Physiologically Based Pharmacokinetic (PBPK) Modeling of Meropenem in Preterm and Term Infants

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Abstract

Background: Meropenem is a broad-spectrum carbapenem antibiotic approved by the U.S. Food and Drug Administration for use in pediatric patients, including treating complicated intra-abdominal infections (cIAIs) in infants < 3 months of age. The impact of maturation in glomerular filtration rate (GFR) and tubular secretion by renal transporters on meropenem pharmacokinetics, and the effect on meropenem dosing, remains unknown. We applied physiologically based pharmacokinetic (PBPK) modeling to characterize meropenem's disposition in preterm and term infants.

Methods: An adult meropenem PBPK model was developed in PK-Sim® (v. 8) and scaled to infants accounting for renal transporter ontogeny and GFR maturation. The PBPK model was evaluated using 645 plasma concentrations from 181 infants (gestational age 23–40 weeks; postnatal age 1–95 days). PBPK model-based simulations were performed to evaluate meropenem dosing in the product label for infants < 3 months of age treated for cIAIs.

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Results: Our model predicted plasma concentrations in infants in agreement with the observed data (average fold error of 0.90). The PBPK model-predicted clearance in a virtual infant population was successfully able to capture the *post hoc* estimated clearance of meropenem in this population, estimated by a previously published model. For 90% of virtual infants, a 4 mg/L target plasma concentration was achieved for > 50% of the dosing interval following product label–recommended dosing.

Conclusion: Our PBPK model supports the meropenem dosing regimens recommended in the product label for infants < 3 months of age.

1 Introduction

Meropenem is a broad-spectrum carbapenem antibiotic that inhibits cell wall synthesis by binding to penicillin-binding proteins and exerting bactericidal activity against both Gram-positive and Gram-negative bacteria [1–3]. It is approved by the U.S. Food and Drug Administration (FDA) for use via intravenous (IV) infusion in complicated intra-abdominal infections (cIAIs) (adult and pediatric patients of all ages), complicated skin and skin structure infections (adult and pediatric patients > 3 months of age), and bacterial meningitis (pediatric patients > 3 months of age) [1].

Meropenem pharmacokinetics (PK) in adults is well defined. In multiples studies that included European and Asian adult healthy subjects and patients without systemic infection, meropenem's median (range) weight-normalized clearance was 0.22 L/hr/kg (0.16–0.36), the volume of distribution was 18.2 liters (11.0–28.7), and mean half-life was approximately 0.8 to 1.5 hours [4–8]. Meropenem is primarily cleared renally by both glomerular filtration and renal tubular secretion [8]. About 70% of the drug is cleared unchanged in the urine, 24%–30% is metabolized by dehydropeptidase I (DHP-1 or DPEP1) into its only known inactive metabolite, and ~2% of the drug is eliminated in feces [1]. Organic anion transporters 1 and 3 (OAT1 and OAT3) present in the proximal renal tubule are known to transport meropenem, and OAT inhibitor probenecid has been shown to reduce meropenem's renal clearance [8,9]. Renal function, estimated using creatinine clearance, is the primary determinant of meropenem dosing in adults [1].

Meropenem PK has also been reported in pediatric subjects of different ages. In pediatric subjects ranging from newborns to 12 years of age, including premature infants, creatinine clearance, age, and body weight were significant covariates determining meropenem clearance [10–13]. Weight-normalized meropenem clearance was found to be lower in neonates [13,14] compared to pediatric subjects > 2 years of age [10]. Previous studies also suggested that weight- normalized dosing of meropenem, ranging from 20 to 40 mg/kg given every 8 hours, would be sufficient to achieve efficacy in pediatric subjects. One previous study characterized meropenem's population PK (PopPK) in 200 infants < 91 days of age [15]. This study reported that serum creatinine and postmenstrual age (PMA) were significant covariates for meropenem clearance in infants, and an age-dependent dosing scheme for the treatment of complicated intra-abdominal infection in infants < 91 days of age was suggested [15].

Conducting PK studies in infants is challenging, thus often limiting evaluation of dosing regimens for newer indications and increasing the off-label or unlicensed use of drugs in this vulnerable patient population [16–18]. Physiologically based pharmacokinetic (PBPK) modeling can be useful in predicting PK and dose selection in the pediatric population [19]. In neonates, meropenem is currently only approved for cIAIs. A PBPK modeling approach combines drug-, physiology-, and clinical trial design–related information and can be used to predict PK and optimize dosing in vulnerable patient populations [19–21]. Thus, we sought to apply a PBPK modeling approach to characterize meropenem's disposition in adults and then scale the model to infants. Once the model was verified, we sought to use a PBPK modeling approach to evaluate recommended meropenem dosing in infants with cIAIs.

2 Materials and Methods

2.1 Clinical Data Used for PBPK Model Development and Evaluation

Meropenem plasma concentration vs. time profiles from the literature were digitized using Graph Grabber software (Version 2.0, Quintessa, quintessa.org) to develop and evaluate the adult and pediatric PBPK models. For adult PBPK model development, plasma concentration vs. time profiles after a single or multiple dosing of meropenem IV infusion in healthy subjects or hospitalized patients were used (Table S1). After scaling the adult model to the pediatric population, the pediatric PBPK model was evaluated using digitized and available individual-level concentration vs. time data (Table S2).

2.2 Adult PBPK Model Development

A whole-body PBPK model for meropenem was developed for adults using the software PK-Sim® (v. 8.0, Open Systems Pharmacology Suite, open-systems-pharmacology.com). The PBPK model was developed using physicochemical and *in vitro* properties of meropenem as listed in Table 1. To match a previous publication focused on meropenem PK in adults [8], an average European male virtual individual with an age, weight, and height of 26 years, 74 kg and 179 cm, respectively, was created to simulate a mean plasma concentration vs. time profile following a 500 and 1000 mg meropenem IV infusion. Based on the published information, glomerular filtration, renal secretion, biliary clearance, and enzymatic metabolism via the DPEP1 enzyme were considered for the disposition of meropenem [8,22,23]. Meropenem's lipophilicity (logP) was optimized, as was the method for calculation of partition coefficients (Kp). A renal tubular secretion process was defined by OAT3 mediated uptake of meropenem in renal epithelial cells and efflux of intracellular meropenem into urine by hypothetical efflux transporter. The reported maximum rate of transport (V_{max}) by the OAT3 transporter, expressed on human embryonic kidney 293 (HEK293) cells, was converted from pmol/min/mg protein to μmol/L/min using single HEK293 cell protein concentration [24], and this concentration was assumed to be equivalent to OAT3 transporter expressed on the cell membrane. A hypothetical efflux transporter, entirely expressed in the kidney, was added on the renal tubule's apical side to account for tubular secretion. The hypothetical efflux transporter was assumed to have a low affinity for meropenem (Michaelis-Menten constant [K_m] 1500 μM, two-fold higher than the K_m for the OAT3 transporter), and the V_{max} value was optimized. A 25% coefficient of

variation (CV) was assumed, informed by previously reported values, for the expression of the OAT3 and the hypothetical efflux transporter. Variability in the OAT3 transporter kinetic parameters was added based on the literature-reported values (20% CV on K_m, 15% CV on V_{max}) [9].

Meropenem is metabolized via hydrolysis of the beta-lactam ring by the DPEP1 enzyme to its major inactive metabolite ICI 213689 [23], constituting 20%–30% of the total clearance [7]. Due to a lack of information on the expression of DPEP1, a first-order clearance by this enzyme was assumed and optimized based on *in vivo* non-renal clearance values in adults [7,8,25,26]. Optimization of renal and non-renal clearance was based on achieving the literature-reported total systemic clearance, which includes ~70% renal elimination and 20%–30% metabolism via DPEP1.

2.3   Adult PBPK Model Evaluation

An adult, healthy male virtual individual and a virtual adult population of 100 subjects (50% female) were created based on each publication's average demographic information (Table S1 and Table S3). The model's predictive performance was assessed based on a visual comparison of the observed vs. simulated data. From the simulated concentration vs. time profiles, we also calculated the area under the concentration vs. time curve (AUC) extrapolated to infinity and the clearance by noncompartmental analysis in Phoenix® WinNonlin® (v. 8.0, Certara, Princeton, NJ) and compared this result with the literature-reported result. The tidyverse collection of R packages was used for data processing and visualization [27]. Additional information is available in the Electronic Supplementary Material.

2.4   Pediatric PBPK Model Development

2.4.1   Physiological Parameters in the Pediatric Population—The algorithms implemented in PK-Sim® were used to generate a virtual pediatric population of ages 3 months to 12 years [28] and < 3 months of age [29]. As previously described [29], the gestational age (GA) for the infants < 3 months of age varied between 24 weeks preterm to 40 weeks term neonates. The default physiological parameters implemented in PK-Sim® were considered for the current model.

2.4.2   Scaling Unbound Fraction—The default albumin ontogeny in PK-Sim®, defined as the ratio of protein concentration in a child of a specific age to that in adults, was used to account for age-dependent changes in the unbound fraction of meropenem in the pediatric population, including infants < 3 months of age.

2.4.3   Scaling Meropenem Renal Clearance—The renal clearance processes for meropenem were assumed to be similar between adult and pediatric subjects and included both glomerular filtration and tubular secretion. Age-dependent changes in glomerular filtration have been previously described by Rhodin et al. [30] and implemented in PK-Sim® as described by Claassen et al. [29]. Tubular secretion was modeled as OAT3 and a hypothetical efflux transporter–mediated saturable transport process. Ontogeny information for the OAT3 transporter expression in the kidney has been previously described, and

the mean and 95% confidence interval for the time to half-maximal OAT3 expression (TM_{50}) and a Hill coefficient was based on OAT3 transporter protein expression at different postnatal ages (PNA) [31]. Standard deviation was calculated from the reported 90% confidence interval limits of TM_{50} and Hill, as described in Equation 1.

$$\text{SD} = \frac{Upper\ Limit\ of\ Confidence\ interval - Lower\ limit\ of\ Confidence\ interval}{4} \quad (1)$$

Based on this information, an ontogeny function with variability for OAT3 was generated at different PNAs using the software R (version 3.5.3 [32]) and R studio (version 1.1. 463; RStudio, Boston, MA) and Equation 2.

$$\text{Maturation function} = \frac{Age^{Hill}}{Age^{Hill} + TM50^{Hill}} \quad (2)$$

For the age-dependent change in hypothetical efflux transporter expression, an ontogeny function for tubular secretion developed by Hayton [33,34] was used.

Pediatric renal clearance contributed by the glomerular filtration and tubular secretion is scaled from their corresponding adult values using Equations 3 and 4 as previously described [35],

$$CL_{R,\ (child)} = (GFR_{child}/GFR_{adult}) * \left(f_{u,\ p\ (child)}/f_{u,\ p\ (adult)}\right) * CL_{R\ (adult)} \quad (3)$$

$$CL_{TS,\ (child)} = (TS_{child}/TS_{adult}) * \left(f_{u,\ p\ (child)}/f_{u,\ p\ (adult)}\right) * CL_{TS\ (adult)} \quad (4)$$

where $CL_{R,\ (child)}$ and $CL_{R,\ (adult)}$ represent the renal clearance via glomerular filtration in a child and an adult, respectively; $f_{u,p\ (child)}$ and $f_{u,p\ (adult)}$ are the unbound fraction in plasma in a child and an adult, respectively; $CL_{TS,\ (child)}$ and $CL_{TS,\ (adult)}$ are renal clearance via tubular secretion (mediated by OAT3 and the hypothetical TS efflux protein) in a child and an adult, respectively; GFR_{child} and GFR_{adult} are glomerular filtration rate in a child and an adult, respectively; and TS_{child} and TS_{adult} are tubular secretion in a child and an adult, respectively.

2.4.4 Scaling Meropenem Non-Renal Clearance—Non-renal clearance of meropenem in the pediatric population was assumed similar to adults and mediated by DPEP1. Due to a lack of information on DPEP1 expression as a function of age, no ontogeny was considered. Thus, non-renal clearance was scaled by age-based maturation of organ weight.

2.4.5 Pediatric PBPK Model Evaluation—The scaled PBPK model was first verified using digitized meropenem plasma concentration vs. time data from the literature (Table S2). The PBPK model was further evaluated using opportunistically collected clinical data obtained from 200 infants with a GA ranging from 22 to 40 weeks and a PNA ranging from 1 to 95 days, treated with meropenem for cIAIs. The detailed demographic characteristics

for these subjects were previously published [36], and the data were previously analyzed using a nonlinear mixed-effect modeling approach implemented in NONMEM (version 7.4.1; Icon Development Solutions, Ellicott City, MD) [15]. The final dataset used for model evaluation had 181 subjects and 645 plasma concentrations. Out of 645 plasma samples, 15% were from infants that were GA < 32 weeks and PNA < 14 days (group 1); 53% from infants that were GA < 32 weeks and PNA   14 days (group 2); 13% from infants that were GA   32 weeks and PNA < 14 days (group 3); and 19% from infants that were GA   32 weeks and PNA   14 days (group 4). All concentrations were dose-normalized and separated into groups based on their age and the corresponding FDA-recommended dosing regimen for meropenem in infants < 3 months of age (Table S3). We created a virtual population comprising 4000 virtual infants matching the age and dosing groups from the clinical data, as described in Table S3. Simulated concentration vs. time data were compared with the observed data by visual and numeric inspection. The average fold error (AFE) for the PBPK model prediction was obtained based on Equation 5.

$$\text{Average fold error (AFE)} = 10^{\frac{1}{n}\Sigma \log\left(\frac{\text{Predicted Median Concentration}}{\text{Observed Concentration}}\right)} \tag{5}$$

AFE within each age group was calculated by summarizing AFE for individual subjects by their postmenstrual age in weeks. Overall, the PBPK model performance was deemed acceptable if the AFEs were between 0.5 and 2. We also compared the PBPK model-predicted steady-state clearance with the *post hoc* empirical Bayesian estimates of clearance obtained from a previously published PopPK analysis [15]. Additional information is available in the Electronic Supplementary Material.

2.4.6 Evaluation of Recommended Dosing Regimens in Infants < 3 Months of Age—The final pediatric PBPK model was used to assess the probability of target attainment in virtual infants < 3 months of age who were administered the meropenem product label dosing recommendations for cIAIs [1]. From the dosing simulation results, the 10th percentile of the percentage of the dosing interval where the unbound concentration in plasma was above minimum inhibitory concentration ($T_{>MIC}$) [3,37,38] for minimum inhibitory concentration (MIC) values of 0.25 to 16 mg/L was calculated and plotted against respective MICs. The 10th percentile corresponds to 90% of virtual infants. Based on previously described criteria, we evaluated if a 50% $T_{>MIC}$ was achieved for a MIC of 4 mg/L and if a 75% $T_{>MIC}$ was achieved for a MIC of 2 mg/L [15].

3   Results

3.1   PBPK Model Development

The physicochemical properties of meropenem were kept mostly unchanged, except for the optimization of logP. Similar to previous reports, meropenem was found to have a low logP value of −1.39, supporting its high water solubility and negative base-10 logarithm of acid dissociation constant (pKa) of 3.47. The kinetic parameters of the OAT3 transporter were mostly kept unchanged except for unitary correction of V_{max} utilizing protein concentration of HEK293 cells as previously described. Affinity (K_m) of the hypothetical efflux transport protein was considered lower than OAT3, and only V_{max} was adjusted to reflect the urinary

excretion of meropenem. Non-renal clearance by DPEP1 enzyme was considered a first-order process with a fixed value of 0.02 L/min, as obtained from literature and reflecting ~30% metabolism of meropenem in adults. The final PBPK model parameters are presented in Table 1.

3.2 Adult PBPK Model

The adult PBPK model of meropenem characterized the adult plasma PK data within the acceptable range for both 500 mg and 1000 mg IV infusions. Observed concentrations ± standard deviation from published adult data [8] were in good agreement with the 90% prediction interval of the simulated meropenem plasma concentration (Fig. 1a, Fig. 1b). A similar observation was made (Fig. 1c, Fig. 1d) when the model was evaluated using observed data from four additional publications (Table S1), including multiple-dose administration of meropenem in healthy subjects (Fig. S1a) and hospitalized patients (Fig. S1b and S1c). The simulated fraction excreted in urine 8 h after infusion ranged from 0.52 to 0.76, with a median value of 0.67. Simulated AUC and clearance were within a two-fold range of the published values (Table 2).

3.3 Pediatric PBPK Model

3.3.1 PBPK Model Evaluation with Digitized Published Data—The scaled pediatric PBPK model was first evaluated with published plasma concentration vs. time data (Table S2) using a virtual pediatric population of 200 subjects that mimics the respective publications' demographic characteristics. A simulated concentration vs. time profile adequately captured the observed data (Fig. 2, Fig. S2). We also compared the simulated PK parameters (AUC and clearance) with the values reported in each publication (when available) (Table 3), and the PBPK model-predicted parameters were found within two-fold of the reported parameters.

3.3.2 PBPK Model Evaluation in Infants < 3 Months of Age—The final PBPK model was evaluated with 645 plasma concentrations from 181 infants < 3 months of age first by visual comparison of the simulated vs. observed data (Fig. 3). The overall model AFE was 0.9. If samples collected from infants with a GA < 24 weeks are removed (due to the lower limit of GA in PK-Sim® being 24 weeks), the overall model AFE is 0.96. The median AFE, including all samples, was 0.67, 0.57, 0.92, and 2.25 for group 1 (GA < 32 weeks, PNA < 14 days), group 2 (GA < 32 weeks, PNA 14 days), group 3 (GA 32 weeks, PNA < 14 days) and group 4 (GA 32 weeks, PNA 14 days), respectively. The median AFE for GA 24 weeks was 0.72, 0.59, 0.92, and 2.25 for group 1, group 2, group 3, and group 4. Thus, although for group 4, the AFE is slightly greater than 2, the overall AFE indicates good model performance in infants. Overall, comparable weight-normalized clearance estimates were obtained using PBPK and PopPK modeling approaches [15] (Fig. 4).

3.4 Dosing Simulations in Infants < 3 Months of Age

Across all dosing groups, greater than 90% of virtual infants achieve at least 50% $T_{>MIC}$ for a MIC of 4 mg/L or 75% $T_{>MIC}$ for a MIC of 2 mg/L (Fig. 5).

4 Discussion

Meropenem is frequently used to treat bacterial infections (e.g., complicated skin and skin-structure infections, bacterial meningitis, and cIAIs) in pediatric patients [37,39]. It is currently approved by the FDA only to treat cIAIs in infants < 3 months of age. We developed a PBPK model of meropenem in infants < 3 months of age, which improves our understanding of meropenem disposition in this vulnerable age group. The PBPK model-derived clearance of meropenem in the virtual infant population is comparable with individual estimated clearance using standard PopPK methodology. The PopPK model was previously developed with extensive plasma concentration data from infants < 3 months of age treated with meropenem for cIAIs. Further, our analyses confirmed the existing FDA-approved label dosing regimen for this population. As there are logistical and ethical challenges associated with performing PK studies in infants, our model could be useful in investigating meropenem dosing in other infections for infants < 3 months of age without performing extensive PK studies.

Our PBPK model included elimination via glomerular filtration, OAT3-mediated uptake into renal proximal tubular cells, efflux via a hypothetical renal efflux transport protein, and non-renal clearance by DPEP1 as well as biliary clearance of meropenem informed by a previous publication. To predict meropenem's PK in preterm and term infants, we leveraged the virtual populations in PK-Sim® that accounted for developmental changes, including age-dependent changes in glomerular filtration, organ weights, blood flow rates, and tissue composition [28,29,35]. There are previously published meropenem pediatric PBPK models [40,41], but these previous studies focused model evaluation on pediatric patients > 3 months of age. In this analysis, we leveraged extensive individual-level data collected from preterm and term infants < 3 months of age to evaluate meropenem's PK early in life. Previously published PBPK models partitioned meropenem's clearance into renal clearance and an additional/nonspecific clearance pathway [40,41]. Therefore, although we obtained comparable simulated meropenem clearance values for these two pathways, our model sought to account for the specific mechanistic processes that modulate meropenem PK.

Recently published data for OAT3 transporter ontogeny were used to account for the maturation of the OAT3 transporter [31]. The published OAT3 transporter ontogeny was developed based on protein concentration in term infants, where no GA information was available. Although no mammalian efflux transporter for meropenem has been identified yet, *in vitro* experiments using rat ileal segments suggested active secretion of meropenem in rat intestine [42]. A generic maturation function, developed by Hayton [33], for active renal secretion was used to model a hypothetical efflux transport protein's age-dependent changes. It is important to note that the Hayton maturation function's development included only term infants > 40 weeks GA [43]. Although *in vitro* data were available for DPEP1, ultimately, we assumed a first-order clearance process and optimized intrinsic clearance to match previously reported values for non-renal clearance (simulated vs. observed: 0.02 vs. 0.03–0.08 L/min [7,8,25,26]). Due to a lack of information on DPEP1 expression and ontogeny, we were unable to use any maturation function for metabolic clearance of meropenem. Although meropenem has been reported to have low protein binding (~ 1% to 2%) [1], a recent publication reported much higher protein binding (40% to 60%) of

meropenem in patients [44]. As acknowledged by the study's authors, this difference in protein binding could be due, at least in part, to differences in disease status [44]. Given that a clear consensus on the observed variability for meropenem protein binding has not been reached [45], we used the product label reported fraction unbound in plasma (0.98) in our model. But, we acknowledge that as meropenem is a drug with low extraction ratio, higher protein binding in patients could significantly reduce the clearance of meropenem and could be one reason for observed differences between PBPK model-predicted and observed data.

The adult and pediatric PBPK model-simulated concentration vs. time, AUC and clearance values were in good agreement with previously published data. Performance of the population simulations in infants < 3 months of age, evaluated using individual-level data, was assessed using AFE, ranging between 0.57 and 2.25. The highest AFE (suggesting slight overprediction) of 2.25 was observed for the group with a GA   32 weeks and PNA   14 days. The lowest AFE value of 0.57 (suggesting underprediction) was observed for the group with a GA < 32 weeks and PNA   14 days. Therefore, although the data were well captured overall, some trends with age may be related to the underlying model assumptions (e.g., maturation of key mechanisms in neonates as discussed previously) or patient-related variables (e.g., renal dysfunction) that are not captured in the model. Of note, AFE was calculated based on the differences between observed and median predicted concentration. Thus it does not account for the variability.

The current model also does not capture the possible effect of disease and co-medications on the observed concentration of meropenem in infants. Fourteen percent of patients had necrotizing enterocolitis (NEC) Grade I, 27% had NEC Grade II, and about 8% had spontaneous perforations. Such severe infection and inflammation can lead to changes in kidney function [46,47] that can affect meropenem exposure. Along with meropenem, these infants were also treated with, among other drugs, vancomycin (50% of subjects), gentamicin (46%), furosemide (38%), fentanyl (33%), and morphine (26%), alone or in combination. Some of these co-treatments are well known for their effect on renal function and OAT transporter-mediated tubular secretion process [48,49].

The PBPK model clearance predictions for infants were compared with the estimates obtained from a previously published PopPK analysis. When these data were visualized as a function of PMA, an age-dependent increase in clearance was observed as expected (Fig. 4). Overall, there was good agreement between simulated PBPK model predictions and the individual estimates obtained using the PopPK model that included creatinine and PMA as covariates. At PMA values < 30 weeks, the PopPK model individual estimates were on the lower end of the PBPK model range, whereas the opposite is true at PMA values > 35 weeks. This is consistent with the trends observed when AFE values were evaluated across age groups. Therefore, although there was generally good agreement between these two methodologies, some age-dependent trends can be observed [15].

The PBPK model was applied to evaluate suggested meropenem dosing for infants < 3 months of age with cIAIs. Using a criterion of 50% $T_{>MIC}$ for a MIC of 4 mg/L or 75% $T_{>MIC}$ for a MIC of 2 mg/L, favorable target attainment was observed across all dosing groups. These PBPK model simulation results are in agreement with the

previously published PopPK analyses [15]. Therefore, these analyses suggest that both PBPK and PopPK modeling approaches were able to support similar meropenem dosing recommendations for infants < 3 months of age. Although in infants < 3 months of age meropenem is only indicated for complicated intra-abdominal infection, different dosing regimens of meropenem have been proposed for other indications (e.g., meningitis, sepsis, and pneumonia) [37,39]. While a 40% $T_{>MIC}$ is generally considered a bactericidal target for meropenem, the literature supports a higher %$T_{>MIC}$ (e.g. 64%, 80%) in critically ill patients, including infants and children [2,37,50]. Given that the individual-level data we used for model evaluation was collected from infants with suspected or confirmed intra-abdominal infections, we restricted our analysis to the FDA-approved drug label dosing regimens.

Our analysis is not without limitations. Although we sought to mechanistically account for the key variables that affect meropenem's disposition, due to lack of data for some physiological processes, we optimized required model parameters and assumed a hypothetical efflux transporter in the kidney. Although we made these assumptions, there was still an acceptable agreement between the observed and simulated clearance and AUC values, and the fraction excreted unchanged in the urine. Second, we matched virtual subject demographic characteristics with those of the observed data. However, because the PK data available for infants < 3 months of age were collected from patients with suspected or confirmed intra-abdominal infections, there may be disease alterations in these patients that were not captured in our simulations.

5 Conclusion

Our meropenem PBPK model confirms that product label dosing regimens for infants < 3 months of age are expected to result in adequate drug exposure and supports the use of PBPK modeling to characterize drug disposition in infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Conflicts of interest

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Data availability

Meropenem infant PK data was accessed through the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (DASH, https://dash.nichd.nih.gov/).

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Key Points

- Meropenem is a carbapenem antibiotic approved by the U.S. Food and Drug Administration for the treatment of complicated intra-abdominal infections in infants < 3 months of age.

- Physiologically based pharmacokinetic modeling of meropenem disposition in infants < 3 months of age showed that age- and weight-based dosing recommendations in the product label are expected to result in adequate drug exposure.

- Meropenem weight-normalized clearance estimates in infants obtained using PBPK and population pharmacokinetic modeling were compared and, generally, both methodologies resulted in comparable estimates.
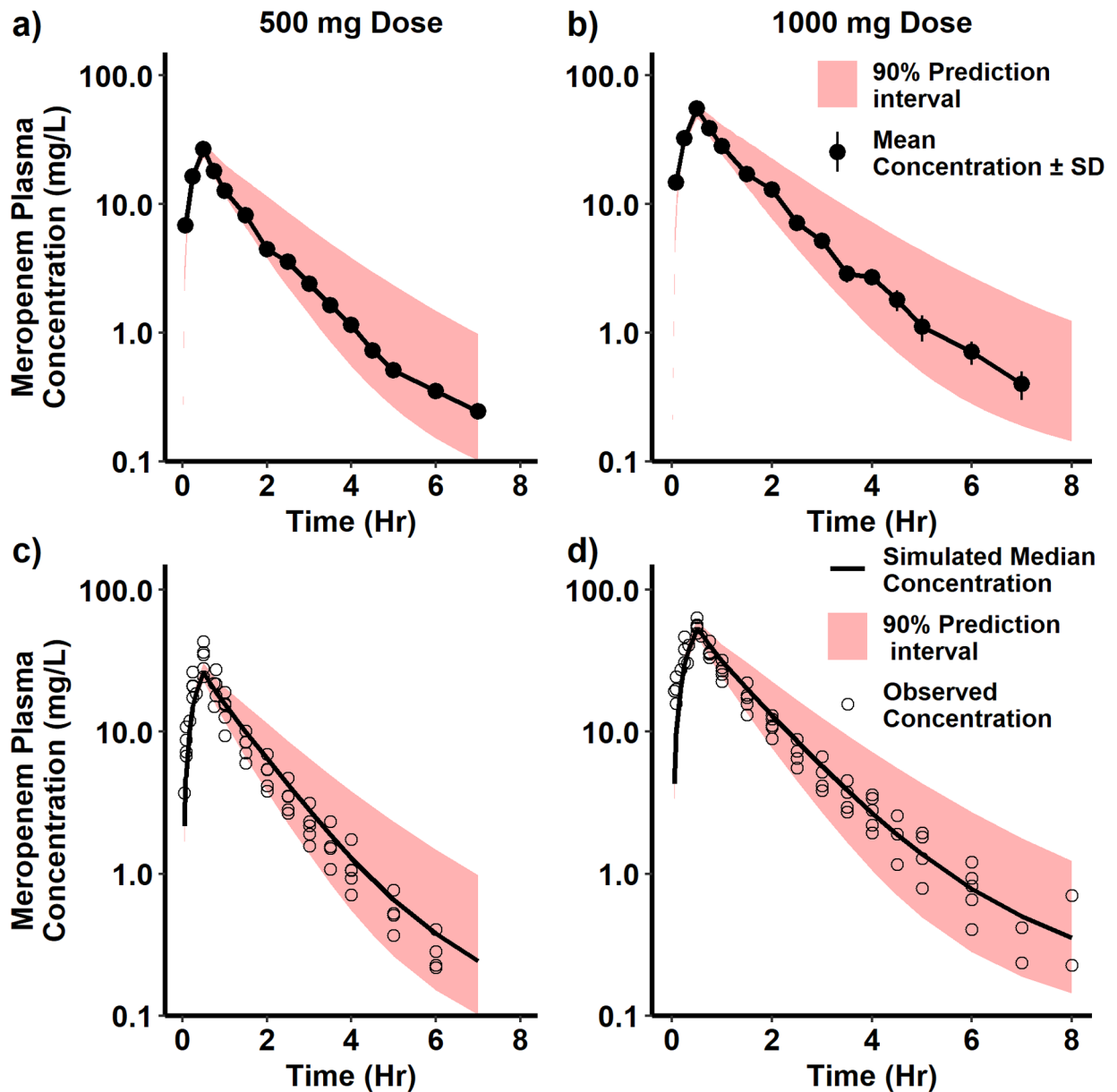
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Fig. 1.
Simulation of meropenem concentration vs. time for one hundred virtual adults. The adult meropenem PBPK model was developed and evaluated using published plasma meropenem concentration vs. time data digitized for a 0.5 and 1 g intravenous (IV) infusion administered over 30 minutes. In a) and b), digitized observed mean plasma concentration vs. time data (black circles with ± standard deviation as black lines) [8] were compared with the 90% prediction interval of the simulated meropenem plasma concentration vs. time profile (red shaded region). In c) and d), digitized observed plasma concentration vs. time data (black circles) [6,7,25,26] were compared with the median and 90% prediction interval of the simulated meropenem plasma concentration vs. time profile (red shaded region).
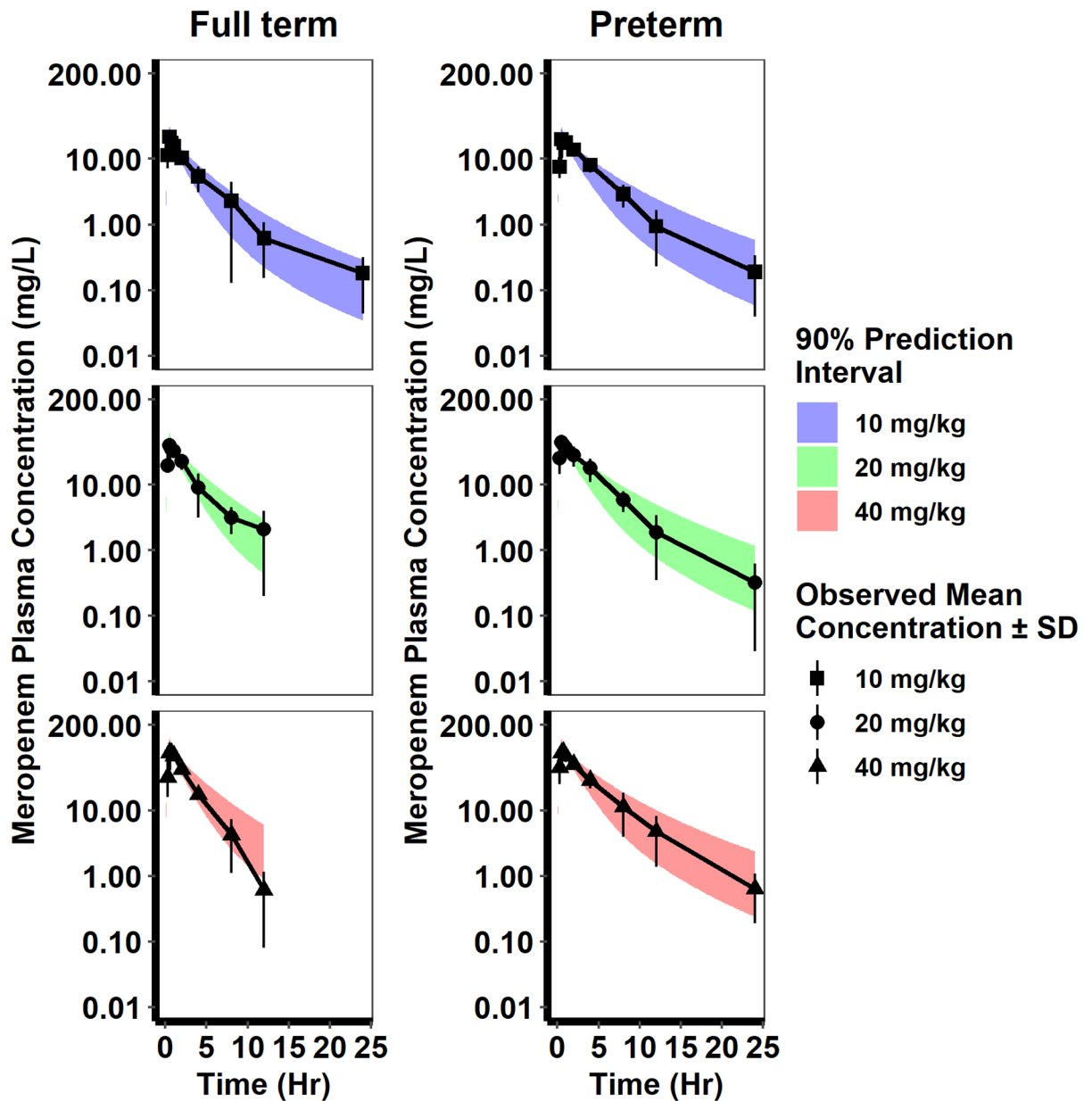
Fig 2.

Pediatric PBPK model evaluation. The adult PBPK model was scaled to infants and evaluated using digitized published data for preterm and term infants [13]. A virtual population (n=200) was generated based on published demographic information, simulations were performed using the PBPK model, and the results plotted as the 90% prediction interval (shaded region) overlaid with mean (± standard deviation [SD]) observed meropenem plasma concentration vs. time data after a single IV infusion (30 minutes duration). The colors and symbols represent different body weight-based dosing regimens. For the full-term infant simulations, the virtual infants' gestational age and postnatal age were 37 to 42 weeks and one day, respectively. For the preterm infant simulations, the virtual infants' gestational age and postnatal age was 29 to 36 weeks and one day, respectively.
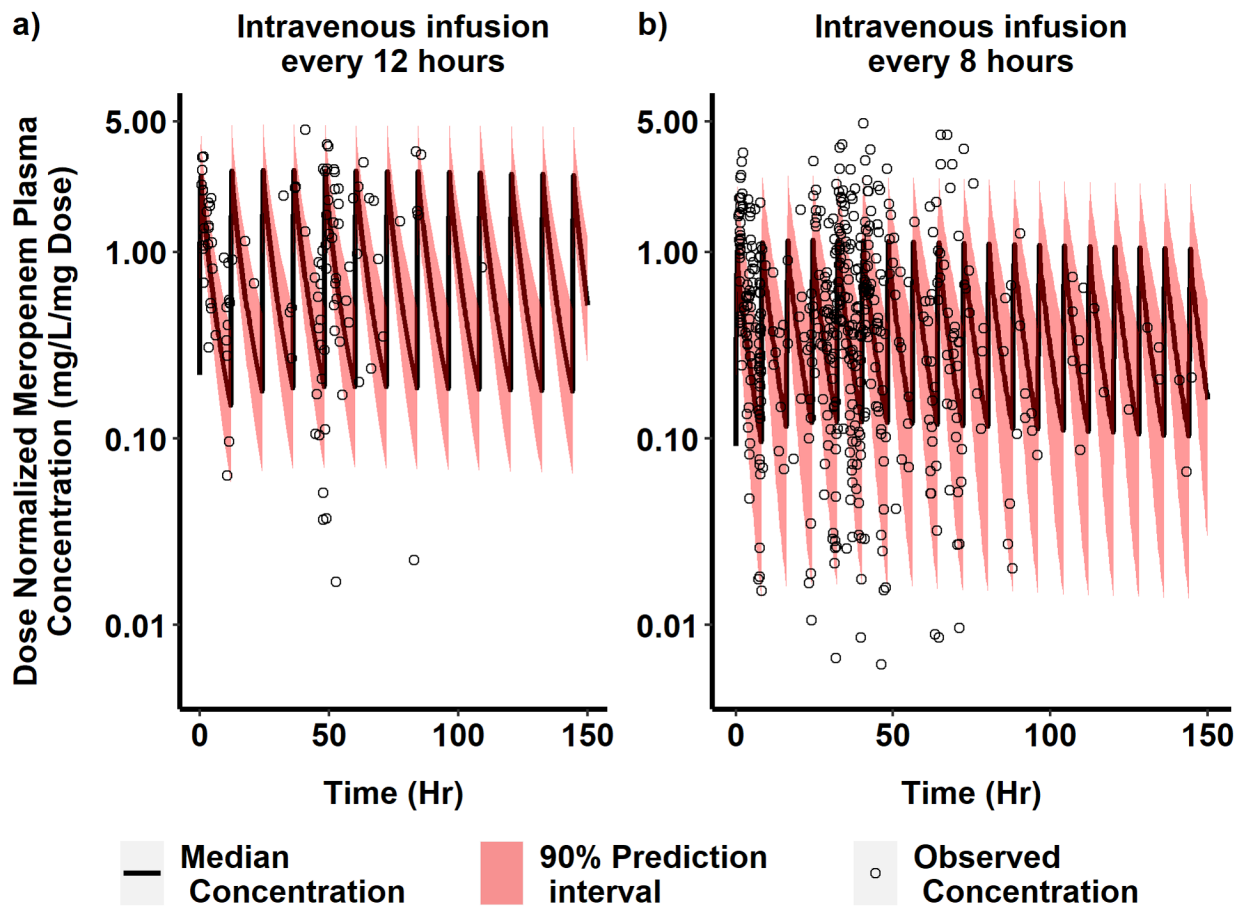
Fig. 3.
Observed vs PBPK model simulated dose-normalized meropenem concentration vs. time in infants. Dose-normalized and time-corrected observed plasma concentrations of meropenem (black circles) were compared with the 90% prediction interval (red shaded region) and the median (solid black line) simulated meropenem plasma concentration vs. time profile for a virtual neonatal population dosed 1 mg/kg of meropenem by intravenous (IV) infusion over 30 minutes. In a), 1000 virtual infants with gestational age (GA) < 32 weeks and postnatal age (PNA) < 14 days received meropenem every 12 hours. In b), 3000 virtual infants (1000 virtual infants per each of the following age groups: GA < 32 weeks and PNA ≥ 14 days; GA ≥ 32 weeks and PNA < 14 days; and GA ≥ 32 weeks and PNA ≥ 14 days) received meropenem every 8 hours. For the ease of visualization, x-axis is restricted up to 150 h, and the lower limit of y-axis is restricted up to 0.005 mg/L. These axes restrictions removed six concentrations from a) after 150 h time, and 29 concentrations from b) (19 of them were after 150 h and ten were below 0.005 mg/L/mg Dose).
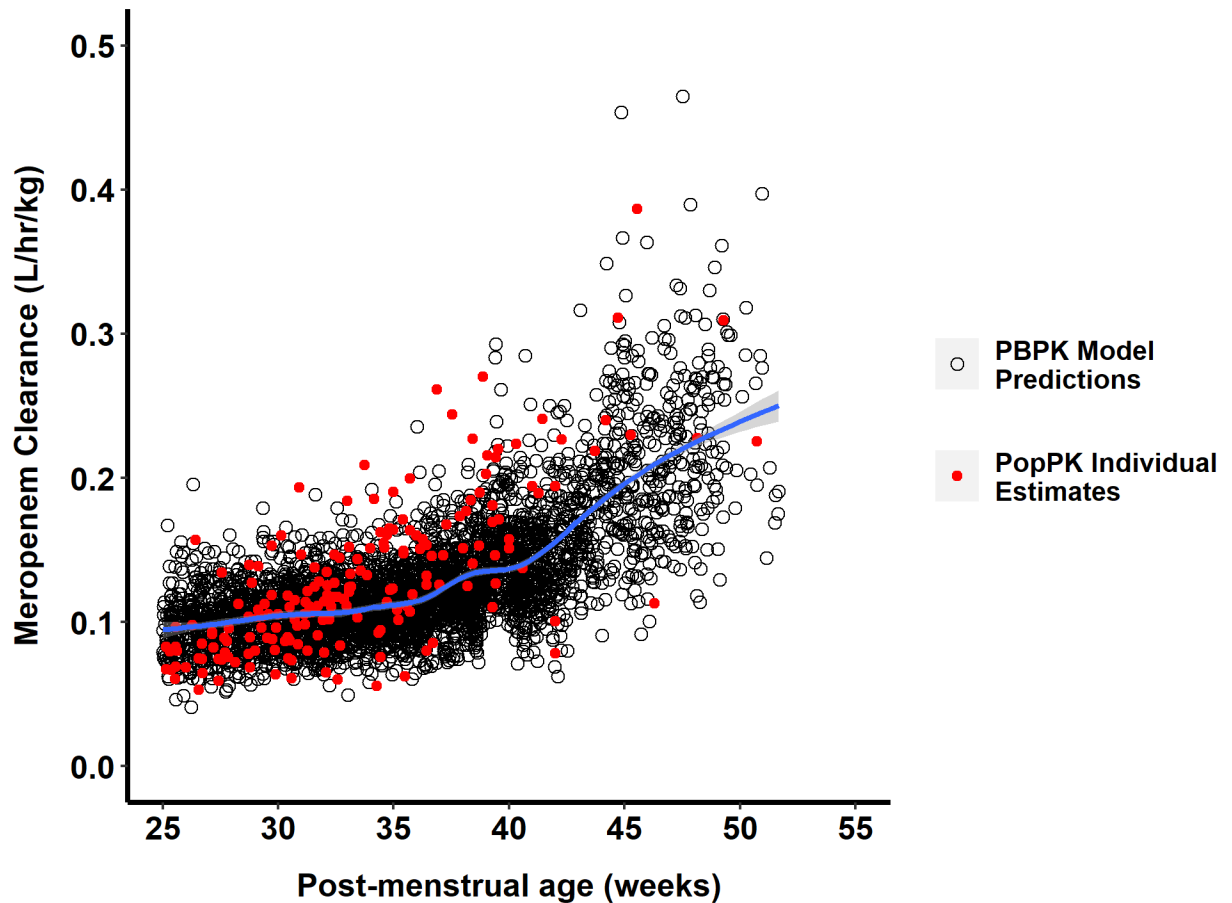
Fig. 4.

Comparison of body weight-normalized meropenem clearance in a virtual population of 4000 infants using the final physiologically based pharmacokinetic (PBPK) model (black open circles) and individual estimates of body weight-normalized clearance obtained from a previously published population pharmacokinetic (PopPK) analysis (red solid circles) [15] by postmenstrual age. The blue line indicates the smooth line based on a generalized additive model (default when sample size >1000) using the geom smooth function in the R package ggplot2. The virtual population for PBPK model simulations is comprised of 1000 virtual infants for each of the following age groups: gestational age (GA) < 32 weeks and postnatal age (PNA) < 14 days; GA < 32 weeks and PNA 14 days; GA 32 weeks and PNA < 14 days; and GA 32 weeks and PNA 14 days of age. The body weight and height range for each age group were selected to match the observed data's demographic characteristics (Table S3).
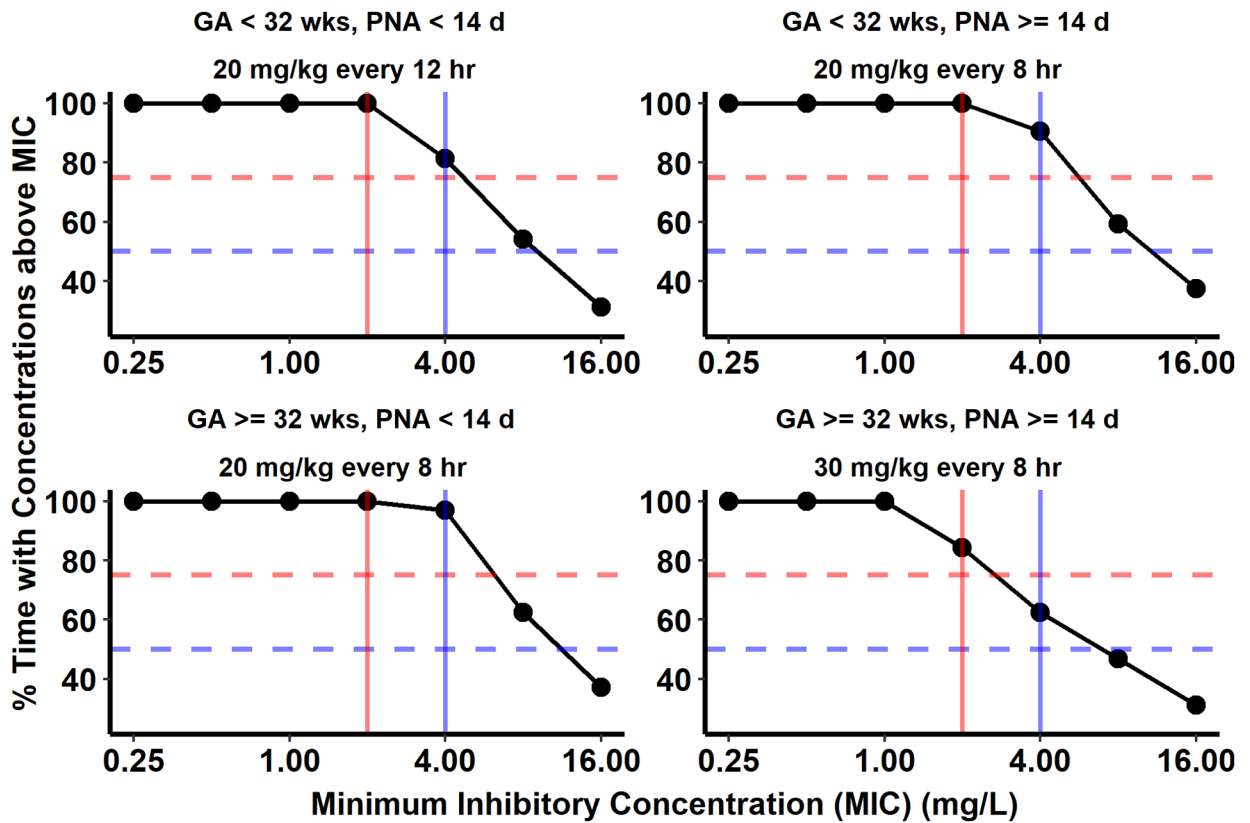
Fig. 5.

Target attainment analysis performed using the final physiologically based pharmacokinetic (PBPK) model to evaluate the product label recommended meropenem dosing for infants < 3 months of age with complicated intra-abdominal infections. One thousand virtual infants for each age cohort (stratified into four gestational age [GA] and postnatal age [PNA] groups) were dosed with the label recommended meropenem intravenous (IV) dosing. The percentage of the dosing interval for which the meropenem steady-state unbound plasma concentration was above the minimum inhibitory concentrations (MIC) of 0.25 to 16 mg/L was calculated for 90% of virtual infants (solid black line) and plotted against MIC on the x-axis. The horizontal dotted blue and red lines indicate the achievement of unbound plasma concentration higher than MICs for 50% and 75% of the dose interval, respectively. The two vertical lines indicate 2 mg/L (red) and 4 mg/L (blue) MICs. The intersection of the blue horizontal line and vertical lines indicates unbound plasma concentration achievement above 2 and 4 mg/L for 50% of the dosing interval.

Table 1

Meropenem physiologically based pharmacokinetic model parameters

Parameter	Reported Values	Final values
Physicochemical properties		
Molecular weight	383.5 g/mol	383.5 g/mol
Solubility	5.63 mg/ml at pH 7 [51] 14 mg/ml [52]	5.63 mg/ml
pKa	3.47 [40] 7.4 [52]	3.47
	−4.35 [40]	−1.39[*]
Lipophilicity (logP)	−3.28 [23]	-
	−0.69 [51]	-
Partition coefficients	Rodgers and Rowland [40,53]	Rodgers and Rowland [53]
Cellular permeabilities	-	PK-Sim® Standard
Pharmacokinetic properties		
Biliary Clearance	0.0422 L/h [22]	6.5E-04 L/h/kg
OAT3 K_m	847 ± 160 µM [9]	850 µM
OAT3 V_{max}	48.5 ± 7.5 pmol/min/mg [9]	600 µmol/L/min [24]
Hypothetical renal efflux transport protein V_{max}	-	200 µmol/L/min[*]
Hypothetical renal efflux transport protein K_m	-	1500 µM
DPEP1 V_{max}	8.58 ± 0.21 Units/mg protein [23]	-
DPEP1 K_m	3.56 ± 0.15 mM [23]	First order intrinsic clearance, 0.02 L/min[a]
f_u	0.98 [6,40]	-
Protein binding partner	Albumin	-

DPEP1, dehydropeptidase 1 or renal dipeptidase 1; K_m, Michaelis-Menten constant; OAT3, organic anion transporter subfamily 3; pKa, acid dissociation constant; V_{max}, maximum velocity of transport/reaction; f_u, unbound fraction

[*] Optimized values

[a] Optimized based on the reported *in vivo* non-renal clearance of meropenem.

Table 2

Comparison of observed and physiologically based pharmacokinetic (PBPK) model simulated area under the plasma concentration vs. time curve (AUC) and clearance following single-dose administration in adults

Dose (mg)	AUC (mg*h/L)[a]					Clearance (L/h)						Reference
	Observed		Simulated		Ratio[b]	Observed		Simulated		Ratio[b]		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD			
500	30.1	4.69	37.92	9.82	1.26	16.98	2.68	13.94	3.13	0.82		[8]
1000	66.9	11.27	76.28	19.85	1.14	15.24	2.35	13.86	3.08	0.91		
500	28.1	4.3	38.35	8.50	1.36	18.12	2.70	13.66	2.93	0.75		[7]
1000	77.2	11.8	77.39	17.09	1.00	13.44	1.98	13.53	2.89	1.01		
500	39.6	6.8	40.75	10.36	1.03	-	-	13.01	3.11	-		[26]
500	28	15	48.86	16.01	1.75	-	-	11.18	3.21	-		[25]
1000	77.5	11.5	80.62	18.23	1.04	11.28	1.86	13.03	2.95	1.16		[6]

SD, standard deviation.

[a] The area under the plasma concentration vs. time curve (AUC) for the physiologically based pharmacokinetic (PBPK) simulated data was calculated by extrapolation to infinity.

[b] The ratio is calculated as the ratio of the mean simulated/mean observed.

Table 3

Comparison of observed and physiologically based pharmacokinetic (PBPK) model simulated area under the plasma concentration vs. time curve (AUC) and clearance after single and multiple-dose administration of meropenem in the pediatric population[a]

	AUC (mg*h/L)[b]					Clearance (L/h/kg)					
	Observed		Simulated			Observed		Simulated			
Dose (mg/kg)	Mean	SD	Mean	SD	Ratio[c]	Mean	SD	Mean	SD	Ratio[c]	Reference
10	-	-	42.36	9.83	-	0.312	0.08	0.24	0.06	0.77	
20	-	-	85.50	19.79	-	0.312	0.1	0.24	0.06	0.77	[10]
40	-	-	173.80	40.06	-	0.39	0.12	0.24	0.06	0.62	
15, Day 1	99.1	28.9	110.83	22.34	1.12	0.16	0.005	0.14	0.03	0.88	
15, Day 5	99.8	48.5	115.30	29.68	1.16	0.16	0.07	-	-	-	[14][d]

[a] Pediatric population included subjects with postnatal age (PNA) ranging from 0.23 to 12.3 years[10]; and infants with GA of 27 to 32 weeks and PNA of 5 to 44 days [14].

[b] Area under the plasma concentration vs. time curve (AUC) for the PBPK simulated data is reported from time 0 hr to the last observed time point.

[c] The ratio is calculated as the ratio of mean simulated/mean observed

[d] Subjects received 15 mg/kg meropenem dosed as an intravenous infusion over 1 min every 12 hours for five days. AUC was calculated from 0 h to 12 h for the first dose and from 108 hr to 120 hr for the last dose. Clearance at steady state was reported based on a noncompartment analysis of the simulated data.