Introduction

Sepsis and bacterial meningitis are major causes of mortality and morbidity in neonates and infants and can be considered as part of a single continuum in that septic infants can develop meningitis.1,2 Late-onset sepsis (LOS) is defined as sepsis starting 72 h or more after birth.

Meropenem is a broad-spectrum carbapenem antibiotic with activity against common pathogens causing neonatal sepsis and meningitis. It is bactericidal against Escherichia coli, Klebsiella spp., Enterobacter spp. and Pseudomonas spp.,1 which are known to cause LOS, and also against pathogens responsible for bacterial meningitis such as Streptococcus agalactiae (i.e. group B streptococci), E. coli, Listeria monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae and Neisseria meningitidis.3,4

Meropenem pharmacodynamics (PD) is usually described by the percentage of time when concentrations are above the MIC (%T>MIC). Approximately 40%T>MIC is believed to be sufficient for a bactericidal effect;5,6 however, for immunocompromised patients, including neonates, higher targets have been suggested7 and a recent study looking at meropenem PD indices determined the PD target for neonates to be 61%T>MIC.8 For lower respiratory tract
infections, %T > 5 × MIC was suggested. Meropenem is predomin-
antly renally eliminated and approximately 75% is excreted
unchanged in the urine. As a polar, hydrophilic molecule, mer-
openem’s penetration into the CSF through the blood–brain barrier
is limited under normal, healthy conditions, but this may increase
when the meninges are inflamed. Meropenem is currently unlicensed in infants below 3 months of age and, whilst there are studies describing its pharmacokinetics (PK) in neonates and infants, only Smith et al. studied both plasma and CSF concentrations, including single CSF concentra-
tions from only six patients. Since the concentration–time profile of meropenem differs between plasma and CSF, taking the ratio of CSF to plasma is confounded by time after dose. To correctly assess the fractional CSF penetration necessitates sufficient sample numbers and timing for a model-based estimation. Consequently, sufficient information on meropenem’s disposition to infer dosing in this population is lacking. The NeoMero Consortium recently completed two studies with PK sampling from both plasma and CSF: NeoMero-1 (Efficacy, pharmacoki-
etics and safety of meropenem in subjects below 90 days of age (inclusive) with clinical or confirmed late-onset sepsis: a European multicentre randomised phase III trial) compared meropenem with standard of care (β-lactam plus aminoglycoside); and NeoMero-2 (Pharmacokinetics and safety of meropenem in sub-
jects below 90 days of age (inclusive) with probable and confirmed meningitis: a European multicentre phase I–II trial). Since some patients recruited to NeoMero-1 developed meningitis and trans-
ferred to NeoMero-2, the aim of this study was to report a joint analysis of the plasma and CSF PK results from both studies. We further sought links with outcome (PD) in NeoMero-1 (LOS) in order to inform dosing for LOS.

Patients and methods

Ethics

In NeoMero-1, subjects were recruited from 15 centres in six different coun-
tries (Estonia, Greece, Italy, Lithuania, Spain and Turkey). There were,
on average, 8 subjects/centre (range 1–25). In NeoMero-2, there were
21 centres in seven countries (Estonia, Greece, Italy, Lithuania, the
Netherlands, Spain and the UK) recruiting, on average, 2 subjects/centre
(range 1–9). Independent Ethics Committees in each country approved
the studies, which were registered on EudraCT (2011-001515-31 and
2011-001521-25) and clinicaltrials.gov (NCT01551394 and NCT01556124).

Patient recruitment

The inclusion criteria for NeoMero-1 were: diagnosis of sepsis and postnatal
age (PNA) < 90 days, and ≥ 72 h of life at sepsis onset. Sepsis was defined as:
(i) sepsis confirmed by a positive bacterial culture, accompanied by an
abnormal clinical or laboratory measurement; or (ii) clinical sepsis, i.e. in
as: (i) sepsis confirmed by a positive bacterial culture, accompanied by an

Meropenem administration

Meropenem was supplied by Chiesi Pharmaceuticals, Italy. A 12 hourly dose
interval was used in patients with < 32 weeks’ gestational age (GA) and
< 2 weeks’ PNA, and 8 hourly in all others. For LOS 20 mg/kg was used and
for meningitis 40 mg/kg was used, these doses and frequencies having
been previously used off-label. Meropenem was infused over 30 min, which
was determined using a now-published model (interim version provided
during the protocol development by Professor Caparelli) and simulating the
PTA with different infusion lengths, specifically bolus, 30 min, 1 h and 2 h
infusions. Whilst the 2 h infusion gave a greater PTA, concerns about use of
line space and possible reduced CNS penetration led to a pragmatic deci-
sion to use 30 min infusions.

PK sampling

Plasma sampling for PK was designed to minimize invasiveness whilst max-
imizing information gained. Three optimally timed PK samples were there-
fore decided to be taken from ≥ 56 subjects, spread evenly over each of the
given age groups: < 32 weeks GA and < 2 weeks PNA; < 32 weeks GA and
≥ 2 weeks PNA; ≥ 32 weeks GA and < 2 weeks PNA; and ≥ 32 weeks GA and
≥ 2 weeks PNA. The remaining patients would contribute a single trough
test. Owing to logistical constraints in that meropenem could be started
at any time, and in an emergency setting, PK sampling was planned to take
place at steady-state. The PK model mentioned in the previous section and
demographics from a previous European neonatal/infant sepsis study22
were used to define optimal sampling times. ED-optimal design (PopED
software23) was used, including interindividual variability. For the three-
sample cohort, optimal times were immediately following the end of the
infusion, 5–6 h post-dose for 8 hourly dosing, 7–8 h post-dose for the young
preterm group dosed 12 hourly and a trough sample immediately before a
dose. For the single sampling optimal design, a trough sample proved most
informative. Since it was not possible to take CSF samples specifically for PK,
these were opportunistically collected when lumbar puncture was per-
formed for other study-specific purposes, with accurate recordings of time,
date and dose history.

Sample handling and meropenem assay

Blood samples were immediately spun down and plasma extracted.
All samples were frozen within 1 h of collection and stored at − 80 °C prior to
analysis. Ultra-HPLC coupled with tandem MS (UHPLC-MS/MS) was used to
determine plasma and CSF meropenem concentrations. To prepare 50 µL
of plasma and CSF samples for the analysis, protein precipitation with
methanol and microfiltration (using 0.22 µm filters), respectively, were
used. In both cases we used etoposone as an internal standard. The limit
of detection for the plasma assay was 10 ng/mL and the limit of detection
for the CSF assay was 2 ng/mL. The between-day variability was 4.1%–5% over
the whole calibration range, including the limit of quantification (LoQ)
of 80 ng/mL for the plasma assay; and 3%–5% for the CSF assay with an
LoQ of 6 ng/mL.

PK modelling

PK modelling was undertaken using the first-order conditional estimation
method with interaction (FOCEI) in NONMEM 7.3 (ICON Development
Solutions, Ellicott City, MD, USA). Firstly the plasma model was deter-
mined, followed by addition of a compartment for the CSF concentrations.
For the plasma PK, one-, two- and three-compartment structural models
were tested to define the basic structural model. Between-subject variability
was assumed to follow a log-normal distribution, and for the residual error,
proportional, additive, combined and Box–Cox power transformation (with

by University College London user
on 15 May 2018
both the shape and the scedasticity parameters estimated were tested. To delineate size and age from other possible covariates, body weight and postmenstrual age were included \textit{a priori} in the model with allometric weight scaling and a function describing renal function maturation, respectively.\textsuperscript{26} The parameters of the maturation function were fixed to values from a previous study of human glomerular filtration development.\textsuperscript{27} However, since meropenem is renally cleared, and renal function improves in the days after birth independently of postmenstrual age, we also tested the effects of PNA and serum creatinine (corrected for postmenstrual age\textsuperscript{18}) on CL. A covariate was included in the final model, if (after the inclusion) it produced a drop in the objective function value (OFV) (ΔOFV) of >6.63, which corresponds to a P value of <0.01. The significance of a covariate was also tested by a randomization test\textsuperscript{28,30} (n = 1000) performed using PnS.\textsuperscript{31} Since most patients were expected to contribute one CSF sample, the CSF volume was fixed to 0.15 L/70 kg\textsuperscript{12} and so two parameters were estimated: the inter-compartmental CL between plasma and CSF, and the fraction of meropenem penetration from the central compartment into the CSF. Markers of CNS inflammation (CSF proteins, lactate concentration, glucose concentration or number of white blood cells per unit of volume) may correlate with blood–brain barrier function; therefore, the effects of these covariates on penetration fraction were investigated. When these covariates were missing, they were replaced with the median. Basic goodness-of-fit plots [observations versus predictions, conditional weighted residuals (CWRES) versus time and prediction] in addition to visual predictive checks with 1000 replicates were used during model-building and to select the final model. A non-parametric bootstrap analysis was performed (n = 1000) on the final model to test parameter robustness and derive uncertainty around the parameter estimates.

**PD analysis of LOS**

For NeoMero-1 patients with culture-proven Gram-negative bloodstream infections for which an MIC could be determined and who received at least 24 h of treatment, the model was used to generate individual AUC\textsubscript{0–24MIC}, C\textsubscript{max}\textsubscript{MIC}, C\textsubscript{min}\textsubscript{MIC} and %T\textsubscript{MAX}. These were compared with whether the patient successfully completed the treatment course with clinical/laboratory improvement (success) or if treatment had to be modified at the discretion of the treating physician or the patient died (failure). These endpoints were measured at the test-of-cure visit 2 ± 1 days after the end of planned therapy (11 ± 3 days). The Kruskal–Wallis test was used to compare the two groups.

**Simulations**

Monte Carlo simulations (n = 1000) using the final model estimates were used to generate %T\textsubscript{MAX} curves for different dosing regimens and the following MIC values: 0.25, 0.5, 1, 2, 4, 8 and 16 mg/L. The unbound fraction of meropenem was fixed to 0.98.\textsuperscript{31} The %T\textsubscript{MAX} curves were generated using plasma (for LOS) or CSF (for meningitis) predictions. The PD target was set to 61%T\textsubscript{MAX}\textsuperscript{9} and simulations were done for all four age groups.

**Results**

**Demographics and PK samples**

A total of 167 patients underwent PK sampling in the NeoMero studies, with 123 from NeoMero-1 (5 of whom were diagnosed with probable or confirmed bacterial meningitis and transferred to NeoMero-2) and 49 (including the 5 from NeoMero-1) in NeoMero-2. At enrolment, their median (range) weight was 2.12 (0.48–6.32) kg, PNA was 13 (1–90) days and gestational age (GA) was 33.3 (22.6–41.9) weeks. Patients from the NeoMero-1 study were more premature (median GA of 31.9 weeks versus 37.1 weeks in NeoMero-2) and therefore also weighed less than the patients from the NeoMero-2 study. Demographics are presented in Table 1.

Three optimally timed plasma samples were collected from 109 patients, whilst 44 provided a single trough sample. Sampling numbers from the remaining patients were two (nine patients), four (four patients) and seven (one patient). There was an even spread in PNA and GA of optimally timed samples with 25, 18, 20 and 24 patients, respectively, providing three optimal samples in each of the pre-defined age categories (<32 weeks GA and <2 weeks PNA; <32 weeks GA and >2 weeks PNA; >32 weeks GA and <2 weeks PNA; and >32 weeks GA and >2 weeks PNA). Following sample analysis, 11 meropenem peak plasma samples were below 10 mg/L indicating possible data entry error and were thus excluded from the analysis to prevent biasing the model development. The influence of these data points was tested with the final plasma model and, although the changes in the typical final model parameter estimates were below 10%, the interindividual variability and the uncertainty approximately doubled, again giving a reason for their exclusion. The data set for model-building therefore contained 401 plasma samples and 78 CSF samples (CSF was obtained from 56 patients). The median (range) of CSF sampling time was 5.27 (0–12.0) h post-dose. Plots of the raw data are presented in Figure 1. One CSF protein concentration was also excluded from the analysis, as it was not deemed biologically plausible (102 g/L).

**Meropenem clearance is significantly related to renal function, and CSF penetration to CSF protein concentration**

The final plasma population PK model was a one-compartment model. Weight was included with allometric scaling (with exponents fixed to 1 for central volume and 0.632 for CL\textsuperscript{27}) and postmenstrual age was included with a maturation function (with parameters fixed to values from a study of renal development\textsuperscript{27}). PNA did not significantly improve the model fit; however, serum creatinine concentration (standardized by postmenstrual age) proved to have a significant effect on meropenem clearance (ΔOFV of 19.7) and was therefore also included in the final model.

An additional compartment was added to describe meropenem CSF PK and to estimate the penetration of meropenem from plasma to the CSF. Out of the tested covariates, both the CSF lactate concentration and the CSF total protein concentration proved to significantly explain the CSF penetration (ΔOFVs of 24.3 and 24.4, respectively). However, since there were fewer missing measurements for CSF protein concentration (there were 86 protein and 54 lactate concentrations available, with 58 and 41 of these, respectively, taken at the time of CSF meropenem sampling), this covariate was included in the final model. The significance of the covariates was also confirmed by a randomization test\textsuperscript{29,30}.

Initially, a proportional model was chosen for the residual error of both plasma and CSF data; however, Box–Cox power transformations of the residual error\textsuperscript{29} resulted in an improved fit (ΔOFV of 67.8) and there was an improvement in the distribution of the residuals; therefore, this residual error model was used. The estimate for the scedasticity parameter corresponding to the CSF concentrations was approximately zero and there was no
improvement whether it was estimated or not; therefore, it was fixed to zero. The final model parameters are presented in Table 2.

The diagnostic plots showed adequate fit to the data (i.e. agreement between the measured and predicted concentrations was observed and there was no particular trend in the residual plots) (Figure 2) and the visual predictive check (using 1000 replicates) confirmed that the model had good simulation properties (Figure 3).

In vitro PD target reached in all culture-proven cases

In the NeoMero-1 study there were 24 individuals with culture-proven LOS with a Gram-negative organism for which MIC values were available and at least 24 h of meropenem had been administered. Of these, 12 patients considered to have been successfully treated (no need to modify the treatment course), whereas 12 patients failed (2 died, 9 required treatment modification at the discretion of the treating physician and 1 still had unresolved symptoms). The mean MIC in the 12 successes was 0.27 mg/L, whereas in the 12 failures the mean MIC was 0.98 mg/L (P = 0.38). All patients had a %T\textsubscript{MIC} above 61% (the proposed in vitro-derived target\textsuperscript{2}); there was no difference in AUC\textsubscript{0-24}/MIC ratio (P = 0.53) or in C\textsubscript{min}/MIC ratio (P = 0.73) in patients classified as treatment failures versus successes (Figure 4). Simulations of %T\textsubscript{MIC} showed little difference between bolus and 30 min infusions (data not shown) and so a comparison of 20 and 40 mg/kg bolus versus continuous infusion are shown in Figure 5 (with a frequency of 8 hourly or 12 hourly for those <32 weeks gestation and <2 weeks PNA as per our study dosing).

Discussion

This population PK model describing plasma and CSF disposition of meropenem in infants aged <90 days with LOS and/or bacterial meningitis represents the largest study of meropenem PK in infants aged <90 days to have been reported to date, which also included the highest number of collected CSF samples in this population. The generally accepted target of 40% T\textsubscript{MIC} is believed to be adequate for bactericidal effects of carbapenems,\textsuperscript{3} but a recent in vitro study has suggested that differences in the PK profile in neonatal patients means a higher target of 61% T\textsubscript{MIC} is warranted.\textsuperscript{8} All of our patients with culture-proven Gram-negative LOS achieved this target, but it should be noted that most MIC values were ≤0.25 mg/L. Simulations showed that 90% of patients should achieve 61% T\textsubscript{MIC} for organisms with an MIC of ≤2 mg/L and so our major finding is that, for meropenem-susceptible organisms, a 20 mg/kg bolus appears to be a sufficient dose for LOS (Figure 5).

A recent randomized controlled trial of continuous versus 30 min meropenem infusion in neonates with culture-proven infection found decreased mortality and ventilator support required in the continuous infusion group.\textsuperscript{3,4} Whilst no MICs were recorded in this study, which also found surprisingly high failure of microbial eradication at 7 days (30% overall), it is not the only clinical study to report improved outcomes with differing meropenem C\textsubscript{min}. High %T\textsubscript{MIC} has also been reported to be associated with improved clinical outcomes in adult lower respiratory tract infection,\textsuperscript{9} with a breakpoint of C\textsubscript{min} of 5 times the MIC being associated with maximum benefit.

The simulations in Figure 5 show that the same dose given as a continuous infusion achieves higher C\textsubscript{min}/MIC ratios. Simulations

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**Table 1. Demographics of included subjects**

<table>
<thead>
<tr>
<th></th>
<th>All data</th>
<th>NeoMero-1</th>
<th>NeoMero-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects\textsuperscript{a}</td>
<td>167</td>
<td>123</td>
<td>49</td>
</tr>
<tr>
<td>Weight (kg), median (range)</td>
<td>2.12 (0.48–6.32)</td>
<td>1.68 (0.48–5.01)</td>
<td>3.11 (0.60–6.32)</td>
</tr>
<tr>
<td>GA (weeks), median (range)</td>
<td>33.3 (22.6–41.9)</td>
<td>31.9 (22.6–41.3)</td>
<td>37.1 (23.4–41.9)</td>
</tr>
<tr>
<td>PNA (days), median (range)</td>
<td>13 (1–90)</td>
<td>15 (3–83)</td>
<td>9 (1–90)</td>
</tr>
<tr>
<td>Postmenstrual age (weeks), median (range)</td>
<td>37.4 (23.7–51.3)</td>
<td>36.0 (23.7–51.3)</td>
<td>38.8 (24.9–51.1)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>78 (46.7)</td>
<td>59 (48.4)</td>
<td>19 (42.2)</td>
</tr>
<tr>
<td>Number of plasma samples</td>
<td>401</td>
<td>255</td>
<td>147</td>
</tr>
<tr>
<td>Plasma samples per patient, mean</td>
<td>2.4</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Number of CSF samples</td>
<td>78</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>CSF samples per patient, mean</td>
<td>0.47</td>
<td>0.26</td>
<td>0.94</td>
</tr>
<tr>
<td>Plasma concentration (mg/L), median (range)</td>
<td>7.94 (0.01–147.7)</td>
<td>5.27 (0.01–147.7)</td>
<td>12.4 (0.1–139.0)</td>
</tr>
<tr>
<td>CSF concentration (mg/L), median (range)</td>
<td>1.58 (0.04–35.4)</td>
<td>1.23 (0.04–7.34)</td>
<td>1.90 (0.05–35.4)</td>
</tr>
<tr>
<td>Plasma time after the dose (h), median (range)</td>
<td>5.66 (0–12.4)</td>
<td>5.93 (0–12.4)</td>
<td>5.19 (0–12.2)</td>
</tr>
<tr>
<td>CSF time after the dose (h), median (range)</td>
<td>5.27 (0–12.0)</td>
<td>5.99 (0–12.0)</td>
<td>5.03 (0–11.5)</td>
</tr>
<tr>
<td>Creatinine (μmol/L), median (range)</td>
<td>32.0 (3.54–197.4)</td>
<td>34.5 (3.54–197.4)</td>
<td>27.0 (6.0–133)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L), median (range)</td>
<td>23.0 (0.3–280)</td>
<td>23.2 (0.3–242)</td>
<td>22.4 (0.4–280)</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL), median (range)</td>
<td>2.7 (0.1–377.2)</td>
<td>2.8 (0.1–128.6)</td>
<td>1.8 (0.1–377.2)</td>
</tr>
</tbody>
</table>

For creatinine, C-reactive protein and procalcitonin, the summary statistics represent all samples recorded during the study. Day 0 = first day of life. Weight, PNA and GA—at enrolment.\textsuperscript{a} Five infants switched from NeoMero-1 to NeoMero-2.
from our model based on a breakpoint of 2 mg/L showed that standard 20 mg/kg dosing would achieve the in vitro-derived target of 61% $T_{\geq MIC}$ in 90% of patients, but if the MIC were to increase to 4 mg/L as organisms become intermediately resistant, it would be necessary to increase dosing to 40 mg/kg. The use of a continuous infusion with an 8 hourly dose of 40 mg/kg (i.e. 120 mg/kg in 24 h) would be required to achieve a $C_{\text{min}}:MIC$ ratio of $>5$ for an MIC of around 1 mg/L and continuous infusions do clearly increase plasma %$T_{\text{MIC}}$ (Figure 5). Simply moving to continuous infusions may, however, not be appropriate, particularly in this clinical setting where patients with LOS can go on to develop meningitis. As can be seen in Figure 5, continuous infusions give substantially lower CNS concentrations for the same total daily dose. This is likely due to low $C_{\text{max}}$ resulting in lower peripheral concentrations. The association between longer meropenem infusions and lower $C_{\text{max}}$ has also been previously shown.14

The data in our study have substantially increased the literature on meropenem CSF PK, which enables simulated dosing schemes to balance circulating and CSF concentrations. The only study that focused on meropenem plasma and CSF disposition in infants (<3 months of age) to date involved six patients, who provided nine CSF samples.15 Smith et al.15 reported that uptake of meropenem into the CSF was 70%, determined by comparing plasma and CSF concentrations at the same timepoint. This method is suboptimal since the CSF and plasma time courses vary as $\beta$-lactams enter the CSF through paracellular pathways,35 resulting in a delayed peak CSF concentration. Our model-based typical estimate for the fraction of meropenem penetration from plasma into the CSF was 8.4%, which is at the lower end of the values previously reported in the literature: 10% up to 30%,35,36 or 40%37 and this could be because the meninges were not inflamed13 in many of the NeoMero-1 patients without meningitis; median CSF protein and CSF lactate concentrations were almost in normal ranges (1.2 g/L and 1.8 mmol/L, respectively). We did find a significant increase in CNS penetration with increasing CSF protein concentration, with penetration reaching over 40% when CSF protein concentration exceeded 6 g/L. Overall the CNS penetration results show that the fraction entering the CNS is low and comparable with other populations, although when inflammation is present, as evidenced by the presence of proteins in the CSF, penetration significantly increases.

The values of the PK parameters for a typical infant from this study (weight = 2.1 kg, postmenstrual age = 37.4 weeks, serum creatinine = 32 $\mu$mol/L, CSF protein concentration = 1.2 mmol/L and serum creatinine, standardized by postmenstrual age = 60 $\mu$mol/L) were: $CL = 0.39$ L/h and $V = 1.17$ L.
Table 2. Population PK model final parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SE</th>
<th>%CV</th>
<th>η-shrinkage (%)</th>
<th>Bootstrap, median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h/70 kg)</td>
<td>16.7</td>
<td>1.07</td>
<td>—</td>
<td>—</td>
<td>16.7 (14.7, 18.9)</td>
</tr>
<tr>
<td>θ_creatinine</td>
<td>−0.40</td>
<td>0.094</td>
<td>—</td>
<td>—</td>
<td>−0.40 (−0.58, −0.21)</td>
</tr>
<tr>
<td>V (L/70 kg)</td>
<td>38.6</td>
<td>2.15</td>
<td>—</td>
<td>—</td>
<td>38.6 (34.9, 43.4)</td>
</tr>
<tr>
<td>CL_{CSF} (L/h/70 kg)</td>
<td>0.017</td>
<td>0.004</td>
<td>—</td>
<td>—</td>
<td>0.016 (0.001, 0.030)</td>
</tr>
<tr>
<td>CSF uptake^a</td>
<td>2.39</td>
<td>0.205</td>
<td>—</td>
<td>—</td>
<td>2.38 (2.01, 2.82)</td>
</tr>
<tr>
<td>θ_{CSF proteins}^a</td>
<td>−0.17</td>
<td>0.110</td>
<td>—</td>
<td>—</td>
<td>−0.17 (−0.43, 0.015)</td>
</tr>
<tr>
<td>IIV on CL</td>
<td>0.255</td>
<td>0.058</td>
<td>50.5</td>
<td>13.5</td>
<td>0.248 (0.154, 0.370)</td>
</tr>
<tr>
<td>IIV on V</td>
<td>0.153</td>
<td>0.059</td>
<td>39.1</td>
<td>31.0</td>
<td>0.154 (0.042, 0.282)</td>
</tr>
<tr>
<td>Cov IIV CL-V</td>
<td>0.167</td>
<td>0.055</td>
<td>—</td>
<td>—</td>
<td>0.163 (0.070, 0.277)</td>
</tr>
<tr>
<td>RUV_{plasma}</td>
<td>0.679</td>
<td>0.108</td>
<td>—</td>
<td>—</td>
<td>0.664 (0.489, 0.900)</td>
</tr>
<tr>
<td>RUV_{CSF}</td>
<td>1.19</td>
<td>0.125</td>
<td>—</td>
<td>—</td>
<td>1.15 (0.941, 1.391)</td>
</tr>
<tr>
<td>Lambda_{plasma}</td>
<td>0.280</td>
<td>0.107</td>
<td>—</td>
<td>—</td>
<td>0.275 (0.064, 0.482)</td>
</tr>
<tr>
<td>Lambda_{CSF}</td>
<td>0.285</td>
<td>0.107</td>
<td>—</td>
<td>—</td>
<td>0.279 (0.066, 0.485)</td>
</tr>
<tr>
<td>Delta_{plasma}</td>
<td>−0.174</td>
<td>0.052</td>
<td>—</td>
<td>—</td>
<td>−0.178 (−0.287, −0.063)</td>
</tr>
</tbody>
</table>

SE, standard error from NONMEM covariance step; CV, coefficient of variation; IIV, between-subject variability; Cov, covariance; RUV, residual error; θ, estimated covariate effect.

Lambda and delta are parameters from the dynamic-transform-both-side approach for residual error modelling (more specifically, lambda is the shape parameter and delta is the scedasticity parameter; together they are a part of the Box–Cox power parameter, zeta = lambda + delta).

^aIndicates that the value is on the logit scale.

Figure 2. Basic goodness-of-fit plots for the final model. The top two plots show observed concentration (DV) versus population predictions (PRED) for plasma and CSF samples. The bottom two plots show CWRES versus time after dose (TAD) for plasma and CSF samples.
Figure 3. Visual predictive check showing the 2.5th, 50th and 97.5th percentiles of the observed data (lines and open circles) compared with the 95% CIs of the corresponding simulations from the final model (shaded areas). The top panel shows plasma and CSF for NeoMero-1 and the bottom panel shows plasma and CSF for NeoMero-2.

Figure 4. Box-and-whisker plots of the probability of treatment failure versus $C_{\text{min}}/\text{MIC}$ (left) and $\text{AUC}_{0-24}/\text{MIC}$ (right) ratios for the LOS patients with Gram-negative organisms and corresponding meropenem MIC. Open circles represent the raw data for each patient and filled circles represent patients who died.
are in agreement with what has been previously reported in the literature. For example, van den Anker et al. found that CL was 0.43 L/h and V was 0.97 L for a population of premature and mature infants. When only premature infants with an approximate weight of 1 kg were studied, the CL was lower, specifically 0.06 L/h and 0.15 L/h. A lower clearance of 0.13 L/h was also reported by Smith; however, in all these cases the infants weighed around 1 kg, which would explain the lower CL estimate. This also is the reason for a 12-hourly frequency to be retained in the youngest premature age group.

Since meropenem showed low potential for nephrotoxicity, higher doses do not necessarily mean increased toxicity. Therefore, if needed, the doses could be increased or meropenem could be given more frequently.

Conclusions

A PK model describing plasma and CSF meropenem data in young infants with confirmed or suspected LOS and/or meningitis was developed using data from one of the largest infant sepsis trials to have been conducted in this population. Dosing of 20 mg/kg as an 8 hourly bolus may be adequate for LOS at current MIC targets, but in future 40 mg/kg may be necessary owing to increasing pathogen MICs. Increasing infusion times (up to continuous infusion) improves circulating %\( T_{>\text{MIC}} \), but decreases CSF %\( T_{>\text{MIC}} \).

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Transparency declarations

None to declare.

References


Figure 5. Simulated %\( T_{>\text{MIC}} \) for various dose schemes. The top row gives values for plasma and the bottom row gives values for CSF. A comparison of 20 mg/kg versus 40 mg/kg as either a bolus or continuous infusion (cont) is shown. The continuous black line gives the %\( T_{>\text{MIC}} \) for the typical patient (50th percentile), whereas the broken black line gives the %\( T_{>\text{MIC}} \) for at least 90% of patients (10th percentile). Targets are highlighted by grey lines: the horizontal broken grey line represents 61%\( T_{>\text{MIC}} \), the vertical broken grey line represents an MIC cut-off of 2 mg/L and the continuous grey line represents 10 mg/L (5 \times MIC).


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