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Determining Population and Developmental Pharmacokinetics of Metronidazole Using Plasma and Dried Blood Spot Samples from Premature Infants

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Abstract

Background—Limited pharmacokinetic (PK) data of metronidazole in premature infants has led to various dosing recommendations. Surrogate efficacy targets for metronidazole are ill-defined and therefore aimed to exceed minimum inhibitory concentration of organisms responsible for intra-abdominal infections.

Methods—We evaluated the PK of metronidazole using plasma and dried blood spot (DBS) samples from infants 32 weeks gestational age in an open-label, PK, multicenter (N=3) study using population PK modeling (NONMEM). Monte Carlo simulations (N=1000 virtual subjects)

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were used to evaluate the surrogate efficacy target. Metabolic ratios of parent and metabolite were calculated.

Results—Twenty-four premature infants (111 plasma and 51 DBS samples) were enrolled: median (range) gestational age at birth 25 (23–31) weeks, postnatal age 27 (1–82) days, postmenstrual age (PMA) 31 (24–39) weeks, and weight 740 (431–1466) g. Population clearance (CL, L/h/kg) was $0.038 \times (\text{PMA}/30)^{2.45}$ and volume of distribution (L/kg) of 0.93. PK parameter estimates and precision were similar between plasma and DBS samples. Metabolic ratios correlated with CL.

Conclusion—Simulations suggested the majority of infants in the neonatal intensive care unit (>80%) would meet the surrogate efficacy target using PMA-based dosing.

Keywords

neonate; drug; pharmacokinetics; metronidazole; dried blood spots

Metronidazole is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with serious infections caused by susceptible anaerobic bacteria but is not approved for use in children. In spite of this, metronidazole is extensively used “off-label” in children to treat anaerobic intra-abdominal infections (e.g., perforated appendicitis).¹ In premature infants, metronidazole use is typically restricted to treatment of anaerobic bacteremia, central nervous system infections, and complicated intra-abdominal infections such as necrotizing enterocolitis.^{2,3} Because infection in premature infants is associated with devastating outcomes including death and neurodevelopmental impairment,^{4,5} appropriate dosing recommendations for agents such as metronidazole are needed. Recommended metronidazole dosing for premature infants in sources such as Neofax and The Harriet Lane Handbook^{6,7} rely on multiple combinations of birth weight, postmenstrual age (PMA), and postnatal age (PNA), which are cumbersome to implement clinically and, more importantly, are supported by very small and limited clinical trials in this population.

The clinical pharmacology of metronidazole has not been well characterized in either premature or term neonates and young infants. While the drug is extensively metabolized by the liver, the predominant pathways for its biotransformation have not been well described.⁸ An impact of ontogeny on metronidazole clearance is presumed in that the half-life in infants is 2–3 times longer when compared with adults,⁹ and PMA is associated with systemic clearance.^{10,11}

Pharmacokinetic (PK) studies in neonates and young infants are scarce due in large part to the difficulty in obtaining repeated blood samples in numbers sufficient to accurately estimate both individual and population-specific PK parameters. To overcome this challenge, the use of ultra-low-volume sampling techniques such as dried blood spots (DBS) to evaluate the PK of drugs is increasing. DBS require only 30 µL of whole blood for PK sampling—an approximately 20 times lower sample volume than in traditional venous or arterial samples. The advantages of DBS extend beyond favorable PK sample volumes. For example, DBS do not require centrifugation or freezing of the sample prior to analysis and provide a measurement of drug concentration in whole blood—a potential consideration for drugs capable of extensively partitioning into the red blood cell. Despite the attributes of DBS and the fact that the technology has been used for decades in pediatrics for screening of inborn errors of metabolism, its use to support pediatric PK studies is limited to one published report¹¹ that evaluated the PK of metronidazole with DBS samples collected from premature infants during routine medical care. The report, however, did not assess the in vivo comparability of DBS and plasma samples. To address this information gap, we

conducted a PK study of metronidazole in premature infants using plasma and DBS samples.

METHODS

Study Design

This was an open-label, prospective, early-phase, multi-center (N=3), PK and safety study of metronidazole in premature infants 32 weeks gestational age at birth (GA) and <91 days PNA with suspected serious infection. Infants were excluded if they had a history of anaphylaxis to metronidazole or nitromidazole derivatives. Metronidazole was administered intravenously over 30 minutes as a loading dose (15 mg/kg) followed by maintenance doses (7.5 mg/kg) every 12 (<14 postnatal days; cohort 1) to 24 hours (14–90 postnatal days; cohort 2) for up to five days. Clinical data were collected through an electronic data capture system and included demographic information (e.g., GA, PNA, birth weight, current weight, race, sex, ethnicity), laboratory values (e.g., serum creatinine, liver function tests, albumin) if obtained with routine medical care, concomitant medications of interest (all antimicrobials, cimetidine, and phenobarbital), and microbiological cultures from sterile sites. The study was approved by the institutional review boards at each center, and informed consent was obtained from a parent or guardian prior to enrollment.

PK Sample Collection

PK samples (200 µL) were collected around the loading dose and after a minimum of three doses as follows: within 30 minutes prior to infusion of study drug; within 10 minutes, 3–4 hours, 6–8 hours after the end of the infusion; and within 30 minutes prior to the next dose. Samples were also collected as follows for cohort 1: 24–25 hours, 48–49 hours, and 72–73 hours, and for cohort 2: 12–13 hours, 24–25 hours, and 36–37 hours after the end of infusion of study drug. Due to the critically ill nature of the subjects, deviation from the planned sampling scheme occurred. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and refrigerated or placed on ice immediately after collection and then centrifuged (4°C) for 10 minutes. Plasma was transferred into bar-coded cryovials prior to storage at –70°C. DBS samples (30 µL) were collected at the same time as plasma PK samples by directly placing (spotting) whole blood into Type C DMPK Wattman Cards; two spots were collected at each time point. Samples from all participating sites were shipped on dry ice to a central laboratory where they were stored at –70°C for a maximum of nine months prior to analysis.

Bioanalytical Assay

A liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) assay for metronidazole and hydroxy-metronidazole detection in human plasma (10 µL) and DBS (30 µL and 3 mm punch) was developed and validated according to FDA guidance and Good Laboratory Practice regulations. Sample analysis was performed on a triple quadrupole mass spectrometer Thermo Fisher TSQ Quantum Ultra AM (Thermo Fisher Scientific, Waltham, MA, USA) operated with positive mode, electrospray ionization. Instrument parameters were optimized for metronidazole (172 → 128 m/z) and hydroxy-metronidazole (188 → 123 m/z) transitions. Deuterated metronidazole and hydroxy-metronidazole were used as internal standards. HPLC separation was achieved using an Agilent Poroshell SB C18 reverse-phase (Agilent Technologies, Santa Clara, CA, USA) with a flow-rate of 0.2 ml/min using a gradient mobile phase. Mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of methanol. Analytical data were acquired by LC Quan (Version V2.5.6, Thermo Fisher Scientific, Waltham, MA, USA). The lower limit of quantitation of metronidazole and hydroxy-metronidazole in plasma and DBS was 0.05 mg/L. Parent drug and metabolite were extracted from plasma via protein precipitation and from DBS using

methanol solvent. Intraday and interday coefficients of variation for parent drug and metabolite in plasma and DBS were <14% at concentrations ranging from 0.05–50 mg/L.

Population PK Analysis

PK data were analyzed with a nonlinear mixed effect modeling approach using the computer program NONMEM (version 7) in conjunction with WINGS for NONMEM version 7.03 (Auckland, NZ). Plasma samples were used in the model-building process. Output was summarized using STATA 10 (College Station, TX, USA). The first-order conditional estimation method with interaction was used for all model runs. One- and two-compartment structural PK models were evaluated. Inter-individual (IIV) random effects were evaluated on clearance (CL) and volume (V). An exponential model for IIV variance was used, and a proportional error model was deemed appropriate to describe residual variability. The potential impact of clinical covariates on PK parameters was explored if a relationship was suggested by visual inspection of scatter and box plots (continuous and categorical variables, respectively) of the individual deviations from the population-typical value for CL and V (ETAs) against covariates. Body weight was assumed to be a significant covariate for CL and V and was included in the base model prior to assessment of other potential covariates. The following covariates were evaluated: GA (weeks), PNA (days), PMA (defined as GA plus PNA in weeks [PNA/7]), serum creatinine, albumin, race, sex, ethnicity, and concomitant medication use. Once covariates were identified by visual inspection and physiologic plausibility, incorporation of covariates into the model was planned via standard forward addition backward elimination methods. Covariates that reduced the objective function by more than 3.84 ($P < 0.05$) during univariable analysis were to be included in a subsequent multivariable analysis. In the multivariable step, a reduction of 7.88 ($P < 0.005$) was required for retention of a covariate in the final model. Continuous covariates were scaled to their median values. Covariates that exhibited time-dependent changes (e.g., weight, PNA) were permitted to change with time. Missing body weights and laboratory values were imputed with closest value carried forward or back filled for up to 7 days. Missing serum creatinine values were imputed based on an exponential model of serum creatinine and PMA derived from the data.¹² Empirical Bayesian estimates of individual infant PK parameters were generated from the final model using the post-hoc subroutine and were summarized by cohort.

Model Evaluation

Models were evaluated based on successful minimization, goodness-of-fit plots, precision of parameter estimates, bootstrap procedures, and visual predictive check. The precision of the final population PK model parameter estimates were evaluated using non-parametric bootstrapping (1000 replicates) to generate the 95% confidence intervals for parameter estimates. For the visual predictive check, the final model was used to generate 1000 Monte Carlo simulation replicates per time point of metronidazole exposure, and simulated results were compared with those observed in the study. The number of observed concentrations outside of the 90% prediction interval for each time point was quantified. The dosing and covariate values used to generate the predictions in the visual predictive check were the same as those used in the study population. A predictive performance check was also performed. Root mean square error and mean absolute error were calculated from the data from all subjects included in the analysis.¹³

Metabolic Ratio

The metronidazole metabolic ratio was calculated for each subject by dividing the hydroxy-metronidazole area under the curve (AUC) during a steady-state dosing interval (AUC_{tau}) by the parent AUC_{tau} . The observed data were used to calculate AUC using the trapezoidal rule with non-compartmental methods in Phoenix WinNonLin (Certa, Cary, NC, USA). The

relationship between metronidazole weight-normalized CL derived from the final population PK model and metabolic ratio was explored visually using scatter plots. Metabolic ratios between infants who achieved the surrogate pharmacodynamic (PD) target and those who failed to meet the target were compared using the Mann-Whitney test.

Assessment of Dose-exposure Relationship

For a target efficacy exposure, we used a minimum inhibitory concentration (MIC) of 8 mg/L. This MIC target is consistent with the Clinical and Laboratory Standards Institute (CLSI)-recommended MIC susceptibility breakpoint of metronidazole for anaerobic organisms.¹⁴ A conservative approach was used when selecting metronidazole minimum concentrations at steady state ($C_{min,ss}$, troughs) as the surrogate PK-PD target for this critically ill population. Well-defined surrogate efficacy PK-PD targets for metronidazole against anaerobic bacteria are lacking,¹⁵ and prior investigators have used $C_{min,ss}$ to optimize metronidazole dosing in infants.^{10,11} In addition, target exposures of 2 mg/L were also evaluated as those represent MICs commonly identified in clinical practice.^{16,17} Metronidazole exposures in the study population were compared with exposures achieved in adults treated with metronidazole for intra-abdominal infections.¹⁸ Metronidazole peak and trough concentrations at steady state were predicted for each subject using individual empirical Bayesian estimates from the final model and dosing prescribed in the study. The proportion of subjects in the study who met the surrogate PD target was calculated by cohort.

The final population PK model was used to explore dose-exposure relationships of commonly used metronidazole dosing recommendations listed in Neofax,⁶ the Harriet Lane Handbook,⁷ and a previously proposed PMA-based dosing regimen.¹⁰ Monte Carlo simulations were used to simulate metronidazole exposures in 1000 subjects randomly selected from the Pediatrix Medical Group database. This administrative database contains information of all infants (N~800,000) discharged from 322 U.S. neonatal intensive care units managed by the Pediatrix Medical Group from 1997 to 2011. The database prospectively captures information from daily progress notes generated by clinicians on all infants cared for by the Pediatrix Medical Group. Demographic ranges for GA, PNA, PMA, and serum creatinine were included when generating the random sample to match demographic distribution of study subjects. Subjects were randomly selected from all infants with suspected infection, defined as having a blood culture obtained and receiving ampicillin, gentamicin, or both on the day of the culture. Random numbers were generated from the uniform distribution using the pseudo-random number generator from STATA 10 (College Station, TX, USA). The proportion of simulated subject profiles that met the surrogate PD target was calculated for each dosing recommendation guideline.

DBS Analysis

Differences in drug concentrations between plasma and DBS specimens were evaluated in the random effects error model of the final population model using a fixed effect parameter (σ_{DBS}), as well as separate residual variability estimates for plasma and DBS samples in NONMEM. In addition, population PK parameters were estimated separately using plasma and DBS samples (NONMEM), and the percent difference between PK parameter estimates with DBS samples relative to plasma was calculated. Linear regression was used to evaluate the correlation between plasma and DBS metronidazole and hydroxy-metronidazole concentrations in paired plasma-DBS samples, as well as the correlation between DBS-to-plasma concentration ratio and plasma concentrations using STATA 10 (College Station, TX, USA).

RESULTS

Study Population

Twenty-four subjects from three centers were enrolled in this opportunistic, open-label PK study (Table 1). The cohort represented a convenience sample of patients who required medical treatment with metronidazole based either upon microbiologic culture results or signs of clinically presumed infection. The median (range) maintenance dose was 7.4 mg/kg (4.2–15.6), and 21 patients received a median (range) loading dose of 15.0 mg/kg (13.6–19.0).

PK Specimens

Of 134 plasma PK samples collected, 23 were excluded from the population PK analysis: one lacked sufficient sample volume for analysis, 16 were baseline samples prior to first dose of study drug (concentration = 0), and six were potentially contaminated; 111 plasma samples were used in the modeling process. Fifty-one DBS samples (46 concurrent with plasma) from 23 subjects were collected; one was excluded from the population PK analysis for the same reason as a corresponding plasma sample. The median (range) of plasma PK sampling time was 7.4 (0.5–72.6) hours after dose, and the median concentration was 12.8 (0.6–33.9) mg/L. An average of 4.8 plasma samples per infant (range 1–11) was included in the analysis.

Population PK Model Building

Application of standard goodness-of-fit criteria revealed that a one-compartment model provided the best fit of the drug concentration vs. time data (see Figure, Supplemental Digital Content 1, <http://links.lww.com/INF/B551>). Body weight was included in the base CL and V models using a power function with a fixed exponent of 1 (see Table, Supplemental Digital Content 2, <http://links.lww.com/INF/B552>). Estimation of the body size exponent (weight¹) and allometric scaling (weight^{3/4}) of CL were explored as potential body size models for CL; however, they were rejected due to lack of improvement in model fit. Surrogate markers of ontogeny of drug-metabolizing enzymes (PNA, PMA) as well as serum creatinine showed correlation with individual deviations from the typical CL value (ETA1); however, only PNA and PMA resulted in a significant decrease in the objective function value (OFV) (see Table, Supplemental Digital Content 2, <http://links.lww.com/INF/B552>). The largest drop in OFV occurred when PNA was added to the model (see Table, Supplemental Digital Content 3, <http://links.lww.com/INF/B553>); however, the PMA model was selected as the final model and used to optimize dosing because PMA-based dosing has compared favorably with other regimens in a prior metronidazole PK study.¹⁰ In addition, PMA-based dosing would integrate better with other neonatal populations and dosing transitions with current dosing recommendations. A multivariable step was not performed because no other covariates were significantly associated with metronidazole CL.

Population PK Model Evaluation

The PMA model had good precision as evidenced by relative standard errors around the CL and V parameter point estimates of 3–10% and by 95% confidence intervals generated by bootstrapping (N=1000 simulated trials, 100% successful runs) (see Table, Supplemental Digital Content 3, <http://links.lww.com/INF/B553>). Goodness-of-fit diagnostic plots for the final model are shown in Figure, Supplemental Digital Content 1, <http://links.lww.com/INF/B551>. The visual predictive check revealed a good fit between observed and predicted metronidazole concentrations (see Figure, Supplemental Digital Content 1, <http://links.lww.com/INF/B551>); 4.5% (5/111) of observed concentrations were outside of the

90% prediction interval. The root mean square error and mean absolute error were 1.50 mg/L and 0.19 mg/L, respectively.

Bayesian Estimates of CL, V, Half-life, and Metabolic Ratio

The median individual empirical Bayesian estimates for CL, V, and apparent elimination half-life were summarized by PNA cohort (Table 2). There was a trend towards increasing median metronidazole weight-normalized CL and decreasing half-life with increasing PNA group. Consistent with the influence of maturational covariates on metronidazole CL in the final population PK model, half-life decreased with increasing PMA (see Figure, Supplemental Digital Content 4, <http://links.lww.com/INF/B554>). Seventeen subjects (PNA and PMA median [range] 31 [1–83] days and 32 [25–39] weeks, respectively) had sufficient observed concentration vs. time data to reliably calculate hydroxy-metronidazole AUC after multiple doses. Hydroxy-metronidazole exposure (AUC_{tau}) represented only 12% (range 1.3–103) of total metronidazole exposure (AUC_{tau}). Weight-normalized CL increased with increasing metabolic ratio, and infants in the oldest cohort had the highest metabolic ratios (see Figure, Supplemental Digital Content 4, <http://links.lww.com/INF/B554>). Of 17 infants with metabolic ratio data, 13 (76%) had predicted metronidazole trough concentrations at steady state ≥ 8 mg/L and had lower metabolic ratios relative to infants with trough concentrations < 8 mg/L (median 0.11 [range 0.01–0.31] vs. 0.40 [0.11–1.03], $P=0.023$).

Dose-exposure Relationship

In cohort 1, 56% (5/9) of participants achieved the conservative surrogate PD target (steady-state trough concentrations $>$ than a MIC of 8 mg/L), whereas 67% of participants in cohort 2 achieved the surrogate PD target with the protocol-derived dosing. Median trough concentrations at steady state ($C_{min,ss}$) were lower for the youngest participants (PNA < 14 days) when compared with infants in cohort 2. In spite of this finding, the overwhelming majority of infants achieved predicted metronidazole trough concentrations > 2 mg/L (Table 2). The PMA-based dosing regimen in Monte Carlo simulations achieved exposures comparable with adults and compared favorably with dosing regimens recommended in Neofax⁶ and the Harriet Lane Handbook (see Figure, Supplemental Digital Content 4, <http://links.lww.com/INF/B554>).⁷ The simulated mean (standard deviation [SD], range) maximum and minimum metronidazole concentrations at steady state were 24.6 (10.3, 8.1–72.1) mg/L and 16.9 (10.1, 1.6–63.9) mg/L, respectively. Eighty percent of infants from the Pediatrix Medical Group database achieved the conservative surrogate PD target, and 99% achieved metronidazole trough concentrations > 2 mg/L. This finding was maintained across PMAs (Table 2; Figure, Supplemental Digital Content 4, <http://links.lww.com/INF/B554>).

DBS Analysis

There were 50 DBS concentrations included in the NONMEM analysis including both plasma and DBS concentrations. On average, metronidazole concentrations in DBS samples were approximately 15% lower than those measured from plasma. When point estimates were estimated using plasma or DBS samples alone, the values for typical population PK parameters (CL, V) and residual errors were similar (within 15%) (see Table, Supplemental Digital Content 3, <http://links.lww.com/INF/B553>). Of the 50 DBS samples, 46 were collected within 30 minutes of a plasma sample. Forty-five samples were included in the linear regression analysis for the parent compound. One outlier metronidazole concentration (DBS concentration = 12.2 mg/L and corresponding plasma concentration = 3.2 mg/L) was excluded. Forty-three samples were included for the linear regression analysis of the metabolite; two concentrations were below the limit of assay quantification. A strong correlation between DBS and plasma samples was observed (see Figure, Supplemental Digital Content 5, <http://links.lww.com/INF/B555>). This was evident for both parent ($r^2 = 0.95$, slope = 0.80 [95% confidence interval 0.74, 0.85], $P < 0.001$) and metabolite

concentrations ($r^2 = 0.95$, slope = 0.79 [0.73, 0.85], $P < 0.001$). The DBS vs. plasma concentration relationship was maintained throughout the plasma concentration range for both parent ($r^2 = 0.04$, slope = -0.003 [-0.008 , 0.001], $P = 0.168$) and metabolite ($r^2 = 0.09$, slope = -0.02 [-0.046 , 0.002], $P = 0.051$) as evidenced by regression slopes not significantly different from zero (see Figure, Supplemental Digital Content 5, <http://links.lww.com/INF/B555>).

DISCUSSION

Assessment of plasma vs. DBS differences in drug concentrations in vivo are critical because these can affect dosing recommendations often targeted to achieve surrogate PD end points that are based on plasma (as opposed to whole blood) drug concentrations. The present study showed that plasma or DBS samples can be used to characterize the PK of metronidazole in premature infants. On average, metronidazole concentrations in DBS samples were similar (within 15%) to plasma, which confirms in vivo that the drug partitions into red blood cells.¹⁹ If metronidazole does not partition into red blood cells, we would have observed lower DBS concentrations as red blood cells serve as a diluent of whole blood (DBS) drug concentration measurements. This difference did not influence the accuracy and precision of population-typical CL and V estimates. In the setting of the clinical trial, the use of DBS samples not only provided a more feasible approach to PK studies in premature infants, but also provided in vivo information of the whole blood and plasma drug concentration relationship.

The PK of metronidazole from the current study supports the finding that development has a significant impact on the disposition of this drug. Metronidazole CL was significantly associated and increased disproportionately with surrogate covariates of maturation including PNA and PMA. This finding is consistent with prior investigations of metronidazole PK in infants^{10,11} and was expected given the predominant hepatic metabolism for this drug. Pending specific identification of the enzymes responsible for metronidazole metabolism in humans, comparison of our PK data with those from other extensively metabolized drug substrates is not possible.

In our population of premature infants, metronidazole CL increased rapidly (on average, by 100%) after the first two weeks of life. In spite of this change, average CL in the youngest and older cohorts represented 30% and 50%, respectively, of total adult CL,²⁰ justifying the need for dosing modifications in this population. This is further corroborated by the low metabolic ratio observed in premature infants (~12%), a finding suggestive of reduced activity of drug-metabolizing pathways. Interestingly, the infants who achieved the surrogate PD target had the lowest metabolic ratio, and within those infants there was substantial variability (~30-fold difference) in metabolizing capacity. This finding could be due to maturational differences and/or have a pharmacogenomics basis should the enzymes responsible for metronidazole CL be polymorphically expressed.

The population PK parameter estimates in the present study are comparable with prior reports in premature infants^{10,11} but, on average, showed higher CL and V (~50% and 30%, respectively) for typical infants of similar PMA. These differences could be due to demographic differences in the study populations, variability in expression of drug-metabolizing enzymes, use of concomitant medications, and sample size required to accurately characterize relationships between maturational covariates and PK parameters. In spite of these differences, PMA-based dosing proposed by our research team in an earlier metronidazole PK study¹⁰ performed well in the present population. The PMA-based dosing scheme also compared favorably against commonly used dosing references in clinical practice. This suggests that metronidazole dosing guidelines for premature infants must

consider apparent developmental differences in the drug's CL similar to what has been successfully achieved using PMA-based dosing for other therapeutics (e.g., amikacin, vancomycin, acetaminophen).^{21–23}

Considering developmental differences in drug disposition allowed for achievement of the surrogate efficacy target in the majority of infants regardless of PMA. Moreover, Monte Carlo simulations showed that the PMA-based dosing regimen outperformed current recommendations found in popular dosing guidelines. Importantly, this was established using a sample of infants from the exact population of interest having a true representation of the clinically important covariate distribution. The ability to combine PMA-based dosing with a sample of infants from a real population highlights the robustness of the findings and facilitates applicability to clinical practice.

In summary, the population PK of metronidazole in infants in this study showed that DBS can be used to evaluate the PK of metronidazole and that PNA and PMA are significant covariates associated with drug clearance. A dosing strategy based on PMA (7.5 mg/kg every 12 hours in infants PMA <34 weeks and 7.5 mg/kg every 8 hours in infants PMA 34–40 weeks, with a loading dose of 15 mg/kg) was developed to account for developmental changes in metronidazole disposition, as well as for simplicity in clinical application. This dosing scheme would achieve the surrogate PD target in the majority (~80%) of infants <90 days of age and exposures comparable with those seen in adult patients with intra-abdominal infections receiving metronidazole.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Clinical Data by Postnatal Age Group

Clinical information	Age cohort		
	Cohort 1 PNA <14 days (N=9)	Cohort 2 PNA 14 days (N=15)	Total (N=24)
Gestational age (weeks)	25 (23, 31)	26 (24, 31)	25 (23, 31)
Postnatal age (days)	8 (1, 13)	35 (14, 82)	27 (1, 82)
Postmenstrual age (weeks)	25 (24, 32)	33 (26, 39)	31 (24, 39)
Birth weight (g)	720 (570, 1466)	757 (431, 1252)	740 (431, 1466)
Male sex (%)	5 (55.6)	3 (20.0)	8 (33.3)
Hispanic ethnicity (%)	2 (22.2)	4 (26.7)	6 (25.0)
Race (%)			
Black	3 (33)	4 (27)	7 (29)
White	6 (67)	10 (67)	16 (67)
Other	0	1 (7)	1 (4)
Serum creatinine	1.1 (0.5, 2.4)	0.4 (0.1, 1.9)	0.5 (0.1, 2.4)
Phenobarbital use (%)	2 (22)	1 (7)	3 (13)

Data are median (range) for continuous data and n (%) for categorical data. PNA, postnatal age. Phenobarbital use after start of study drug.

TABLE 2

Individual Empirical Bayesian Pharmacokinetic Parameter Estimates by Postnatal Age Group

	Postnatal age (days)		
	Cohort 1: <14 N=9	Cohort 2: 14 N=15	Overall N=24
CL (L/h/kg)	0.027 (0.017, 0.059)	0.042 (0.015, 0.129)	0.038 (0.015, 0.129)
V (L/kg)	0.96 (0.75, 1.03)	0.94 (0.83, 0.99)	0.95 (0.75, 1.03)
Half-life (h)	24.3 (11.2, 35.7)	15.1 (5.0, 44.8)	16.7 (5.0, 44.8)
Cmin _{ss} (mg/L)	8.0 (2.4, 14.2)	11.1 (2.0, 38.7)	11.0 (2.0, 38.7)

Data are median (range). Cmin_{ss}, minimum concentrations at steady state; CL, clearance; V, volume of distribution.