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Population Pharmacokinetics and Dosing Optimization of Ceftazidime in Term Asphyxiated Neonates during Controlled Therapeutic Hypothermia

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ABSTRACT Ceftazidime is an antibiotic commonly used to treat bacterial infections in term neonates undergoing controlled therapeutic hypothermia (TH) for hypoxic-ischemic encephalopathy after perinatal asphyxia. We aimed to describe the population pharmacokinetics (PK) of ceftazidime in asphyxiated neonates during hypothermia, rewarming, and normothermia and propose a population-based rational dosing regimen with optimal PK/pharmacodynamic (PD) target attainment. Data were collected in the PharmaCool prospective observational multicenter study. A population PK model was constructed, and the probability of target attainment (PTA) was assessed during all phases of controlled TH using targets of 100% of the time that the concentration in the blood exceeds the MIC ($T_{>MIC}$) (for efficacy purposes and 100% $T_{>4\times MIC}$ and 100% $T_{>5\times MIC}$ to prevent resistance). A total of 35 patients with 338 ceftazidime concentrations were included. An allometrically scaled one-compartment model with postnatal age and body temperature as covariates on clearance was constructed. For a typical patient receiving the current dose of 100 mg/kg of body weight/day in 2 doses and assuming a worst-case MIC of 8 mg/L for *Pseudomonas aeruginosa*, the PTA was 99.7% for 100% $T_{>MIC}$ during hypothermia (33.7°C; postnatal age [PNA] of 2 days). The PTA decreased to 87.7% for 100% $T_{>MIC}$ during normothermia (36.7°C; PNA of 5 days). Therefore, a dosing regimen of 100 mg/kg/day in 2 doses during hypothermia and rewarming and 150 mg/kg/day in 3 doses during the following normothermic phase is advised. Higher-dosing regimens (150 mg/kg/day in 3 doses during hypothermia and 200 mg/kg/day in 4 doses during normothermia) could be considered when achievements of 100% $T_{>4\times MIC}$ and 100% $T_{>5\times MIC}$ are desired.

KEYWORDS antimicrobial therapy, ceftazidime, neonates, population pharmacokinetics, therapeutic hypothermia

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Hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia is a serious clinical condition with considerable morbidity and mortality rates in term neonates (1). Controlled therapeutic hypothermia (TH) is currently the standard of care for neonates suffering from moderate to severe HIE after perinatal asphyxia as it has demonstrated a significant neuroprotective effect (2, 3). Antibiotics are frequently prescribed for asphyxiated neonates directly after birth and during controlled TH as perinatal infections cannot be reliably ruled out as a possible cause of asphyxia. However, controlled TH may alter antibiotic pharmacokinetics (PK) due to pathophysiological changes such as altered hepatic and renal clearance (CL), consequently influencing the achievement of PK/pharmacodynamic (PD) targets (4, 5).

Ceftazidime, a third-generation cephalosporin, is commonly used as a first-line treatment option for infections caused by *Pseudomonas aeruginosa*. It also has a high level of activity against many other Gram-negative pathogens such as *Escherichia coli* and *Klebsiella*. Ceftazidime exhibits low protein binding and is almost exclusively cleared unchanged via glomerular filtration, making the PK of ceftazidime susceptible to alterations in renal CL (6).

Timely and adequate treatment of neonatal infections is pivotal for preventing microbiological failure. The clinical outcome of ceftazidime is related to the time that the unbound drug concentration remains above the MIC of the targeted pathogen ($T_{>MIC}$) (7). However, a consensus regarding the minimum threshold is lacking. PK/PD target attainment of 100% $T_{>MIC}$ might suffice, but a more aggressive threshold of 100% $T_{>4\times MIC}$ or even 100% $T_{>5\times MIC}$ is suggested for critically ill patients to ensure treatment success and prevent resistance development (8). The latter is of particular concern when treating a proven infection with *P. aeruginosa* since this pathogen can acquire resistance to antimicrobial therapy through mutations (9).

Despite its widespread clinical use, the optimal dosage of ceftazidime for suspected or proven neonatal *P. aeruginosa* infections remains largely unknown, with studies suggesting a large range of different dosing regimens (10–12). Studies describing its PK in neonates during controlled TH are lacking. Therefore, the primary objective of this study is to describe the population PK of ceftazidime in asphyxiated neonates with HIE during all phases of controlled TH (i.e., hypothermia, rewarming, and normothermia). Also, a population-based rational dosing regimen with optimal PK/PD target attainment during controlled TH is proposed.

RESULTS

Patients and samples. A total of 35 term neonates were included, and 338 samples were available for analysis. In total, 15 samples (4%) were below the limit of quantification (LOQ) and were excluded from the data analysis. Patient characteristics and blood samples drawn are shown in Table 1. All patients were treated with an intermittent ceftazidime dosing regimen of 100 mg/kg of body weight/day in 2 doses. Plasma concentrations ranged from 0.52 mg/L to 219.6 mg/L. The ceftazidime concentration versus time after the dose is shown in Fig. S1 in the supplemental material.

Pharmacokinetic analysis. A one-compartmental model with first-order elimination provided the best fit for the logarithmically transformed ceftazidime data. The model was parameterized in terms of CL and the volume of distribution (V). Parameters were allometrically scaled *a priori* to a weight of 70 kg (allometric scaling parameters of 0.75 for CL and 1.0 for V) (13). Estimations of the allometric exponents of CL and V did not improve the model. The interindividual variability (IIV) could be estimated for CL and V and was correlated (r = 0.4). An additive-error model best described residual variability. During forward inclusion, body temperature (TEMP), postnatal age (PNA), urine output (UO), postmenstrual age (PMA), and gestational age (GA) were identified as significant covariates on CL (with decreases in the objective function values [OFVs] of 184.2, 180.6, 145.4, 86.0, and 4.9 points, respectively [$P < 0.05$]). After backward deletion, TEMP and PNA remained in the model with a significant association with CL ($P < 0.001$). No significant correlations were found between the covariates and V. Incorporating sigmoidal maturation models on CL did

TABLE 1 Patient characteristics and samples drawn[e]

Characteristic	Value for ceftazidime population ($n = 35$)[a]
No. of male patients (%)	20 (57.1)
Median birth wt (g) (range)	3,410 (2,500–4,745)
Median GA (wks) (range)[b]	40.6 (37.4–42.0)
Median PNA (days) (range)[c]	2.6 (2.0–5.3)
Median PMA (days) (range)[c]	286.8 (269.9–298.0)
Median SCr (μmol/L) (range)[d]	56.0 (27.7–113.0)
Median urine output (mL/kg/h) (range)[d]	3.0 (1.0–4.4)
Median ASAT (U/L) (range)[d]	85.5 (32.9–723.7)
Median ALAT (U/L) (range)[d]	38.0 (5.5–404.2)
No. of patients with MOF (%)[d]	23 (65.7)
No. of patients taking inotropic medication (%)[d]	25 (71.4)
Median Thompson score (range)[b]	10 (5–15)
Median duration ceftazidime treatment (days) (range)	3 (1–5)
Total no. of samples (range)	
During the study period	338
Per patient during the study period	10 (1–16)
During the hypothermic phase	193
Per patient during the hypothermic phase	7 (0–11)
During the rewarming phase	54
Per patient during the rewarming phase	1 (0–6)
During the normothermic phase	91
Per patient during the normothermic phase	2 (0–6)

[a]Baseline characteristics are depicted as medians and ranges for continuous variables and as numbers and percentages for categorical variables.
[b]Measured at admittance.
[c]Measured at the end of the study period.
[d]Measured throughout the study period.
[e]GA, gestational age; PNA, postnatal age; PMA, postmenstrual age; SCr, serum creatinine; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; MOF, multiorgan failure.

not improve and destabilized the model (14). With TEMP and PNA incorporated on CL in the model, the estimate for IIV on CL dropped from 34.4% to 24.7%. The final parameters are shown in Table 2. As shown by the visual predictive check (VPC) and the goodness-of-fit (GOF) plots, the final model had an acceptable fit (Fig. S2 and S3). The NONMEM control stream of the final model is shown in Data perhaps S4. Higher TEMP (33.5°C to 37.0°C) and PNA (days 2 to 5) increased the typical ceftazidime CL, with 33.8% and 22.3%, respectively.

Dosing simulations and PK/PD target attainment. The influence of TEMP and PNA on ceftazidime CL is illustrated in the simulated concentration-time profile for a dosing regimen of 100 mg/kg/day in 2 doses in a typical critically ill neonate (3,410 g) (Fig. 1). During the hypothermic phase (0 to 72 h), considerably higher ceftazidime concentrations were reached than in the rewarming (72 to 96 h) and normothermic

TABLE 2 Parameter estimates for the different model-building steps[a]

	Structural model		Final model[b]		Bootstrap ($n = 1,000$)		
Parameter	Estimate	RSE (%) (shrinkage)	Estimate	RSE (%) (shrinkage)	Estimate	2.5% CI	97.5% CI
CL (L/h/70 kg)	1.9	7	1.79	7	1.83	1.59	2.14
V (L/70 kg)	29.7	7	36.1	6	36.65	32.44	51.63
Additive error	0.325	10	0.23	11	0.22	0.18	0.27
IIV on CL (% CV)	34.4	10 (3)	24.7	11 (5)	25.5	19.3	37.1
IIV on *V* (% CV)	13.2	58 (38)	25	27 (16)	26.0	11.5	84.4
IIV on the additive residual error	47.5	16 (3)	56.7	19 (0.1)	52.4	24.5	75.4
PNA on CL			0.21	46	0.22	0.08	0.40
TEMP on CL			2.93	37	2.84	1.0	4.83

[a]CI, confidence interval; CL, clearance; CV, coefficient of variation {expressed as −1}; IIV, interindividual variability; PNA, postnatal age; RSE, relative standard error; TEMP, body temperature; *V*, volume of distribution; WT, weight; TVCL, typical value for clearance; TVV1, typical value for volume of distribution.
[b]For the final model, $TVCL = 1.79 \times (WT/70{,}000)_{0.75} \times (PNA/2.60)_{0.213} \times (TEMP/33.5)_{2.93}$ and $TVV1 = 36.1 \times (WT/70{,}000)_{1}$.

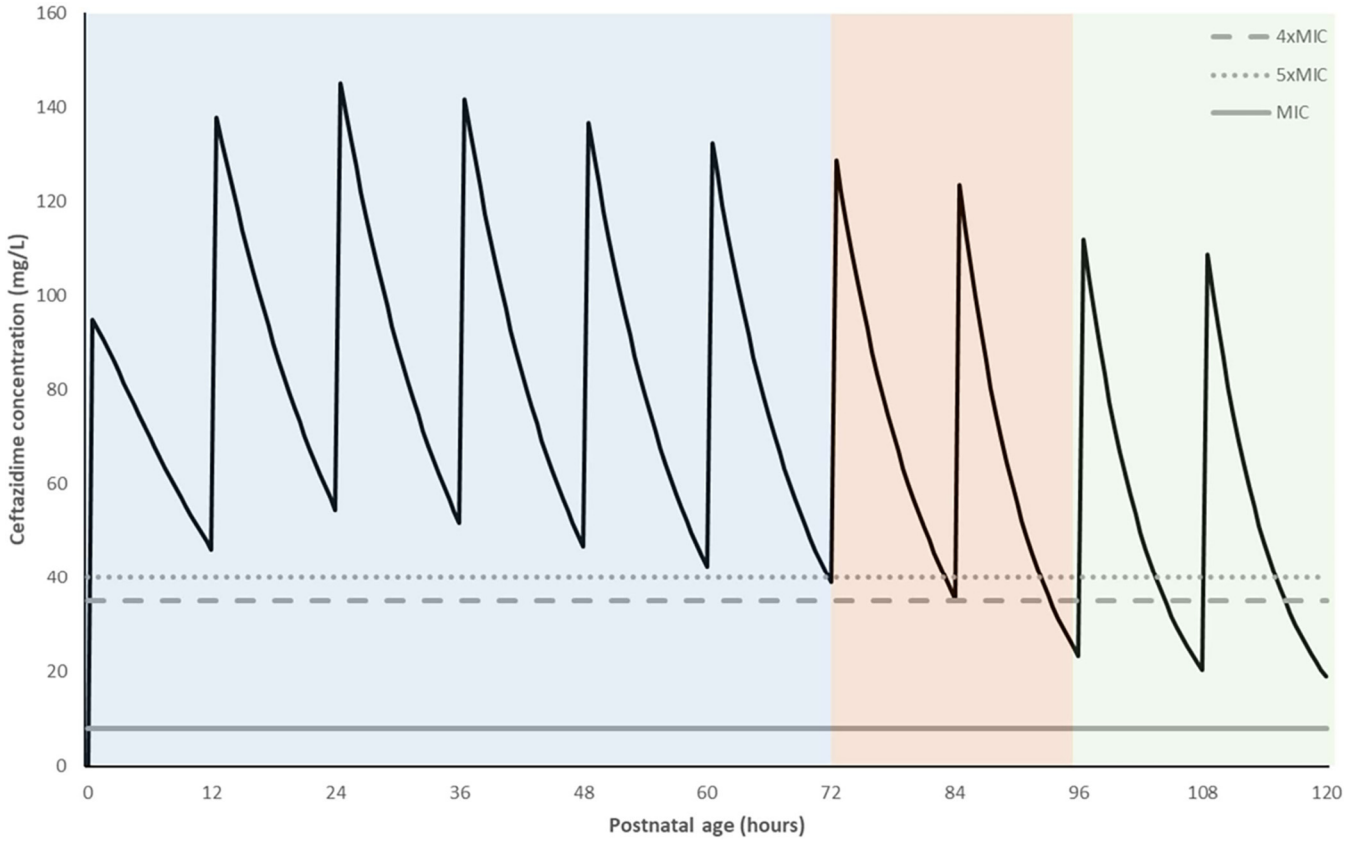

FIG 1 Illustration of the effect of TEMP on the concentration-time curve of ceftazidime for a typical patient (3,410 g) receiving 100 mg/kg/day in 2 doses. The MIC, 4× MIC, and 5× MIC are displayed for the worst-case MIC of 8 mg/L for *P. aeruginosa* (36). The blue box represents the hypothermic phase (0 to 72 h), the orange box represents the rewarming phase (72 to 96 h), and the green box represents the normothermic phase (>96 h).

(96 to 120 h) phases. Also, higher PK/PD targets (100% $T_{>4\times MIC}$ or 100% $T_{>5\times MIC}$) were not reached during the rewarming phase and the following normothermic phase.

The probabilities of target attainment (PTAs) for the different dosing regimens and different MICs were calculated at a PNA of 48 h for the hypothermic phase (Fig. 2) and subsequently at a PNA of 120 h, reflecting the following normothermic phase (Fig. 3).

During the hypothermic phase, simulations showed that the PTAs for the current dosing regimen (100 mg/kg/day in 2 doses) were 99.7% for 100% $T_{>MIC}$, 74.0% for 100% $T_{>4\times MIC}$, and 58.1% for 100% $T_{>5\times MIC}$ when targeting the worst-case MIC for *P. aeruginosa* of 8 mg/L. The same dosing regimen resulted in a PTA of 87.7% for 100% $T_{>MIC}$ and decreased PTAs of 13.6% and 5.8% for 100% $T_{>4\times MIC}$ and 100% $T_{>5\times MIC}$, respectively, for simulated neonates during the following normothermic phase.

The PTA during the hypothermic phase for the currently used dosing regimen of 100 mg/kg/day in 2 doses was ≥90% for 100% $T_{>MIC}$. For the higher PK/PD targets of 100% $T_{>4\times MIC}$ and 100% $T_{>5\times MIC}$, a dosing regimen of 150 mg/kg/day in 3 doses was needed to achieve a PTA of ≥90% (Fig. 2). During normothermia, a dosing regimen of 150 mg/kg/day in 3 doses was sufficient to achieve a PTA of ≥90% for 100% $T_{>MIC}$. However, a dosing regimen of 200 mg/kg/day in 4 doses was needed to reach a PTA of ≥90% for 100% $T_{>4\times MIC}$ and 100% $T_{>5\times MIC}$ during all phases (Fig. 3).

DISCUSSION

To the best of our knowledge, this is the first prospective study in which the population PK of ceftazidime in term asphyxiated neonates during controlled TH is evaluated and described.

A one-compartment model with allometric scaling best described the ceftazidime PK data. Interindividual variability could be largely explained by TEMP and PNA. A

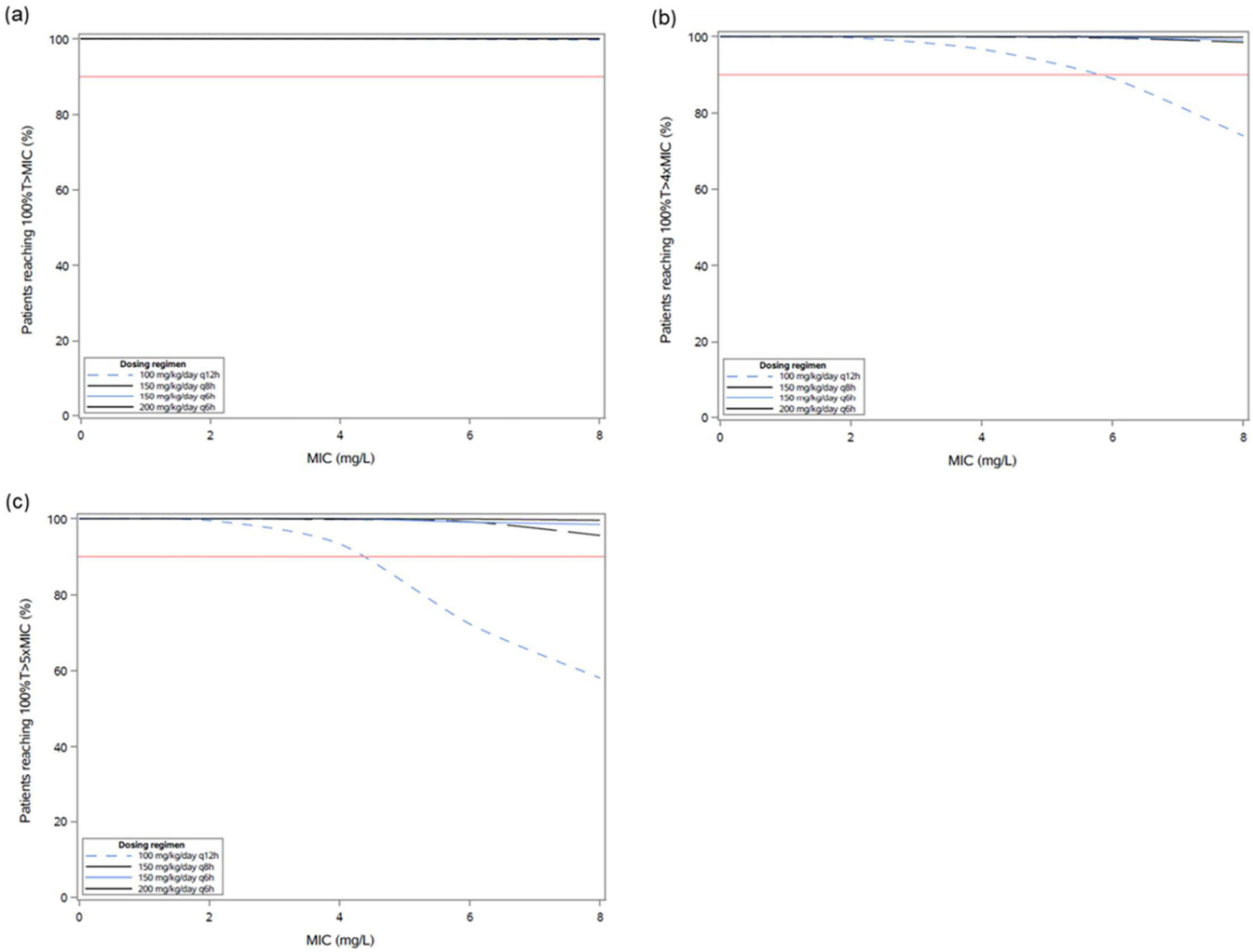

FIG 2 Monte Carlo simulations (n = 1,050) and PTA for achieving PK/PD target attainment at a PNA of 48 h (day 2 of hypothermia; median TEMP of 33.7°C) for four different ceftazidime i.v. dosing regimens administered to term asphyxiated neonates. (a) Achievement of 100% $T_{>MIC}$; (b) achievement of 100% $T_{>4\times MIC}$; (c) achievement of 100% $T_{>5\times MIC}$. The red lines indicate a PTA of ≥90%. q12h, every 12 h; q8h, every 8 h; q6h, every 6 h.

lower TEMP significantly reduces ceftazidime CL. TEMP having an influence on ceftazidime CL is not surprising as controlled TH decreases the heart rate and cardiac output, subsequently leading to reduced end-organ perfusion (15). Also, asphyxiated neonates are more at risk for multiorgan failure due to resuscitation, and this could also have a negative impact on ceftazidime CL (16). This may partially explain the low CL of 0.03 L/h/kg that we found compared to those in two recent studies on the PK of ceftazidime in nonhypothermic and nonasphyxiated Chinese term neonates (0.27 L/h/kg and 0.11 L/h/kg) (11, 12). Older neonates and infants (aged 1 to 81 days) were also included in those two studies, making their population and ours (neonates aged up to 5 days) difficult to compare. However, three relatively older studies conducted with term and preterm neonates showed CL values similar to ours, i.e., 0.04 L/h/kg in term asphyxiated neonates and 0.01 to 0.13 L/h/kg in preterm neonates (17–19).

We also identified PNA as an independent significant covariate for ceftazidime CL. Ceftazidime CL increases with PNA. Since ceftazidime is predominantly cleared via glomerular filtration, functional end-organ maturation is also expected to have an influence (20). In line with our findings, the above-mentioned PK studies by Li et al. and Wang et al. found age and PNA to be predictors of ceftazidime CL (11, 12). Additionally, the latter study also identified GA and PMA as significant covariates for CL (12). We observed a similar trend in our population for GA and PMA, but only PNA significantly improved our final model. The finding that PNA is the most influential

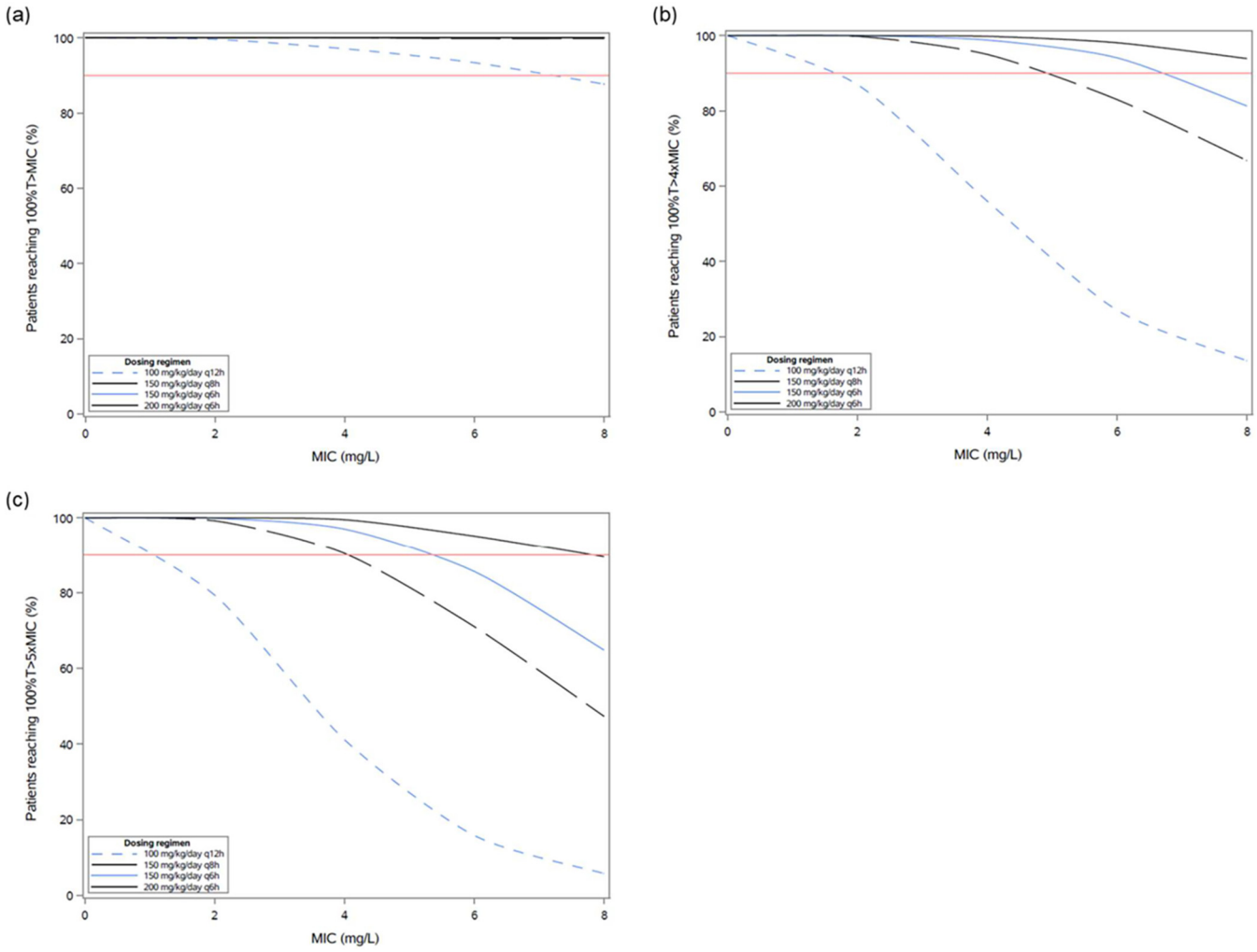

FIG 3 Monte Carlo simulations (n = 1,050) and PTA for achieving PK/PD target attainment at a PNA of 120 h (normothermia; median TEMP of 36.6°C) for four different ceftazidime i.v. dosing regimens administered to term asphyxiated neonates. (a) Achievement of 100% $T_{>MIC}$; (b) achievement of 100% $T_{>4\times MIC}$; (c) achievement of 100% $T_{>5\times MIC}$. The red lines indicate a PTA of ≥90%.

on CL instead of GA is congruent with previously reported findings (17, 18). A clear distinction between the effects of PNA and TEMP on CL is difficult. Both increase over time, with PNA increasing linearly but TEMP being constant during hypothermia and normothermia. Nevertheless, we were still able to differentiate between the two covariates: ceftazidime CL increased 22.3% from PNA day 2 to day 5 and 33.8% from hypothermia (33.5°C) to normothermia (37.0°C).

Surprisingly, serum creatinine (SCr) CL or UO proved not to be significant covariates in our PK model or the two above-mentioned PK models of Li et al. and Wang et al. (11, 12). In clinical practice, determining and defining kidney function in neonates remains a challenge as there is still no clear consensus on the normal ranges for the glomerular filtration rate for infants of different gestational ages or postnatal ages. Specific renal function biomarkers are not available for neonates. The SCr value in the first days of life also reflects maternal SCr and is therefore not a reliable parameter (21). We hypothesized that UO would be the most suitable predictor of ceftazidime CL, as we have seen previously for the fully renally cleared antibiotics amoxicillin and benzylpenicillin (22, 23). However, UO has a narrow distribution in our relatively small study population (median, 3.0 mL/kg/h [range, 1.0 to 4.4 mL/kg/h]), making it more difficult to determine its possible influence.

Our model-based simulations show that the PTA for achieving 100% $T_{>MIC}$ with ceftazidime at 100 mg/kg/day in 2 doses and 150 mg/kg/day in 3 doses is adequate when

targeting *P. aeruginosa* as a worst-case scenario for the vast majority of neonates during the hypothermic phase and the following normothermic phase, respectively. However, when deciding to target a more aggressive PK/PD threshold of 100% $T_{>4\times MIC}$ or 100% $T_{>5\times MIC}$, the current dosing regimen does not suffice. In that case, a dosing regimen of 150 mg/kg/day in 3 doses during hypothermia and 200 mg/kg/day in 4 doses during normothermia is needed. There is an especially high risk of not reaching these targets during normothermia. It can be debated whether these higher PK/PD targets should be pursued in neonates since research into maximizing the effectiveness of β-lactams in critically ill pediatric populations is lacking, and both 100% $T_{>MIC}$ and 100% $T_{>4\times MIC}$ are simultaneously used in studies (24). For antimicrobial stewardship reasons, treatment with ceftazidime for neonatal infections should be reserved for targeting *P. aeruginosa* since a strong correlation exists between ceftazidime usage and the prevalence of ceftazidime-resistant *P. aeruginosa* (25). In critically ill adults, a proven infection with *P. aeruginosa* has been shown to be an independent risk factor for microbiological failure and resistance development (8). A more aggressive PK/PD threshold of 100% $T_{>5\times MIC}$ seems to prevent colonization by multidrug-resistant *P. aeruginosa* isolates during antimicrobial treatment with β-lactam antibiotics (8, 9). Since 2010, EUCAST increased the MIC breakpoint of ceftazidime for *Pseudomonas* spp. from 4 to 8 mg/L to account for the full range of wild-type MIC distributions (26). As a result, doubling the ceftazidime dose when targeting *Pseudomonas* spp. in adults is advised (27). Since dosing recommendations for pediatric populations are based largely on research conducted well before 2010, this increased clinical breakpoint was not taken into account. Consequently, we believe that since the rate of mortality from *P. aeruginosa* bacteremia remains markedly high in pediatric populations, ceftazidime treatment should also be optimized in neonates, especially when considering that asphyxiated neonates are already by definition critically ill (28). However, clinical data on these higher targets of 100% $T_{>4\times MIC}$ and 100% $T_{>5\times MIC}$ in asphyxiated neonates are lacking, especially with regard to possible toxicity.

In our study, as well as in the above-mentioned studies, the relationship between ceftazidime concentrations and toxicity was not investigated. Ceftazidime is a drug with low toxicity, and no formal cutoff concentration for toxicity has been defined (29). In children with cystic fibrosis, relatively high ceftazidime doses are administered, which are generally well tolerated (30). As for other β-lactam antibiotics, neurotoxicity has been reported for ceftazidime, especially in elderly patients with renal failure (29). Neonatal neurotoxicity has rarely been seen (31). Some suggest using the cutoff trough concentration for toxicity of 100 mg/L of cefepime as a surrogate for ceftazidime, but there is no evidence to substantiate this (32). Especially when targeting a difficult-to-treat pathogen such as *P. aeruginosa*, the risk of toxicity should be balanced carefully with inadequate treatment. In our study, 25% and 10% of the simulated neonates had trough levels above 100 mg/L during hypothermia and normothermia, respectively, when using a dosing regimen for the PK/PD target of 100% $T_{>5\times MIC}$ of 150 mg/kg/day in 3 doses during hypothermia and 200 mg/kg/day in 4 doses during normothermia. Consequently, this would also lead to higher maximum plasma levels, for which an extended infusion of ceftazidime may prove valuable. Continuous infusion is often not possible in neonates due to sparse intravenous (i.v.) access. Research into different administration modes and PK/PD target attainment and toxicity in neonates is warranted.

When comparing our proposed dosing regimen of 100 mg/kg/day in 2 doses and 150 mg/kg/day in 3 doses to the regimens in the existing literature, we found similar and somewhat higher dosing regimen suggestions of 180 mg/kg/day in 3 doses (for a body weight of 3 kg, a PMA of >300 days, and an MIC of 8 mg/L) and 140 mg/kg/day in 3 doses (for a GA of >37 weeks) in older nonasphyxiated neonates not receiving controlled TH (11, 12). Those two studies used a PTA of 70% $T_{>MIC}$ for a worst-case MIC of 8 mg/L, while we primarily targeted 100% $T_{>MIC}$ for efficacy purposes.

Our study has some limitations to address. First, we validated our model internally by using a resampling of the patients in our study. Using an external data set to further validate our model would increase the external validity. Our model-derived dosing regimens should be prospectively validated. Also, we were not able to include a sigmoidal maximum-effect (E_{max}) maturation function on clearance to account for the further effect of kidney maturation after birth on ceftazidime CL since this did not improve our model. Second, we could not compare our findings to those for a historic control group including noncooled asphyxiated neonates as controlled TH is the standard of care. Moreover, since our findings showed a risk for underexposure to ceftazidime in term asphyxiated neonates, we recommend further studies with the inclusion of nonasphyxiated and noncooled neonates. Third, no MICs of ceftazidime for *P. aeruginosa* or other pathogen isolates were determined at the time as this was not in the scope of the primary study. Nevertheless, our data provide good insight into the PK/PD target attainment of the dosing regimen currently used in clinical practice and underline the need for further research into ceftazidime dosing optimization, especially in normothermic and nonasphyxiated neonates since ceftazidime CL is expected to be higher than that in asphyxiated neonates.

In conclusion, this is the first prospective study in which the PK of ceftazidime, the interpatient variability, and the covariates affecting this variability have been evaluated in term asphyxiated neonates during controlled hypothermia. We demonstrate that both TEMP and PNA have an effect on ceftazidime CL and, therefore, PK/PD target attainment. Neonates are at risk for underexposure during the normothermic phase, especially when targeting a pathogen with an increased MIC. During controlled TH, a dosing regimen of 100 mg/kg/day in 2 doses during hypothermia and rewarming and 150 mg/kg/day in 3 doses during normothermia is advised.

MATERIALS AND METHODS

Study design. This analysis comprised data from the PharmaCool study, a large multicenter prospective observational cohort study conducted in all 10 Dutch and 2 Belgian neonatal intensive care units (NICUs) between November 2010 and October 2014 (WHO International Clinical Trials Registry Platform identifier NTR2529 [https://trialsearch.who.int]). The PharmaCool study protocol was approved by the Institutional Review Board of each participating center. The study design and population were described in detail previously (33).

Study population. The study population consisted of asphyxiated term neonates, all undergoing controlled TH (33). In short, term newborns (gestational age [GA] of >37 weeks) were eligible for inclusion if they had an Apgar score of <5 at a postnatal age (PNA) of 5 min, had continued resuscitation at a PNA of 10 min, had 1 postnatal blood gas analysis with pH <7.0 or a base deficit of >16, had a Thomson sore of >7, and underwent TH at a PNA of <6 h. Exclusion criteria were defined as the presence of congenital hepatic or renal pathology, no central venous line or arterial bloodstream access, or no parental consent.

Controlled TH aims to decrease and stabilize the core body temperature (TEMP) to 33.5°C for 72 h, after which neonates are rewarmed to normothermia (36.5°C) within a time frame of 8 h according to national protocols (33).

Sample and data collection. Patient-specific, demographic, clinical, and laboratory data were collected for each patient, including GA, birth weight, sex, Thompson score, Apgar score, cause of asphyxia, extent and duration of resuscitation, need for a ventilator and/or inotropic support, comedication, mean daily urinary output (UO), serum creatinine (SCr), urea, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and multiorgan failure (MOF). MOF was defined as renal and/or liver failure on top of the existing encephalopathy due to perinatal asphyxia (33). Ceftazidime was dosed as an intermittent intravenous bolus injection of 100 mg/kg/day in 2 doses. The dosing schedule for ceftazidime has not been altered since the above-mentioned study period (30).

Blood samples were drawn from indwelling arterial lines at fixed time points during hypothermia (days 2 and 3), rewarming (day 4), and normothermia (day 5) (33). All samples were directly centrifuged, stored at −80°C, and transported to the central laboratory of Amsterdam UMC Location University of Amsterdam, Pharmacy and Clinical Pharmacology, The Netherlands (33). Ceftazidime plasma samples were analyzed using a validated zwitterionic hydrophilic interaction chromatography-tandem mass spectrometry (ZIC-HILIC-based LC-MS/MS) method. In short, total serum concentrations were measured since the level of ceftazidime protein binding is low (typically <10%) (34). The detection range of the method was 0.5 to 40 mg/L. The accuracy and imprecision at concentrations of 0.5, 10, and 40 mg/L were 103.3% and ≤10.4%, 95.7% and ≤7.3%, and 104.4% and ≤5.7%, respectively. Samples containing concentrations above the higher limit of quantification were diluted 10 times and reanalyzed.

Population pharmacokinetic modeling. Ceftazidime concentration data were analyzed using the first-order conditional estimation with interaction (FOCE-I) algorithm in NONMEM nonlinear mixed-effects modeling software (version 7.4.2; Icon Development Solutions, Gaithersburg, MD, USA).

The model-building process was performed in a stepwise manner, as follows: (i) choice of structural model, (ii) choice of error model, (iii) choice of covariate model, and (iv) model evaluation. One-, two-, and three-compartment models were fitted to the log-transformed data. The population PK of ceftazidime was characterized in terms of CL and the volume of distribution (*V*). Interindividual variabilities (IIVs) in the PK parameters were estimated. Allometric relationships were tested to account for the varying body weights of the neonates and their influence on PK parameters (14). Weight was normalized to a general weight of 70 kg to allow a comparison of parameter estimates to the results previous studies. Since neonates are subjected to organ maturation, maturation models were tested to evaluate the influence of maturation on PK parameter estimates (35). The likelihood ratio test was used to evaluate statistical significance between models (reduction in the objective function value [OFV] of ≥3.8 points, corresponding to a *P* value of <0.05 based on a χ^2 test with 1 degree of freedom). Residual variability was modeled with additive- or proportional-error model or both, and the incorporation of IIV into error parameters was tested.

Covariates that potentially influence ceftazidime CL were predefined based on their biological plausibility and the available literature. Continuous covariates were modeled using a power function equation, where θ_1 is the typical value of the parameter (*P*) in a patient with the median covariate value (COV_{median}) and θ_2 is the fractional change in *P* with each unit of deviation from COV_{median}:

$$P = \theta_1 \times \left(\frac{\mathrm{COV}}{\mathrm{COV}_{\mathrm{median}}}\right)^{\theta_2}$$

Categorical variables were included as follows, where θ_1 is the typical value of the parameter (*P*) for category 1 and θ_2 is the fractional change in *P* between categories 1 and 2:

$$P = \theta_1 \times \theta_2^{\mathrm{COV}}$$

Covariate analysis followed a forward-and-backward-selection process. During this first step, an OFV decrease of ≥3.8 points was considered statistically significant. A more stringent decrease in the OFV of ≥10.83 (*P* value of <0.001) was used in the second part.

Internal validation of the final model was performed using a visual predictive check (VPC) with 1,000 simulations. The robustness of the model was tested by means of a bootstrap analysis with 1,000 simulations.

Dosing simulations. Using the empirical Bayesian estimates from the final PK model, concentration-time profiles were predicted for a dosing regimen of 100 mg/kg/day in 2 doses. This dosing regimen is used in clinical practice in The Netherlands and Belgium for neonates with a PNA of <1 week and a birth weight of ≥2,000 g (30). With this dosing regimen, ceftazidime concentrations were simulated during the first 5 days of life for a typical patient undergoing controlled TH.

Second, the probability of target attainment (PTA) was calculated for different dosing regimens (100 mg/kg/day in 2 doses, 150 mg/kg/day in 3 doses, 150 mg/kg/day in 4 doses, and 200 mg/kg/day in 4 doses). The PTA was defined as the percentage of virtual patients with a ceftazidime concentration above the MIC for a targeted pathogen during the entire dosing interval (100% $T_{>MIC}$). Also, higher thresholds of 100% $T_{>4\times MIC}$ and even 100% $T_{>5\times MIC}$ were tested for achievement. Dosing regimens with a PTA of ≥90% during the hypothermic phase and the following normothermic phase were considered optimal. The target MICs were based on the wild-type MIC distribution for *P. aeruginosa*, with a EUCAST epidemiological cutoff (ECOFF) value of 8 mg/L being the worst-case scenario (36). The MICs for other pathogens susceptible to ceftazidime are considerably lower. Simulation data sets were created by replicating every patient within the original data set 30 times, leading to a simulation data set of 1,050. The PTAs for the different dosing regimens were calculated for individual-predicted trough concentrations at a PNA of 48 h (day 2 of the hypothermic phase) and subsequently at a PNA of 120 h (day 5, reflecting the normothermic phase).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, DOCX file, 0.1 MB.

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