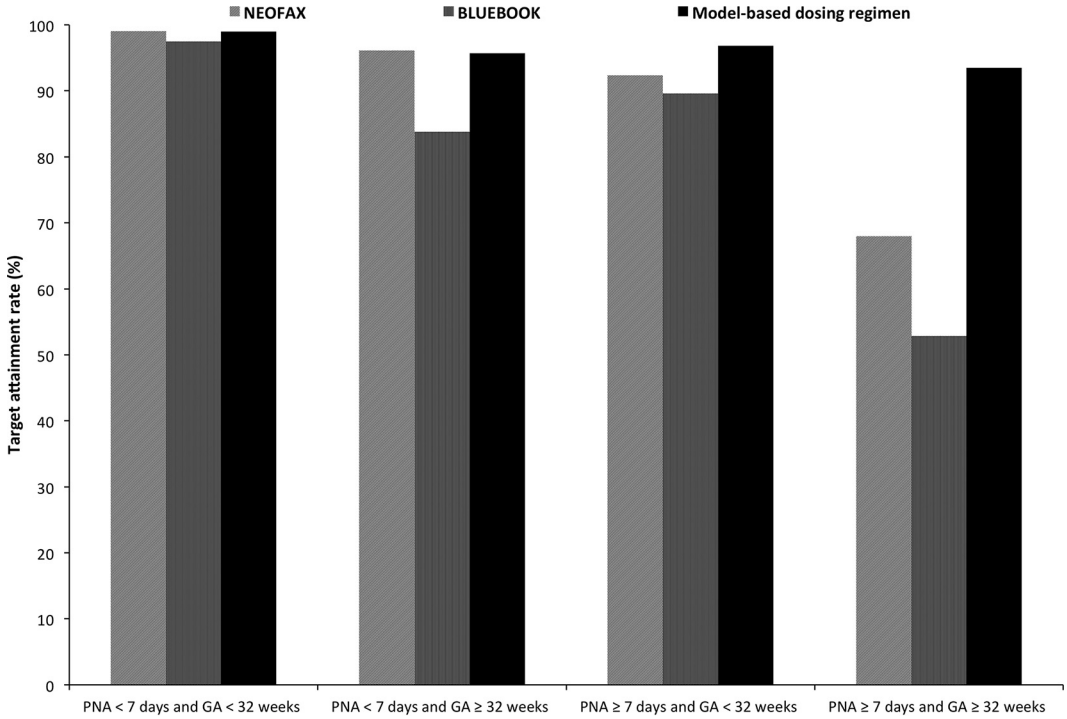

FIG 4 Target attainment rates by age group: model-based dosing regimen compared to reference regimens (17, 18) (1,000 simulated trials). Our model-based dosing regimen consisted of 50 mg/kg/12 h for neonates with a PNA of <7 days, 50 mg/kg/8 h for neonates with a PNA of ≥7 days and a GA of <32 weeks, and 50 mg/kg/6 h for neonates with a PNA of ≥7 days and a GA of ≥32 weeks.

these physiological statements, our data showed that most of the interindividual variability (IIV) of cefotaxime clearance was explained by GA and PNA, reflecting the influence of both antenatal and postnatal renal maturation. Renal function, as reflected by the serum creatinine concentration, did not show a significant impact on cefotaxime clearance in the present study. This can be explained by the narrow range of creatinine values; in addition, it is well-known that creatinine is not the best predictor of renal function in neonates, partly because of the influence of residual maternally derived creatinine (33, 34). The potential role of transporters in renal clearance will also have to be investigated in further studies (35).

The optimization of dosing for antimicrobial therapy should take into consideration developmental pharmacokinetics-pharmacodynamics, microbiology, and safety (36, 37). The pharmacokinetic-pharmacodynamic parameter that correlates with the clinical and bacteriological efficacy of β-lactam antibiotics is the percentage of time that the serum free drug concentration exceeds the MIC for the pathogen (time above the MIC [T_{MIC}]) (12, 38). While a T_{MIC} of at least 40 to 50% of the dosing interval is generally accepted in adults (39), the immunocompromised status of neonates (14, 15) requires a higher T_{MIC} target to ensure efficacy and to avoid the induction of antibiotic resistance (40, 41). We selected a T_{MIC} target of 75% of the dosing interval, which is consistent with the value used in other pharmacokinetic-pharmacodynamic studies of β-lactams in neonates (42–44).

Regarding microbiological aspects, the optimal dose of cefotaxime should cover the pathogens that most frequently cause neonatal sepsis. While group B streptococcus and *Escherichia coli* are the most common pathogens causing neonatal early-onset sepsis (EOS) (PNA, <7 days), coagulase-negative staphylococci, *Staphylococcus aureus*, *Escherichia coli*, and *Enterobacter* and *Klebsiella* species are most commonly isolated in neonatal late-onset sepsis (LOS) (PNA, ≥7 days) (13). The EUCAST susceptibility breakpoints were equal to or less than 2 μg/ml for most of these causative pathogens, except *Staphylococcus aureus*, for which an MIC of 4 μg/ml was required (16). We then selected MICs of 2 mg/liter and 4 mg/liter as the breakpoints for determination of the T_{MIC} for cefotaxime treatment of EOS and LOS, respectively.

From a safety point of view, there are limited side effects associated with cefotaxime use in neonates and infants (2). These are mainly hypersensitivity and gastrointestinal effects (45). Cefotaxime very rarely causes nephrotoxicity or seizures in neonates (46). The favorable safety profile observed in our population is in agreement with these previous findings. There is no reported correlation between drug exposure (AUC value) and adverse events in neonates. As our new dosage regimen recommends that the daily dosage of cefotaxime be increased in older newborns, we used the maximum and well-tolerated individual AUC from our population as a threshold for overdose risk. To ensure comparable safety profiles, we then verified that our model-based dosing regimen did not cause a level of cefotaxime exposure higher than this threshold. Our results have to be confirmed in a further toxicodynamic analysis.

One limitation of our study was that the concentration of desacetylcefotaxime, the metabolite of cefotaxime, was not quantified. The simultaneous quantification of both cefotaxime and desacetylcefotaxime might provide additional information on the level of maturation of the metabolic pathway. However, the contribution of desacetylcefotaxime to the bactericidal activity of cefotaxime therapy was reported to be low (47). Therefore, this issue has a limited impact on cefotaxime dosing optimization. Furthermore, we did not evaluate the cerebrospinal fluid pharmacokinetics of cefotaxime in this study; consequently, we do not provide any dosing recommendation for the treatment of neonatal meningitis.

The use of an opportunistic pharmacokinetic sampling design facilitated patient inclusion and provided dosing recommendations similar to those from a predetermined (i.e., scheduled) pharmacokinetic sampling design (7). However, as shown in our previous study (7), it might be not powerful enough to identify all significant covariates and could underpredict variability. The posterior dosage adaptation based on therapeutic drug monitoring might provide additional benefits to optimize individual antimicrobial therapy. Ultimately, a patient-tailored dose based on modeling and simulation has to be evaluated in clinical practice to confirm its clinical benefits.

Conclusion. A population pharmacokinetic model of cefotaxime in neonates and young infants was developed. Gestational age at birth, postnatal age, and current weight had significant impacts on cefotaxime pharmacokinetics. Dosing regimens of 50 mg/kg BID for newborns with a PNA of <7 days, 50 mg/kg TID for newborns with a PNA of ≥7 days and a GA of <32 weeks, and 50 mg/kg QID for newborns with a PNA of ≥7 days and GA of ≥32 weeks were established on the basis of developmental pharmacokinetic-pharmacodynamic analysis, along with the consideration of microbiological and safety aspects.

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