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ARTICLE

Dosage Regimens for Meropenem in Children with Pseudomonas Infections Do Not Meet Serum Concentration Targets

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There have been literature reports that some recommended meropenem dosage regimens may fail to meet therapeutic targets in some high-risk children and adults. We evaluated this observation in children using literature studies conducted in infants and children. Observed and, as necessary, simulated data from the literature were combined, yielding a data set of 288 subjects (1 day to ~ 17 years). A population pharmacokinetic model was fit to the data and then used to simulate the recommended dosing regimens and estimate the proportion of subjects achieving recommended target exposures. A two-compartment model best fit the data with weight, postnatal age, gestational age, and serum creatinine as covariates. The US Food and Drug Administration (FDA)-approved dosing regimens achieved targets in ~ 90% or more of subjects less than 3 months of age for organisms with minimum inhibitory concentration (MIC)'s of 2 and 4 mg/L; however, only 68.4% and 41.7% of subjects older than 3 months and weighing < 50 kg achieved target exposures for organisms with MIC's of 2 and 4 mg/L, respectively [Correction added on January 23, 2020, after first online publication: "> 3 months" corrected to "less than 3 months".]. Moreover, for subjects weighing more than 50 kg, only 41.3% and 17% achieved these respective targets. Simulation studies were used to explore the impact of changing dose, dosing interval, and infusion duration on the likelihood of achieving therapeutic targets in these groups. Our findings illustrate that current dosing recommendations for children over 3 months of age fail to meet therapeutic targets in an unacceptable fraction of patients. Further investigation is needed to develop new dosing strategies in these patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Meropenem is commonly used to treat life-threatening bacterial infections in infants and children. Very few pharmacokinetic (PK) studies have been performed in children to support current dosing recommendations and some recent studies suggest undertreatment may occur in non-infants.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ We combined information from studies in the literature to generate a single unified PK model for children of all ages (birth through 17 years) and used simulation studies to examine the possibility of undertreatment of serious infection in children in all age groups.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Our results suggest an unacceptable risk of undertreatment in some children beyond infancy, in particular those children over 50 kg in weight.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Alternative dosage regimens that may minimize the likelihood of treatment failures are proposed for further clinical evaluation. The approach of combining data from several PK studies on subpopulations may increase understanding of drug PKs in children.

Meropenem is a broad spectrum carbapenem antibiotic that has potent activity against an array of important gram-positive and gram-negative bacteria, such as *pseudomonus aeruginosa, enterobacteriaceae,* and anaerobes. It is commonly used for treatment of serious infections, including intra-abdominal infections and meningitis in both adult and pediatric patients. The pharmacokinetics (PKs) and pharmacodynamics (PDs) of meropenem have been assessed in pediatric patients.[1–10] Smith *et al.*[10] reported that meropenem disposition in pediatric patients < 3 months of age can best be described by a one-compartment model with weight, albumin, serum creatinine, and postmenstrual age being significant covariates. On the other hand, Blumer *et al.*,[1] Parker *et al.*,[9] Du *et al.*,[6] and Ohata *et al.*,[8] reported that meropenem disposition in children and older infants follows a two-compartment model with weight,[6,8,9] creatinine clearance,[6,9] and postnatal age[6,9] being significant covariates.

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Meropenem demonstrates time-dependent killing of susceptible bacteria. PD studies have indicated that the most predictive PD parameter of efficacy is the percent time above minimum inhibitory concentration that kills 90% (MIC_{90}) of the pathogen, often represented as $T > MIC_{90}$. The efficacy of meropenem in adults has been established to occur when $T > MIC_{90}$ meets or exceeds 40–50% of the dosage interval. MIC_{90} can range between 0.25 mg/L for susceptible pathogens to > 16 mg/L for resistant pathogens. In infants < 3 months of age, due to reduced immunocompetence, it has been suggested that efficacy requires maintaining plasma concentrations above 2 mg/L for 75% of the dosage interval and above 4 mg/L for 50% of the dosage interval.[10]

The current US Food and Drug Administration (FDA)-recommended meropenem dosing regimens for pediatric patients with severe systemic and intra-abdominal infections were derived from a series of PK and PD studies[1,9,10] and are outlined in **Table 1**.[11] In 2011, Ohata *et al.*,[8] evaluated the safety, efficacy, and PK of meropenem in 50 Japanese infants and children and reported that the recommended dosage for severe systemic and intra-abdominal infections (20 mg/kg every 8 hours, administered intravenously over 30 minutes) had a 60% probability of achieving a $T > MIC_{90}$ of 40% of the dosage interval for pseudomonas infections. When dosages of 40 mg/kg every 8 hours with 30-minute infusion times were simulated, the probability only increased to about 75%. This was the first study to highlight the risk of underdosing in pediatric subjects > 3 months of age. Studies in adults have demonstrated a similar risk of undertreatment, particularly with shorter intravenous drug infusion times[12–17] and more recent studies in children have voiced this same concern.[18,19] Intrigued by these findings, we sought to comprehensively evaluate the current meropenem dosage regimen recommendations in US children using available literature data. We also evaluated several alternative dosage regimens by simulation studies to inform further clinical trials in these populations.

Table 1 Currently, FDA recommended dosage regimens of meropenem for children with severe systemic and intra-abdominal infections[11]

Group	Dosage regimen
Infants < 3 months of age	
Group 1 (<GA 32 weeks, PNA < 14 days)	20 mg/kg every 12 hours
Group 2 (<GA 32 weeks, PNA ≥ 14 days)	20 mg/kg every 8 hours
Group 3 (≥GA 32 weeks, PNA < 14 days)	20 mg/kg every 8 hours
Group 4 (≥GA 32 weeks, PNA ≥ 14 days)	30 mg/kg every 8 hours
Children ≥ 3 months of age and < 50 kg	
Group 5	20 mg/kg every 8 hours (max. 1 g)
Children and adults ≥ 50 kg	
Group 6	1 g every 8 hours

FDA, US Food and Drug Administration; GA, gestational age; PNA, postnatal age.

METHODS

Data

A literature search was performed to identify previous PK studies of meropenem in infants and children. Ovid Medline was queried for English language studies published prior to the initiation of our work in February 2016. We searched for the term "meropenem," limited the search to human children, and required one of the following terms: "kinetics," "pharmacokinetics," or "PK." Fifty studies were identified, of which 18 reported original research performed exclusively in pediatric subjects. Two case reports, one study of a drug interaction, and three studies reporting PKs in subjects receiving renal replacement therapy or extracorporeal membrane oxygenation were not considered further. Of the 10 studies reviewed in depth, six were focused on premature and/or term newborns. Because the study of Smith *et al.*[10] included the largest subject population and was conducted at multiple study sites, as described below, and had complete, available study data, the other neonatal studies[20–23] were not included in our modeling efforts. Because the index study suggesting suboptimal treatment was performed in an exclusively Japanese study population,[8] another exclusively Japanese study[24] was omitted from further consideration. Therefore, the studies of Blumer *et al.*,[1] Parker *et al.*,[9] and Du *et al.*[6] were further analyzed for inclusion in our modeling.

The study of Smith *et al.*[10] included 188 infants of 23–40 weeks estimated gestational age and 1–92 days postnatal age in whom 780 serum meropenem concentrations were obtained. The data set from this study was obtained from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) data repository for the Pediatric Trials Network (PTN)[25] and formatted with R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio version 0.99.489 (Boston, MA).

The study of Du *et al.*[6] included all 65 subjects from the previous studies of Blumer *et al.*[1] and Parker *et al.*,[9] in addition to their own data from an additional 34 subjects. The age range of these subjects ranged from 1 month to 17.3 years and subjects had received initial doses of 10–40 mg/kg infused over 5 or 30 minutes. The original data were not available from the respective authors, so a representative population of 100 subjects was generated using Monte Carlo simulations mimicking the demographic distribution reported in Du *et al.*[6] In order to do this, four age groups of 25 subjects were created (2–14, 14–38, 38–66, and 66–200 months of age) with random, uniform distribution in each and random, binomial distributions of sex. Body weights were generated in R based on Centers for Disease Control (CDC) Growth Charts[26] with normal distributions for age and sex. Serum creatinine was generated from the median, upper, and lower limits of normal assuming uniform distribution.[27] Outliers with respect to serum creatinine in the Du *et al.*[6] study were simulated by randomly increasing serum creatinine by 1.2–3.3-fold in 10% of the population. Creatinine clearance was estimated by the method of Cockcroft and Gault.[28] Eight simulated plasma meropenem concentrations were generated for each of these 100 subjects (total of 800 serum meropenem concentrations) based on the model PK parameters, variability statistics, and covariates from Du *et*

al.[6] using Phoenix NLME version 7.0 (Certara, Princeton, NJ). The FDA-recommended dosage of 20 mg/kg every 8 hours infused over 30 minutes was used.

As the Ohata *et al.*[8] study was the index analysis suggesting that currently recommended therapeutic regimens may be inadequate in some pediatric subjects (> 3 months of age), this study was reserved for comparison and these patient's PK data were not included in our analysis.

The combined PK data set for this study, therefore, consisted of the merged data from 188 subjects in the Smith *et al*.[10] study and the data from the 100 simulated subjects replicating those subjects studied by Du *et al*.,[6] Blumer *et al*.,[1] and Parker *et al*.[9] Missing clinical data in the combined data set were imputed using the last value carried forward; except for missing gestational age for infants and children > 120 days of age, for which the gestational age of 40 weeks was imputed. Descriptive statistics for demographic and dosing variables were calculated using the value at the time of first PK sample.

Statistical analysis

The following descriptive statistics were calculated for demographic variables: mean, SD, coefficient of variation, median, and range. With the exception of the PK modeling, all statistical analyses were performed with R using RStudio.

Population PK analysis

Meropenem plasma concentration data following intravenous administration for the combined data set were analyzed using a nonlinear mixed effects modeling approach (Phoenix NLME). Details of the population PK (PopPK) modeling procedures, the analysis of models, and the validation and qualification of the final model are provided in the **Appendix S1**.

Simulation for dosing recommendations

Simulations of plasma meropenem concentrations following intravenous doses to subjects in the combined data set were performed using the final PopPK model and dosage regimens based on FDA-approved dosages for serious infections with organisms requiring high concentrations (e.g., intra-abdominal infections with pseudomonas; **Table 1**).[11] One thousand simulations were performed for each subject group for each tested dosage regimen.

Plasma meropenem concentration targets were selected from the literature[10] and antibiotic sensitivity recommendations (breakpoints) of the FDA[29] and European Committee on Antimicrobial Sensitivity Testing (EUCAST).[30] The breakpoints for meropenem use in pseudomonas infections of ≤ 2 mg/L (sensitive), 4 (intermediate sensitivity—FDA only), and ≥ 8 (resistant) from these groups were deemed to be appropriate guidelines for the choice of > 2 mg/L and > 4 as clinically relevant drug concentration profiles to be achieved in simulations. The time-dependent components for these target concentrations were as follows: infants < 3 months (groups 1–4): > 2 mg/L for 75% of the dosage interval and > 4 mg/L for 50% of the dosage interval[3]; infants and children over age 3 months (groups 5 and 6): > 2 mg/L for 40% of dosage interval, or > 4 mg/L for 40% of dosage interval, depending on the *in vitro* sensitivity of the infecting organism.[8]

Alternative dosing strategy

Three alternative dosing strategies were explored to improve the percent of subjects meeting the target serum concentration for selected patient groups; first, a doubling of the recommended dose given every 8 hours (this dosing, 40 mg/kg every 8 hours (maximum 2 g), coincides with the FDA recommendation for treatment of meningitis in pediatric subjects > 3 months); second, the recommended dose as outlined in **Table 1**[11] but given every 6 hours instead of every 8 hours; and third, administration of the recommended dosages with the intravenous infusion duration increased to 3 hours.

RESULTS

Preliminary analyses

We confirmed that data from the NICHD data repository for the PTN (preterm neonates and infants) were best described by a one-compartment model with covariates, as described by Smith *et al.*[10] Parameter values and variabilities found in our analysis were virtually identical to those described in that report.

Data set development

The pediatric data set, simulated to replicate the patient population of Du *et al.*[6] (and containing the patients studied by Blumer *et al*.[1] and Parker *et al*.[9]) was highly concordant with the reported population characteristics, as depicted in **Table 2**.[6,10]

The infant PK data set of Smith *et al*.[10] (n = 188) and the simulated PK data set from Du *et al*.[9] (n = 100) were, therefore, combined to generate a comprehensive pediatric data set that includes 288 subjects with an age range of 0.00217.3 years (**Table 2**).[6,10]

PopPK model development and qualification

The stepwise development of a new PopPK model for all pediatric subjects was conducted. A two-compartment model best fit the data and was substantially improved by scaling the PK parameters (elimination clearance, intercompartmental

Table 2 Patient demographics of Du *et al*.[6] data sets (reported and simulated) and combined Du *et al*.[6] (simulated) and Smith *et al*.[10] data sets

	Median	Mean	SD	Range
Du—Reported data set[6]				
PNA, years	3.17	4.34	3.8	0.08–17.3
WT, kg	13.5	16.8	12	3.7–65.0
SCR, mg/dL	0.45	0.49	0.4	0.1–3.4
Du—Simulated data set				
PNA, years	3.15	4.65	4.5	0.19–16.3
WT, kg	14.3	20.5	16	5.7–88.3
SCR, mg/dL	0.56	0.57	0.3	0.17–1.65
Du—Simulated data set combined with Smith *et al*.[10] data set				
PNA, years	0.11	1.66	3.45	0.002–16.3
GA, weeks	33	32.9	6.5	22.5–40
WT, kg	2.36	8.29	13.1	0.39–88.3
SCR, mg/dL	0.50	0.58	0.32	0.1–1.9

GA, gestational age; PNA, postnatal age; SCR, serum creatinine; WT, weight.

clearance, volume of the central compartment, and volume of peripheral compartment) by body weight (change in objective function value (OFV) of 1,052; $P < 0.001$). Scaling of clearance and weight with an estimated single exponential scaling term for both volume terms and another for both elimination and intercompartmental clearance improved the model further. A forward covariate search ($P < 0.05$ for inclusion, $P < 0.005$ for removal) was carried out, yielding significant covariates of serum creatinine (SCR), postnatal age (PNA), and gestational age (GA) on clearance (CL), and PNA on CL2 (change in OFV of 185; $P < 0.001$). Substitution of a maturation function (see final model equations below) for the effect of PNA on CL and CL2 produced a further improvement that was enhanced by the inclusion of a Hill coefficient (change in OFV of 236; $P < 0.001$). Additional manual testing of remaining potential covariates failed to identify further significant reduction in the OFV.

The final model was as follows:

$$CL_i = TVCL \cdot (WT_i/70)^{dCLdWT} \cdot \left(PNA_i^{\gamma} / \left(PNA_i^{\gamma} + Age\,50\right)\right) \cdot SCR_i^{dCLdSCR} \cdot \left(GA_i/40\right)^{dCLdGA} \cdot \exp(\eta CL)$$

$$CL2_i = TVCL2 \cdot (WT_i/70)^{dCLdWT} \cdot \left(PNA_i^{\gamma} / \left(PNA_i^{\gamma} + Age50\right)\right) \cdot \exp(\eta CL2)$$

$$V_i = TVV \cdot \left(WT_i/70\right)^{dVdWT} \cdot \exp(\eta V)$$

$$V2_i = TVV2 \cdot (WT_i/70)^{dVdWT} \cdot \exp(\eta V2)$$

$$CObs = C \cdot (1 + \varepsilon)$$

where, CL_i, CL2i, V_i, and V2i are the estimates for the *i*th subject, TVCL and TVV are the typical value estimates of clearance and volume in the central compartment, TVCL2 and TVV2 are the typical value estimates of clearance and volume in the peripheral compartment, WT_i is the weight of the *i*th subject; dCLdWT and dVdWT are the exponents that represent scaling of clearance and volume terms on weight, respectively, PNA_i is the postnatal age of the *i*th subject. ɣ is the Hill coefficient, age 50 is the age at which 50% of the maximum clearance is achieved, SCR_i is the serum creatinine of the i^{th} subject, dCLdSCR is the exponent that represents scaling of CL on SCR, GA_i is the gestational age of the *i*th subject, and dCLdGA is the exponent that represents scaling of CL on GA.

The parameters were estimated with good precision (**Table 3**). Goodness-of-fit plots for the final PopPK model indicated that the model described the data well without bias (provided in **Appendix S1**). As depicted in **Table 3**, all final model parameter estimates were consistent with values obtained using nonparametric bootstrapping. In addition, the prediction-corrected visual predictive check demonstrated that concentrations in our compiled data set (observed and simulated) were concordant with predicted concentrations (i.e., 89.7% were within the 90% prediction interval of

Table 3 Final model parameter estimates

		Parametric	Bootstrap		
Parameter	**Unit**	**Estimate (SE)**	**Median**	**2.5–97.5% CI**	**Shrinkage (%)**
Structural model					
TVV	L/70 kg	29.1 (2.9)	27.9	24.9–32.9	—
TVV2	L/70 kg	31.9 (4.3)	30.6	26.0–38.8	—
TVCL	L/hour/70 kg	37.1 (3.8)	36.3	30.7–44.8	—
TVCL2	L/hour/70 kg	6.10 (1.1)	6.53	4.76–8.55	—
Age 50	y	0.39 (0.05)	0.36	0.28–0.52	—
dCLdSCR	—	−0.25 (0.03)	−0.25	−0.29 to −0.20	—
dCLdGA	—	0.84 (0.16)	0.79	0.40–1.16	—
dVdWT	—	0.97 (0.03)	0.96	0.93–1.00	—
dCLdWT	—	1.20 (0.05)	1.20	1.10–1.28	—
ɣ	—	0.27 (0.04)	0.28	0.22–0.36	—
Intersubject variability					
V	—	0.186 (0.095)	0.178	0.083 (SE)	58
V2	—	0.319 (0.10)	0.325	0.232 (SE)	76
CL	—	0.315 (0.220)	0.316	0.078 (SE)	10
CL2	—	1.14 (0.56)	1.10	0.402 (SE)	39
Residual error					
Proportional (%)	—	0.38 (0.01)	0.38	0.36–0.40	15

ɣ, the Hill coefficient for the maturation equation for CL and CL2, as described in the Methods section; Age 50, the age at which 50% of the maximum clearance is achieved; CI, confidence interval; CL, clearance; dCLdGA, exponent that represents scaling of clearance on gestational age; dCLdSCR, the exponent that represents scaling of clearance on serum creatinine; dCLdWT, the exponent for scaling of both elimination and intracompartmental clearances on body weight; dVdWT, the exponent for scaling of both central and peripheral compartment volumes on body weight; GA, gestational age; PNA, postnatal age; SCR, serum creatinine; TVCL and TVV, the typical value estimates of clearance and volume in the central compartment; TVCL2 and TVV2, the typical value estimates of clearance and volume in the peripheral compartment.

5–95 percentiles) indicating the appropriateness of the final model. Finally, the two data subsets (neonatal data from Smith *et al*.[10] and the simulated data from Du *et al*.[6]) were examined separately with the same visual predictive check approach and were both found to be accurately represented by our model (87.9% of the observed Smith *et al*.[10] data falling within the 90% prediction interval, and 92.9% of the simulated Du *et al*.[6] data).

Using the entire data set of 1,482 observations in 288 subjects (ages 0.02–17 years), we compared the performance of the new, comprehensive pediatric PopPK model with non-neonatal models previously reported in literature.[6,8–10] The observations were compared with the predicted quantiles of the respective structural models and the number of observations falling outside the 90% confidence limits (5%–95%) were tabulated. Each of the tested models performed less favorably than the final model described in this report, for which 10.3% of observations fell outside the 90% confidence limits. Using the model of Du *et al*.,[6] 23.8% of observations fell outside the 90% confidence intervals ($P < 0.001$), whereas models of Ohata *et al*.[8] and Parker *et al*.[9] performed even more unfavorably (56.8% and 86.5%, respectively, $P < 0.001$ for each comparison with the new model).

Simulation analyses and evaluating currently recommended meropenem dosing regimens against PD targets

The final PopPK model was then used to simulate the currently recommended meropenem doses (**Figure 1**). The percentage of subjects in each group achieving the recommended therapeutic targets (i.e., meropenem concentrations > 2 or 4 mg/L for 75% and 50% of the dosage intervals, respectively, for groups 1–4, and meropenem concentrations > 2 or 4 mg/L for 40% of the dosage interval for groups 5 and 6) were identified. Plasma meropenem concentrations in groups 1–4 (preterm and term infants < 3 months) met therapeutic target in 82.9–95.1% and 86.6–95.8% of subjects for MIC > 2 mg/L and 4 mg/L, respectively (**Table 4**). However, for children 3 months to 17 years of age, the plasma concentrations met the therapeutic target period in only 68.4% and 41.3% in groups 5 and 6, respectively, when the target MIC was > 2 mg/L and in only 41.7% and 17% in groups 5 and 6, respectively, when the target MIC was > 4 mg/L (**Table 4**).

Alternative dosing strategies

In order to further explore the shortcomings of currently recommended dosage schedules for children over 3 months of

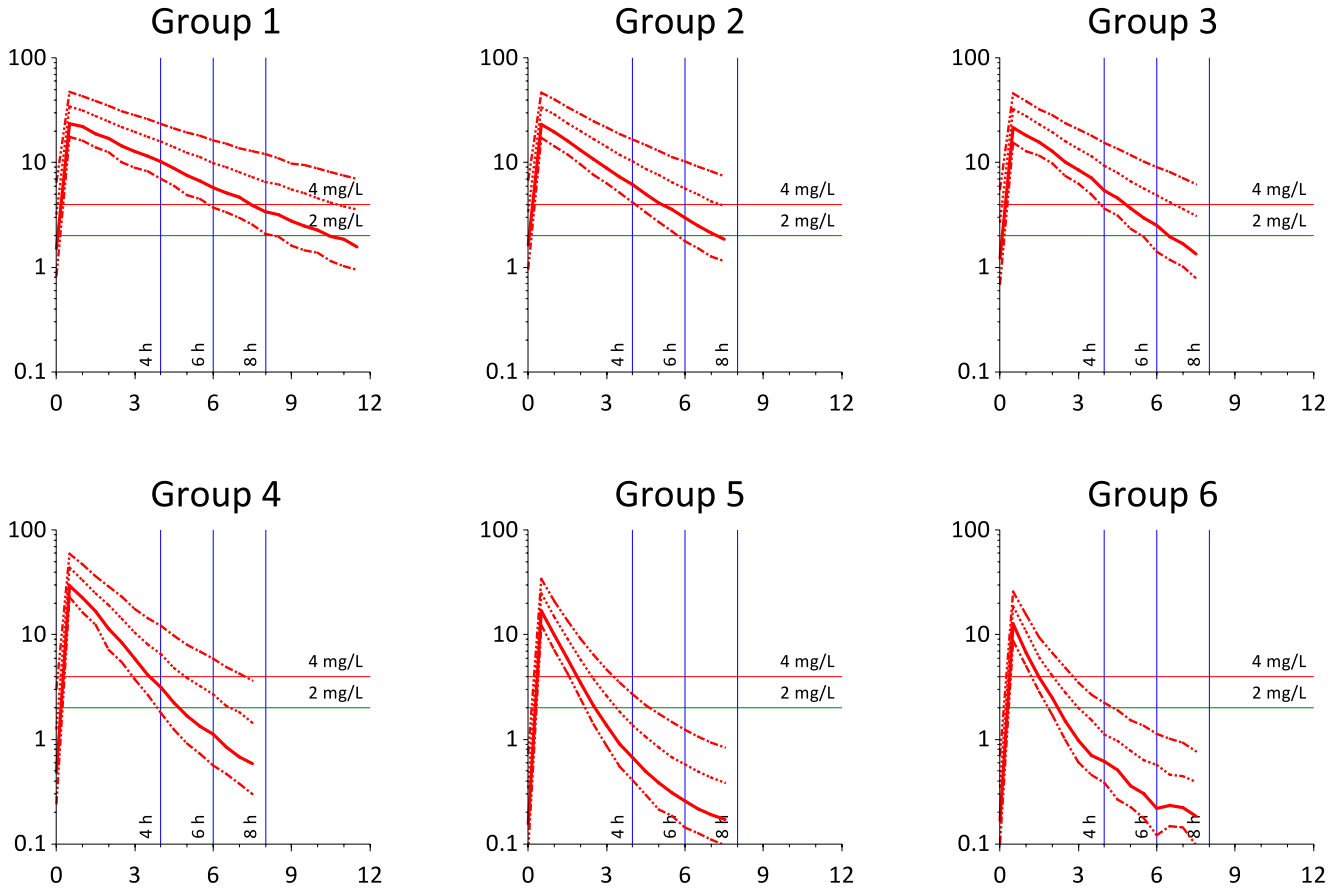

Figure 1 Distributions of steady state, intra-dosage plasma meropenem concentrations in infants and children receiving currently recommended dosage regimens compared with target serum drug concentrations. Each panel depicts one age/size group of subjects, as defined in Table **1**. Within each panel, each graph line represents the percentile of subjects meeting the plasma meropenem concentration at the corresponding time. The lines, from top to bottom, represent the 50 percentile, 25 percentile, 10 percentile, and 5 percentile.

Table 4 Fraction of virtual subjects achieving targets for six subject groups and two bacterial MICs targets

			Dosage strategy							
			FDA approved doses		Increased doses Q8h		Decrease dosage interval (Q6h)		Increased drug infusion time (3 h)	
Group	GA, PNA, age, and/or WT	MIC (mg/L)	Target duration (% of dosage interval)	Dose regimen	% Patients achieving target	Dose regimen	% Patients achieving target	Dose regimen	% Patients achieving target	Dose regimen	% Patients achieving target
1	GA < 32 weeks, PNA < 14 days	2	75%	20 mg/kg Q12h	95.1	—	—	—	—	—	—
		4	50%		95.8						
2	GA < 32 weeks, PNA > 14 days, < 3 months	2	75%	20 mg/kg Q8h	94.2	—	—	—	—	—	—
		4	50%		94.4						
3	GA > 32 weeks, PNA < 14 days	2	75%	20 mg/kg Q8h	94.8	—	—	—	—	—	—
		4	50%		95.7						
4	GA > 32 weeks, PNA > 14 days, < 3 months	2	75%	30 mg/kg Q8h	**82.9**	—	—	—	—	—	—
		4	50%		**86.6**						
5	3 months–17 years, < 50 kg	2	40%	20 mg/kg Q8h	**68.4**	40 mg/kg Q8h	**85.5**	20 mg/kg Q6h	**> 97.5**	20 mg/kg Q8h	**> 97.5**
		4	40%		**41.7**		**68.6**		**94.9**		**90.7**
6	3 months–17 years, > 50 kg	2	40%	1 g Q8h	**41.3**	2 g Q8h	**64.7**	1 g Q6h	**93.9**	1 g Q8h	**94.5**
		4	40%		**17**		**41.2**		**80.1**		**79.6**

FDA-approved dosing regimens and three tested alternative regimens are illustrated.
FDA, US Food and Drug Administration; GA, gestational age; MIC, minimum inhibitory concentration; PNA, postnatal age; WT, weight.

age, we extended our simulation analysis for groups 5 and 6 to evaluate three alternative dosage regimens: increased dose (40 mg/kg, maximum of 2 g, Q8h), decreased dosage interval (20 mg/kg, maximum 1 g, Q6h in lieu of Q8h), and increased dose infusion duration (20 mg/kg, maximum 1 g, Q8h infused over 3 hours instead of 0.5 hours). The results are provided in **Table 4** for MIC targets of 2 mg/L and 4 mg/L, and for a wide range of MIC targets in **Figure 2**. The percentage of subjects achieving a therapeutic target improved to over 85% in group 5 subjects (< 50 kg) with each of these alternative regimens for the potential target of 2 mg/L. For the potential target of 4 mg/L, target attainment was achieved in 68% of virtual subjects receiving an increased dosage, but to over 90% of subjects for the regimens with a shortened interdosage interval or an extended infusion time. Target attainment for the tested dosage regimens in group 6 subjects (> 50 kg) was only 64.7% for subjects receiving an increased dosage for targets of 2 mg/L, but over 90% with either the shortened interdosage interval or the extended infusion time. For targets of 4 mg/L, 80% or less for subjects achieved targets with each of the alternative regimens.

Figure 2 (**a**) The percentage of group 5 subjects (3 months to 7 years; < 50 kg) achieving the target plasma meropenem concentration as a function of the bacterial minimum inhibitory concentration (MIC) at three dosage regimens (all with 0.5 drug infusion time unless otherwise indicated): US Food and Drug Administration (FDA; current approved label): 20 mg/kg Q8h; HiDose: 40 mg/kg Q8h; and infusion: 20 mg/kg Q8h, infused over 3 hours; Q6h: 20 mg/kg Q6h. (**b**) The percentage of group 6 subjects (> 50 kg) achieving the target plasma meropenem concentration as a function of the bacterial MIC at three dosage regimens (all with 0.5 drug infusion time unless otherwise indicated): FDA (current approved label): 1 g Q8h; HiDose: 2 g Q8h; and infusion: 1 g Q8h, infused over 3 h; Q6h: 1 g Q6h. PD, pharmacodynamic.

DISCUSSION

The FDA recommendations for treatment of serious, deep tissue infections with meropenem have been based on carefully performed PK analyses.[1–3,5] Nevertheless, these infections are still associated with significant morbidity and further improvements in treatment are needed.[31–33]

Recent studies in adults suggest that treatment with beta-lactams in critically ill subjects may be associated with shorter $T > MIC_{90}$ than recommended and possibly inadequate clinical responses.[12–17] The report of Ohata *et al.*[8] originally suggested that this may be the case for many children and, since the completion of our studies, two new reports have been published also suggesting an unacceptable risk for undertreatment in this population.[18,19] In order to explore this phenomenon further in pediatrics, we pooled PK data for pediatrics from literature sources, developed a unified PK model for meropenem in pediatrics, and evaluated currently recommended dosage regimens.

Beta-lactam antibiotics, including meropenem, are known to have time sensitive killing *in vivo*.[12,34,35] Therefore, current dosage regimen recommendations are based on achieving a substantial time during which the plasma drug concentration exceeds the *in vitro* MIC for the infecting organism. For adults and children over 3 months of age, it is desirable for the plasma meropenem concentration to exceed the organism's MIC for 40% or more of the dosage interval. For infants under 3 months of age, Smith *et al.*[10] have recommended that longer periods of time over the MIC should be targeted.

The PK model developed in this study performs well in all pediatric age groups from prematurely born infants, through and into adolescence. A two-compartment model fit the data best with scaling model parameters by body weight. Covariates on CL included SCR, GA, and PNA. The PNA was also a covariate on the intercompartmental CL. Precision of all parameter estimates was high and nonparametric bootstrap estimates were in close agreement with their parametric counterparts. Goodness-of-fit plots and visual predictive checks all suggested a good fit of the model to the data.

Our findings suggest that recommended dosage regimens in infants less than 3 months of age meet therapeutic targets in at least 83% of subjects [Correction added on January 23, 2020, after first online publication: "> 3 months" corrected to "less than 3 months".]. However, ~ 32–58% of children over the age 3 months may fail to achieve the desired targets when the MIC of the infecting organism is 2 mg/L and ~ 58–83% of children > 3 months will not achieve the $T > MIC_{90}$ target when the MIC is 4 mg/L. Although doubling the currently recommended dosage administered every 8 hours in these older children would decrease the number of inadequately treated patients, achievement of > 90% target attainment when the target is 2 mg/L requires administering recommended dosages every 6 hours or extending infusion duration to 3 hours. If the target is 4 mg/L, these modified regimens achieve 90% coverage goals in children under 50 kg, however, those over 50 kg may still have inadequate coverage.

There are several important limitations to our study. To begin, the model included both observed data from 188 subjects and simulated data from 100 subjects. Data simulation was needed due to lack of access to data sets in children over 3 months and our objective was to develop a universal PopPK model that characterizes meropenem disposition in all pediatric patients. Our simulated data, however, were in close agreement with the reported Du *et al*.[6] data set (**Table 2**) and balanced in their contribution to our analysis by the size of the total patients studied by Blumer *et al*.,[1] Parker *et al*.,[9] and Du *et al*.[6] Second, the subjects included in our study were selected to have normal renal function and our results cannot be extended to children with abnormal renal function. It is very likely that impaired clearance of meropenem would occur in these patients and, therefore, the time below MIC would be minimized. Finally, studies in adults with serious gram-negative infections have demonstrated the importance of maintaining serum drug concentrations associated with antibiotic killing for substantial portions of the interdose interval in order to achieve infection bacterial eradication. Extrapolation of these findings to children seems to be a minimum threshold and, in circumstances where immune compromise exists, extended periods of adequate serum drug concentrations may be required.[10]

These results raise concerns for the adequate treatment of pediatric patients over the age of 3 months with serious infections being treated with meropenem. It is tempting to conclude that therapeutic drug monitoring would be indicated in order to detect inadequately treated patients and adjust therapy. Although our studies indicate that safe and effective therapy may be achieved with more frequent dosing and with extended infusion durations, optimal regimens that provide desirable outcomes but avoid overdosing await further clinical trials.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Appendix S1. Population PK model building, analysis, and qualification.
Figure S1. Conditional weighted residuals (CWRES) vs. population predicted concentrations (PRED).
Figure S2. Conditional weighted residuals (CWRES) vs. time after dose.
Figure S3. Observed drug concentrations (CObs) vs. population predicted concentrations (PRED).
Figure S4. Observed drug concentrations (CObs) vs. individual predicted concentrations (IPRED).
Figure S5. Individual weighted residuals (IWRES) vs. Individual predicted concentrations (IPRED).

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Data Availability Statement. Drs. Hassan and Green had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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