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Cerebrospinal pharmacokinetic and pharmacodynamic analysis of efficacy of meropenem in paediatric patients with bacterial meningitis

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ABSTRACT

Background: Meropenem is widely used for the treatment of paediatric patients with bacterial meningitis, but the pharmacodynamic (PD) basis for this has not been fully elucidated.
Objectives: A cerebrospinal pharmacokinetic (PK) and PD analysis was performed to identify the optimal dosage regimen for paediatric patients with inflamed central nervous system disease (bacterial meningitis).
Patients and methods: Paediatric data from three clinical studies were used to build a novel population PK model with a cerebrospinal fluid (CSF) compartment, assuming CSF clearance of 0.021 L/h from a physical-anatomical perspective. The bactericidal target attainment rates in CSF [50%$T_{>MIC}$(CSF)], after various dosage regimens, were simulated on the basis of reported or observed minimum inhibitory concentration (MIC) distributions and a newly developed population PK model including CSF concentrations. The effects of increased dose and/or prolonged infusion on target attainment were investigated.
Results: Clinical data from 154 patients {mean age 30.6 [standard deviation (SD) 34.4] months, mean body weight 12.4 (SD 7.6) kg} were used for the population PK analysis. The flat profile of the CSF concentration–time curve and attainment of 50%$T_{>MIC}$(CSF) did not change markedly when the duration of infusion was increased, whereas attainment of 50%$T_{>MIC}$(CSF) was improved by increasing the dose from 20 to 40 mg/kg q8h for penicillin-resistant *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. Thirty-six patients who achieved satisfactory clinical cure showed at least 75.3%$T_{>MIC}$(CSF).
Conclusions: A high dose of meropenem (40 mg/kg q8h) is necessary to achieve clinical efficacy in paediatric patients with bacterial meningitis.

1. Introduction

Bacterial meningitis is an infectious, inflammatory process affecting the meninges [1,2]. Delayed initiation of therapy can lead to morbidity and mortality in patients with acute bacterial meningitis [2,3]. As antimicrobial therapy is often initiated before antimicrobial susceptibility test data are available, empirical treatment for cerebrospinal fluid (CSF) infections should offer bactericidal efficacy against the most likely pathogens [2–4]. Meropenem is a widely used carbapenem with demonstrated efficacy against pathogens causing bacterial meningitis, such as Gram-positive and Gram-negative bacteria, and is a useful agent for treatment of bacterial meningitis in infants and children with a daily dose of 120 mg/kg [2–4]. The Japanese guidelines recommend 40 mg/kg q8h meropenem as initial treatment for bacterial meningitis, and compliance with this has increased its clinical efficacy [2,4]; however, the pharmacodynamic (PD) basis for this has not been fully elucidated. The first report of Monte Carlo simulation for meropenem was published by Drusano [5], and numerous pharmacokinetic (PK) and PD Monte Carlo simulations for meropenem have now been reported using time above minimum inhibitory concentration ($T_{>MIC}$) as the PD target [5–14]. This methodology is considered to be important to predict the antibacterial efficacy of various dosages, using the plasma

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Table 1
Summary of three clinical studies used in the present population pharmacokinetic (PK) analysis and time above minimum inhibitory concentration ($T_{>MIC}$) simulation.

Characteristics	Mean ± SD		
	Study 1	Study 2	Study 3
Patients (*n*)	50	129	72
Patients with bacterial meningitis	5	129	72
Patients for population PK analysis	50	61	43
Patients with plasma and CSF data	5	33	27
Patients without plasma data	0	9	4
Sex (*n*) (male:female)	30:20	79:50	40:32
Body weight (kg): male	15.6 ± 9.3	11.7 ± 6.2	14.6 ± 9.5
Body weight (kg): female	13.5 ± 5.8	11.8 ± 12.6	11.0 ± 5.3
Age (months)	42.4 ± 38.4	25.7 ± 34.8	30.9 ± 30.8
Range	3–161	2–166	2–122
Serum creatinine (mg/dL)	0.30 ± 0.12[a]	0.54 ± 0.29[b]	0.54 ± 0.26[c]
Isolated pathogens from CSF or blood in patients with bacterial meningitis	*H. influenzae*	*S. agalactiae*, *S. pneumoniae*, *H. influenzae* Type b, *H. influenzae* Type e, *H. parainfluenzae*, *N. meningitidis A*, *N. meningitidis B*, *N. meningitidis C*, *Salmonella* Group C	*S. pneumoniae*, *H. influenzae* Type b, *N. meningitidis A*, *N. meningitidis B*, *N. meningitidis C*
Number of isolated pathogens	49[d]	111[e]	49[e]
Clinical outcomes of patients with bacterial meningitis (*n*)	5	79	33
Cured with no sequelae	5	36	17
Survival with mild sequelae	0	21	6
Survival with severe sequelae	0	20	9
Death	0	2	1
CSF samples for population PK analysis (*n*)	11	42	31
Reference	[22]	[23]	[23]

CSF, cerebrospinal fluid; *N. meningitidis, Neisseria meningitidis; H. influenzae, Haemophilus influenzae; H. parainfluenzae, Haemophilus parainfluenzae; S. agalactiae, Streptococcus agalactiae; S. pneumoniae, Streptococcus pneumoniae;* SD, standard deviation.
[a] *n*=49.
[b] *n*=119.
[c] *n*=68.
[d] Including unknown pathogens (*n*=16).
[e] Meropenem treatment group.

concentration [5–14] and the CSF concentration [15–18]. Nevertheless, previous studies did not investigate the relationships between clinical response and $T_{>MIC}$ based on CSF concentrations of meropenem [$T_{>MIC}$(CSF)] [15–18].

Bacterial meningitis increases permeability of the blood–brain barrier (BBB) to various substances [19]. Adinolfi [20] reported that the barriers between blood, CSF and brain in infants reach maturity at the age of 6 months, so drugs administered to children aged <6 months may reach the brain more readily due to immaturity of the BBB. As meropenem has been shown to be effective at the site of infection, it is essential to ascertain the rate and/or degree of penetration of meropenem into the cerebrospinal space in paediatric patients with bacterial meningitis. Dagan *et al.* [21] reported PK data for meropenem in paediatric patients with bacterial meningitis, but did not report on PK/PD analysis.

In this study, the optimal meropenem dosage regimen in paediatric patients with bacterial meningitis was identified by population PK analysis and Monte Carlo simulations based on previous data for the concentration of meropenem in CSF.

2. Patients and methods

2.1. Patients and study design

In total, 251 paediatric patients with bacterial meningitis or other infections were enrolled in three phase III studies between 1993 and 2002 (Table 1) [22,23], where paediatric patients with bacterial meningitis were included and individual data were available. The details of these clinical studies are given elsewhere [22,23]. The patients with bacterial meningitis were included in the analysis of population PK and meropenem penetration to CSF, and other patients were included in plasma PK modelling alone. These clinical studies complied with the ethical principles of good clinical practice in accordance with the Declaration of Helsinki, and were approved by the local ethics committee. The parents or legal guardians of all patients gave written informed consent for participation in these studies. Study 1 was an open-label study. Study 2 was a multicentre, single-blind, randomised, parallel group evaluation, and its protocol was switched to that of Study 3 late in the study period. In Study 3, the randomisation schedule was eliminated, and open-label treatment with meropenem was administered when pneumococcal meningitis was suspected at medical centres that had particular concerns about penicillin-resistant *Streptococcus pneumoniae* (PRSP).

In Study 1, clinical response at completion of treatment was classified as excellent, good, fair, poor or unevaluable. The microbiological response during treatment was classified into five categories, ranging from eradicated to unevaluable [22]. In Studies 2 and 3, clinical and bacteriological responses were assessed at completion of treatment, and 5–7 weeks and 5–7 months after completion of treatment for the presence of neurological and sensory neural sequelae. Assessments for clinical response were adopted from the guidelines of the Infectious Diseases Society of America (IDSA) [1], with the endpoints categorised into four categories ranging from cure to death. Endpoints for microbiological outcome were based on IDSA guidelines, with four categories ranging from

eradication to persistence [23]. Clinical efficacy was considered unevaluable if no pre-therapy pathogen was isolated and if patients were lost at the 5–7-week visit.

The paediatric patients for whom no measured meropenem concentration data were available were excluded from the population PK analysis. As the definitive PK parameters for the CSF compartment could not be obtained using the paediatric dataset alone, the data from five adult patients with bacterial meningitis in an open-label study conducted in Japan [24] were also used, solely to develop the population PK model.

2.2. Meropenem dosage

Meropenem was administered intravenously q8h at an individual dose of 10 mg/kg (n=6), 20 mg/kg (n=36) or 40 mg/kg (n=8) by infusion for ≥0.5 h in Study 1 according to severity of disease or symptoms by the physicians in charge; and 40 mg/kg (n=201) was administered q8h by infusion for 0.5 h in Studies 2 and 3 (Table 1). It was also administered at a dosage of 2 g q8h by infusion for ≥0.5 h in the adult study [24].

2.3. Adjunctive therapy

Dexamethasone was administered to all children with bacterial meningitis at a dosage of 0.15 mg/kg intravenously every 6 h for the first 4 days of therapy, with the first steroid dose given before or at the time of the first dose of study antibiotic [22,23].

2.4. Blood and CSF sampling

Blood and CSF samples were collected to measure meropenem concentrations after more than three meropenem doses. Samples were collected during or after completion of meropenem infusion [22–24] or until as late as 6.5 h after completion of infusion [22,23]. CSF samples were obtained by lumbar puncture. Samples were collected in Becton-Dickinson Vacutainer tubes containing sodium heparin (B-D #6480) and Sarstedt tubes (#60.546), respectively, frozen at -20°C as plasma and CSF after centrifugation, and stored until assay. Samples were also collected for culture and for clinical laboratory tests before, during and on completion of treatment [22–24].

2.5. Analytical procedure and bacteriological tests

Meropenem concentrations in plasma and CSF were determined using high-performance liquid chromatography, validated in accordance with the guidelines of the US Food and Drugs Administration (FDA) [25]. The analytical procedure for CSF was similar to that reported previously for plasma samples [26]. Following standard procedures [27–30], causative pathogens were isolated and identified using blood and CSF samples, and meropenem susceptibility tests were performed by the broth microdilution method or the disk diffusion method.

2.6. Clinical laboratory data

Clinical laboratory evaluation of CSF [white blood cell (WBC) count, glucose and total protein] was performed just before or just after the start of trial treatment [22,23].

2.7. Population PK analysis

Population PK analysis and model validation were conducted in accordance with the FDA and European Medicines Agency guidelines [31,32] using a non-linear mixed-effect model programme (NONMEM, double precision, version 7.3; ICON Development Solutions, LLC, Hanover, MD, USA) [33], with an Intel Visual Fortran Composer XE 2013 (Intel Corp., Santa Clara, CA, USA). The population PK model was developed as follows:

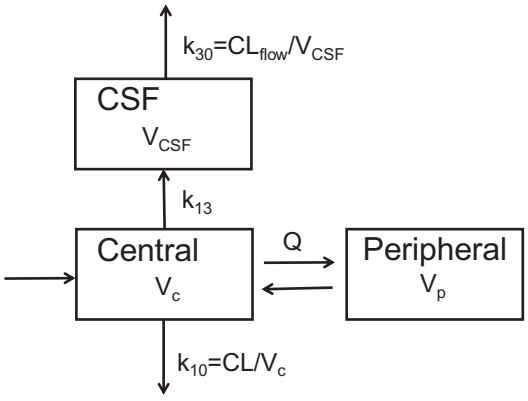

Fig. 1. Compartment model for pharmacokinetic analysis of cerebrospinal fluid (CSF) distribution. CL, total body clearance; V_c, volume of distribution for central compartment; V_p, volume of distribution for peripheral compartment; V_{CSF}, volume of distribution for CSF compartment; k_{13}, first-order inter-compartmental transfer rate constants; k_{10} and k_{30}, first-order rate constants; Q, inter-compartmental clearance between V_c and V_p; CL_{flow}, CSF flow clearance set to 0.021 (L/h) [34]. The method selected was first-order conditional estimation with interaction. An exponential model was selected for the inter-individual and intra-individual variabilities. Elimination from the central compartment and inter-compartmental distribution were modelled as first-order processes.

Step 1 The paediatric population mean values for four plasma parameters [total body clearance (CL), volume of distribution for central compartment (V_c), volume of distribution for peripheral compartment (V_p) and inter-compartmental clearance between V_c and V_p (Q)] and post-hoc parameters were estimated using the previous two-compartment model in the paediatric report [26] as the initial model. The input data were the plasma concentrations of meropenem obtained from 78 paediatric patients in Studies 1–3. The plasma parameters for five adult patients were the empirical Bayes estimates, which were calculated using plasma concentrations and the previously reported two-compartment model [13].

Step 2 A three-compartment model defining the CSF concentrations of meropenem was developed (Fig. 1) using the CSF data from patients who suffered from bacterial meningitis with individual plasma PK parameters obtained in Step 1. In the case of patients for whom plasma data were not available, population mean parameters reflecting body weight were used. The present analysis introduced CSF flow clearance (CL_{flow}) of 0.021 L/h [34] into the model from a physical-anatomical perspective to provide the elimination of meropenem from CSF. Reabsorption of CSF into the bloodstream does not occur directly, but via subarachnoid granulations or the brain extracellular space [19]; the level of this is small relative to the total plasma volume. Considering the slow and limited elimination of meropenem from CSF relative to that from plasma, CL_{flow} was set as direct elimination of meropenem from CSF. During the analysis, the parameters relating to the CSF compartment [V for CSF compartment (V_{CSF}), transfer rate constant from the central compartment to CSF compartment (k_{13}), and covariates] were estimated. The effect of age and body weight on meropenem concentration–time was investigated in the covariate selection process of V_{CSF} and k_{13}.

Table 2
Final estimates of population pharmacokinetic (PK) parameters.

Parameters	Final estimates mean ± SE	
CL (L/h) = $\theta_{CL} \times WT \times exp(\eta_{CL})$	θ_{CL} = 0.526 ± 0.0256	
V_c (L) = $\theta_{Vc} \times WT$	θ_{Vc} = 0.292 ± 0.0248	
Q (L/h) = $\theta_Q \times WT$	θ_Q = 0.114 ± 0.0353	
V_p (L) = $\theta_{Vp} \times WT$	θ_{Vp} = 0.108 ± 0.0207	
V_{CSF} (L) = θ_{VCSF}	θ_{VCSF} = 0.120 ± 0.100	
k_{13} (/h) = θ_{k13} /1000 × (AGE/14) $^{\theta AGE}$ × $exp(\eta_{k13})$	θ_{k13} = 0.534 ± 0.134	
	θ_{AGE} = − 0.589 ± 0.118	
CL_{flow} (L/h) = 0.021	–	
k_{30} (/h) = CL_{flow} / V_{CSF}	–	
CSF/plasma AUC ratio	0.146 (12.4 kg and age 30.6 months)	
Inter-individual variability	**Mean ± SE**	**CV (%)**
ω_{CL}^2	0.0389 ± 0.0154	19.9
ω_{k13}^2	1.64 ± 0.326	204
Intra-individual variability	**Mean ± SE**	**CV (%)**
Y = F × $exp(\varepsilon)$		
σ^2 for plasma	0.274 ± 0.0390	56.1
σ^2 for CSF	0.140 ± 0.0267	38.8

WT, body weight; CL, total body clearance; V_c, volume of distribution for central compartment; V_p, volume of distribution for the peripheral compartment; Q, inter-compartmental clearance between V_c and V_p; V_{CSF}, volume of distribution for the CSF compartment; k_{13}, first-order inter-compartmental transfer rate constants; k_{30}, first-order rate constants; CL_{flow}, CSF flow clearance; CSF/plasma AUC ratio, CSF/plasma ratio of the area under the meropenem concentration curve estimated as population mean at body weight of 12.4 kg and age of 30.6 months with the final population PK model; Y, observed meropenem concentration; F, individual predicted meropenem concentration; SE, standard error.
Due to the complexity of the model, the validity of the final population PK model was confirmed by leave-one-out cross validation.

The change in minimum values of the NONMEM objective function and biological and pharmacological plausibility were used to select suitable models during the model-building process, as reported previously [13,26].

Step 3 To evaluate the validity of the final estimates of the population PK model, leave-one-out cross validation was adopted [31]. The population PK model was fitted to modified data sets obtained by omitting one patient at a time from the original data set (83 modified data sets, n=82 patients in each). The 83 estimates obtained for each parameter were compared with the final estimate. To check the suitability of the final model for PK simulation, a visual predictive check (VPC) [32] was performed.

2.8. Concentration–time profile estimation and PK/PD simulations

Plasma and CSF meropenem concentration–time profiles in individual patients were obtained by post-hoc estimation, and the area under the curve (AUC) for meropenem concentration was calculated by integration of meropenem concentration in each compartment for 8 h at steady state. Monte Carlo simulations were conducted for virtual paediatric plasma and CSF concentrations of meropenem at steady state for each dosage regimen. As the protein binding ratio was very low (2.4% [35]) in plasma, and was not reported in CSF, protein binding by meropenem was disregarded for the estimation of $T_{>MIC}$.

Target bactericidal exposure (50%$T_{>MIC}$ [5,6]) attainment rates at MICs of 0.06–2 mg/L were estimated using simulated meropenem concentration–time profiles at three doses [20, 40 and 80 (off-label dose) mg/kg q8h] and three infusion durations (0.5, 2 or 4 h). Additionally, the rates were estimated against clinically isolated strains [PRSP, *Pseudomonas aeruginosa* and β-lactamase-negative, ampicillin-resistant *Haemophilus influenzae* (BLNAR)] by matching each simulated concentration with an MIC selected at random from the meropenem MIC distributions reported in 2012 [36].

2.9. Statistical analysis

Log-transformed AUCs or CSF/plasma AUC ratios for meropenem in paediatric patients with bacterial meningitis were compared between two groups using Student's t-test, with division by threshold value for clinical laboratory data. P<0.05 was considered to indicate statistical significance in each analysis. The analyses to assess and compare clinical endpoints were reported in previous studies [22,23].

3. Results

3.1. Patients

Patients for the current population PK analysis were 154 children with a mean age of 30.6 [standard deviation (SD) 34.4] months, and a mean body weight of 12.4 (SD 7.6) kg (Table 1). Their clinical data were also used. CSF samples were taken from patients with bacterial meningitis, and plasma samples were taken from other patients with various infections. Five adult patients with bacterial meningitis [mean age 60.6 (SD 15.9) years, mean body weight 56.8 (SD 18.4) kg] were included in the population PK analysis.

3.2. Population PK analysis

In total, 207 plasma samples from 141 paediatric patients (one to four samples each; Table 1) and 14 samples from five adult patients (two to three samples each) were used for plasma PK analysis. For development of the new CSF model, 84 CSF samples from 78 paediatric patients (one to four samples each; Table 1) and 14 CSF samples from five adult patients (two to three samples each [24]) were used, and mean meropenem concentrations in plasma and CSF were 28.7 (SD 29.1) mg/L and 1.82 (SD 2.7) mg/L, respectively.

It was possible to model interindividual variability and the effects of age for the transfer rate constant (k_{13}), using the exponential of individual age divided by median age, multiplied by k_{13} (Table 2). Including the effects of age on V_{CSF} and/or on CL_{flow} did

Table 3
Target attainment rates at bactericidal [50% time above minimum inhibitory concentration (50%$T_{>MIC}$)] exposure of meropenem in cerebrospinal fluid for various MICs at various paediatric dosing regimens.

MIC (mg/L)	Infusion duration (h)								
	20 mg/kg q8h			40 mg/kg q8h			80 mg/kg q8h[a]		
	0.5	2	4	0.5	2	4	0.5	2	4
2	7.8	7.8	6.7	18.5	17.3	16.3	36.0	32.7	31.9
1	18.5	17.3	16.3	36.0	32.7	31.9	52.3	53.7	54.0
0.5	36.0	32.7	31.9	52.3	53.7	54.0	72.4	72.7	74.6
0.25	52.3	53.7	54.0	72.4	72.7	74.6	85.7	85.9	89.1
0.12	73.2	73.5	75.4	86.4	86.6	90.0	94.2	94.5	96.3
0.06	86.4	86.6	90.0	94.2	94.5	96.3	98.3	98.2	98.9

Simulation: 1000 virtual paediatric patients.
[a] Off-label dose.

not improve the fit. As body weight in children is correlated with age, body weight was tested as a covariate instead of age, and the model estimates of V_{CSF} and CL_{flow} proportional to body weight were obtained. As the model with age as a covariate suggested marked changes in k_{13} at young ages, and that seemed reasonable compared with V_{CSF} and CL_{flow} being proportional to body weight, the model with age as a covariate of k_{13} was selected. The parameter estimates in the final population PK model are presented in Table 2.

3.3. Model evaluation

3.3.1. Leave-one-out cross validation

Three parameters (θ_{VCSF}, 1000*θ_{k13} and θ_{AGE}) estimated for 82 data sets were close to the population means estimated using the original data set. One data set gave θ_{VCSF} 2.3 times the population mean value (0.120), but other parameters were within ±35% of the population mean values. The patient omitted from this data set had three CSF data points at the early, intermediate and late time-points, and a higher concentration was found, but there was no reason to exclude this patient from the analysis. Theoretically, change in V_{CSF} by 2.3 times did not affect AUC of meropenem in CSF, and just slightly decreased the peak/trough concentration ratio in CSF.

3.3.2. Visual predictive check

Fig. 2 shows the results of VPC. The observed CSF concentrations were distributed almost within the 95% prediction intervals at each sampling time. The observed plasma concentrations were mostly within the 95% prediction intervals, but data from Studies 2 and 3 showed greater variability. On the basis of these results, simulated plasma and CSF concentrations of meropenem based on the final population PK model were confirmed to be suitable for calculation of $T_{>MIC}$.

3.4. PK/PD simulation for MIC of 0.06–2 mg/L

Table 3 shows the probabilities of achieving 50%$T_{>MIC}$(CSF) against pathogens with six MICs for nine dosing conditions. After administration at 20 mg/kg q8h by 0.5-h infusion, a high target attainment rate (>80%) was achieved for an MIC of 0.06 mg/L. With dose escalation from 20 to 40 mg/kg q8h by 0.5-h infusion, the target attainment rates (e.g. MIC of 0.12 mg/L) increased from 73.2% to 86.4%. Prolonged duration of infusion (e.g. 4 h) had less impact on the target attainment rates (75.4%).

3.5. PK/PD simulations for PRSP, P. aeruginosa and BLNAR

Fig. 3 shows the effect of infusion duration on the probability of achieving the target (50%$T_{>MIC}$), on the basis of plasma concentrations [50%$T_{>MIC}$(plasma)] and CSF concentrations [50%$T_{>MIC}$(CSF)] of meropenem. As for PRSP and *P. aeruginosa*, the target attainment rate for 50%$T_{>MIC}$(plasma) was improved by prolonging the duration of infusion, especially at lower doses, while that for 50%$T_{>MIC}$(CSF) was improved not by prolonging the duration of infusion but by higher dose (Fig. 3A,B). In the case of BLNAR, the target attainment rate for 50%$T_{>MIC}$(plasma) was more than 95% in all conditions, suggesting no need for longer infusion, and a high target attainment rate (close to 80%) for 50%$T_{>MIC}$(CSF) was achieved by a dose of 40 mg/kg q8h (Fig. 3C) without prolonging the duration of infusion.

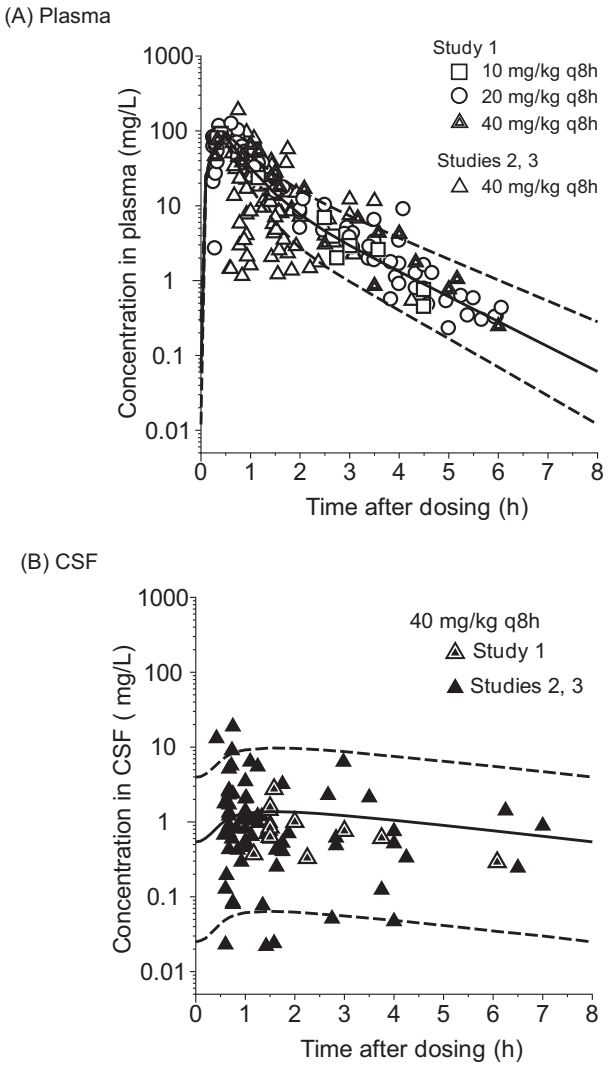

Fig. 2. Observed meropenem concentrations and 95% prediction intervals after multiple administrations to paediatric patients. (A) Plasma concentrations (207 observations) and (B) cerebrospinal fluid (CSF) concentrations (84 observations). The plotted symbols represent measured values. The measured plasma concentrations at 10 mg/kg (open squares) and 20 mg/kg (open circles) are shown adjusted to 40 mg/kg (double open triangles in Study 1 and open triangles in Studies 2 and 3) by multiplying by 4 and 2, respectively. The measured CSF concentrations at 40 mg/kg are shown as double filled triangles in Study 1 and filled triangles in Studies 2 and 3. The solid line indicates the population mean concentration profile at 40 mg/kg q8h by 0.5-h infusion. The broken lines indicate the 2.5th and 97.5th percentiles of the simulated concentrations of 1000 virtual patients, based on the population pharmacokinetic model developed. The ages of virtual patients were simulated by generating logarithmic ages in a uniform distribution, taking into consideration the distribution of observed age and the range of 3–120 months in the analysis population. The body weights of virtual patients were generated at random using an equation, $\log(WT) = 0.3472 \times \log(Age) + 1.3462 + \eta$, with η having a standard deviation of 0.1783, which was obtained by analysis of the observed correlation in the analysis population.

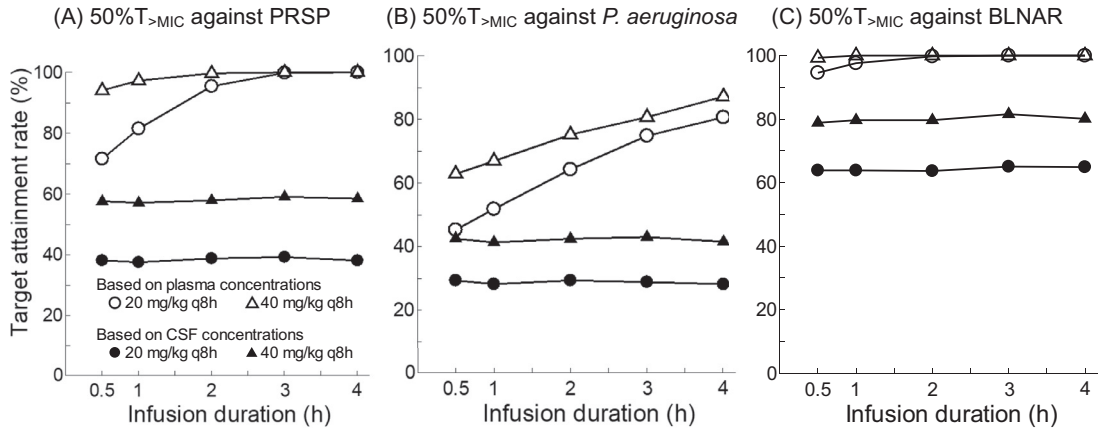

Fig. 3. Probabilities of achieving the target based on paediatric plasma or cerebrospinal fluid (CSF) concentrations of meropenem with three strains. (A) 50%$T_{>MIC}$ against penicillin-resistant *Streptococcus pneumoniae*. (B) 50%$T_{>MIC}$ against *Pseudomonas aeruginosa*. (C) 50%$T_{>MIC}$ against β-lactamase-negative, ampicillin-resistant *Haemophilus influenzae* (BLNAR). The infusion durations for simulation were 0.5, 1, 2, 3 and 4 h at 20 mg/kg q8h (open circles for plasma and filled circles for CSF) and 40 mg/kg q8h (open triangles for plasma and filled triangles for CSF) (A) to (C). Virtual patients (n=2000) were simulated by the same method as those in Fig. 2. Target attainment rates with the following pathogens were estimated using the MIC (mg/L) distribution data for meropenem with clinically isolated strains reported in 2012 [36]: PRSP (MIC_{50} = MIC_{90} = 0.5), *P. aeruginosa* (MIC_{50} = 1; MIC_{90} = 16), and BLNAR (MIC_{50} = MIC_{90} = 0.25). PRSP and BLNAR were selected as common bacterial pathogens in patients with bacterial meningitis [2–4]. *P. aeruginosa* was selected as a representative example commonly associated with more severe infections.

3.6. Meropenem penetration to CSF

Meropenem AUC in CSF was plotted against total protein concentration, WBC count and glucose concentration in CSF before treatment, and CSF/plasma ratio of meropenem AUC was plotted against that of glucose (Fig. 4). AUC in CSF and CSF/plasma AUC ratio of meropenem were greater in patients aged <6 months, while no clear differences between age groups were found for total protein concentration, WBC count or glucose concentration in CSF. There was no clear relationship between meropenem AUC and any of the clinical laboratory data (Fig. 4A–C), other than CSF/plasma glucose ratio (Fig. 4D) with which the AUC ratio of meropenem showed a significant difference (P=0.03) in patients suspected of having bacterial meningitis on the basis of CSF/plasma glucose ratio (<0.4; Fig. 4D).

3.7. Clinical and bacteriological efficacy

In Study 1, both the clinical efficacy and microbial response in all five patients with bacterial meningitis were confirmed at completion of treatment, and the causative pathogen was *H. influenzae* in these patients [22]. Seventy-nine (61%) meropenem-treated patients in Study 2 and 33 (46%) in Study 3 were considered to be evaluable for clinical and microbiological efficacy. At completion of treatment, 97% (77/79 patients in Study 2 and 32/33 in Study 3) of evaluable patients showed a satisfactory clinical response, and almost all evaluable patients [97% (77/79) in Study 2 and 100% (33/33) in Study 3] showed a satisfactory bacteriological response. In Study 2, an unsatisfactory clinical response (death) was reported at completion of treatment for two patients. In Study 3, an unsatisfactory clinical response (death) in one patient was reported, in spite of this patient showing a satisfactory bacteriological response (eradication).

The pathogen-specific MICs (0.008–0.08 mg/L) for the bacteria causing meningitis in 36 paediatric patients in Studies 1 and 2 were used for calculation of $T_{>MIC}$(CSF) based on the predicted CSF concentration–time profile. All dosages were 40 mg/kg q8h by approximately 0.5 h of infusion. $T_{>MIC}$(CSF) was 75.3% (n=1), 82.6% (n=1) and 100% (n=34), which was consistent with these patients showing a satisfactory clinical response.

4. Discussion

This report presents the first PK and PD analysis of efficacy of meropenem based on CSF concentrations obtained from 78 paediatric patients with bacterial meningitis.

The C_{max} of meropenem in CSF is lower and $t_{1/2}$ is greater than in plasma (Fig. 2). The penetration of meropenem to CSF (as population mean CSF/plasma AUC ratio) was estimated as 0.146 (Table 2). In previous studies based on plasma concentrations of meropenem, a prolonged duration of infusion was reported as an alternative method to optimise meropenem PD [5–8,10,12–14,26]. However, since the flat CSF concentration–time profile did not change markedly when the duration of infusion increased, a longer duration of infusion was not theoretically effective for increasing the attainment rates of PD target values [$T_{>MIC}$(CSF)], whereas increasing the dose was more effective for improving the target attainment rates (Table 3 and Fig. 3). In the case of a higher target (>50%) having to be achieved, prolonging the duration of infusion is effective for $T_{>MIC}$(plasma) but not for $T_{>MIC}$(CSF). Independent of the bacteria causing meningitis, it is important to consider the site of infection (plasma or CSF) in the body when deciding upon the meropenem administration strategy. As empirical antimicrobial therapy for patients with suspected acute bacterial meningitis is initiated without identification of the causative pathogen [2–4], and as dose is important to increase exposure in CSF, achievement of clinical efficacy requires starting at a high dose (40 mg/kg q8h) of meropenem. High clinical response rates (97–100%) and high bactericidal activities (97–100%) in Studies 1–3 are consistent with the present simulation results, suggesting the importance of high-dose treatment (40 mg/kg q8h).

In the case of high MIC (>1 mg/L), PK/PD simulation suggested that a sufficient concentration of meropenem can be achieved in less than half of paediatric patients with bacterial meningitis at a standard dose of 40 mg/kg q8h (Table 3). These results are consistent with the susceptibility (≤0.25 mg/L) of meropenem to *Streptococcus pneumoniae, H. influenzae* and *Neisseria meningitidis* according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) [37]. If the causative bacteria are suspected to be PRSP (Fig. 3A), meropenem should be used in combination with ceftriaxone or cefotaxime. In the case of *P. aeruginosa* in Fig. 3B, the target attainment rate at 50%$T_{>MIC}$(CSF) is only approximately 40%,

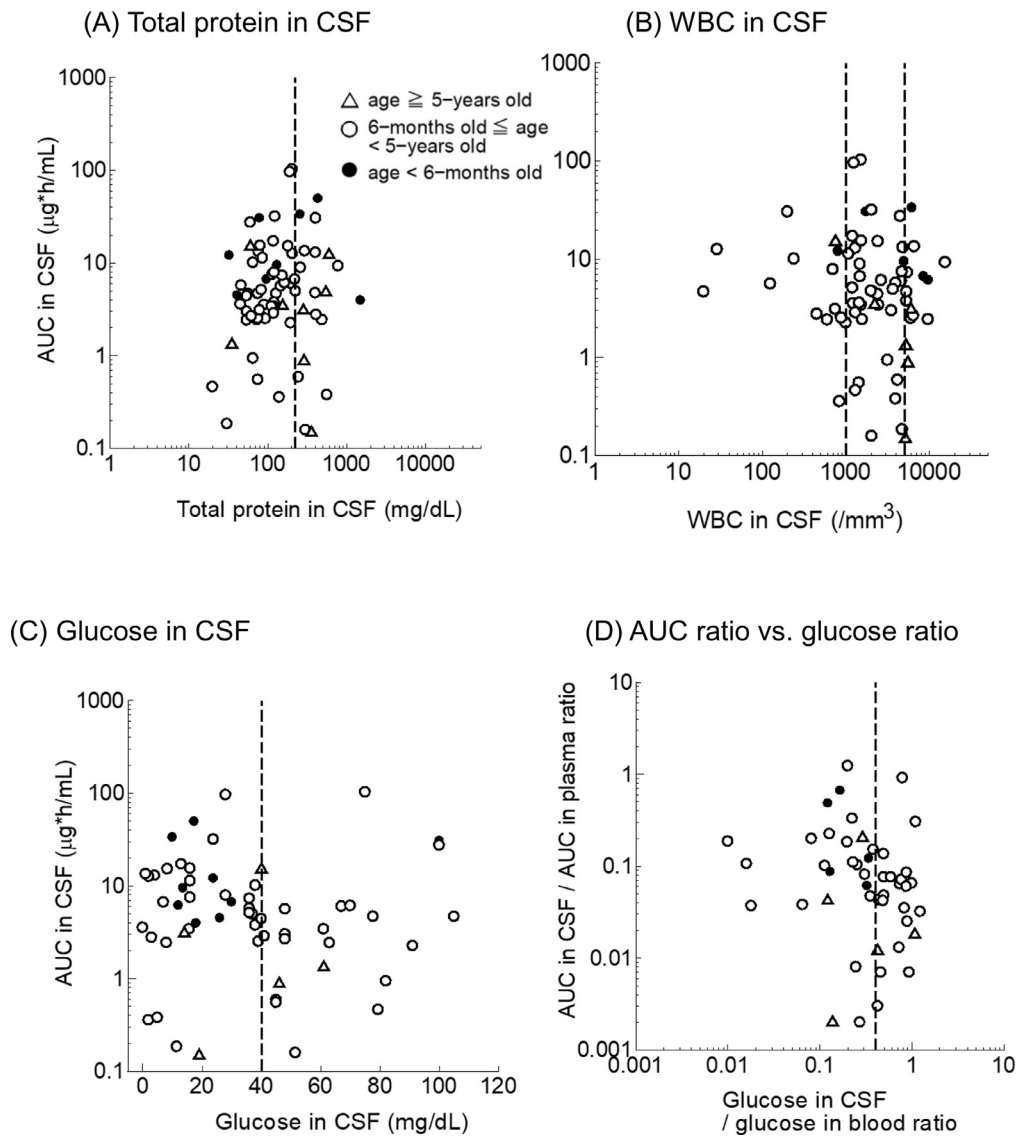

Fig. 4. Scatter plots of meropenem area under the curve (AUC) in cerebrospinal fluid (CSF) vs clinical laboratory data in CSF in paediatric patients with bacterial meningitis. (A) Meropenem AUC vs total protein concentration (n=72). (B) Meropenem AUC vs white blood cell (WBC) count (n=68). (C) Meropenem AUC vs glucose concentration (n=59). (D) Meropenem AUC ratio (CSF/plasma) vs glucose ratio (CSF/plasma) (n=47). Meropenem AUC values for each patient in this study were estimated as post-hoc values based on the observed data with the final population pharmacokinetic model [meropenem in CSF for (A) to (D), and meropenem in plasma for (D)]. Meropenem data were obtained in steady state from paediatric patients with bacterial meningitis aged 3–127 months. Open triangles, open circles and filled circles indicate the data for patients aged ≥5 years, between <5 years and ≥6 months, and <6 months, respectively. Broken lines indicate the thresholds for bacterial meningitis (>220 mg/dL total protein, 1000–5000 /mm^3 WBC, <40 mg/dL glucose in CSF and <0.4 glucose ratio [3]).

but meropenem is used as more effective treatment options are not available.

VPC predicts plasma concentrations from Study 1 well, including those of patients with bacterial meningitis and those obtained at lower doses, but poorly predicts some concentrations from Studies 2 and 3 (Fig. 2A). Given that the disease status in some patients in Studies 2 and 3 was severe, instability in various conditions, such as total water balance in circulated blood, may have caused this large variability, which would have resulted in a wider distribution of plasma concentration than the 95% prediction intervals. The estimated residual variability of plasma concentrations in this study (56.1%) was greater than the previously reported value of 32.0% [26].

Previous studies showed that substrates can permeate immature, loose BBB until 6 months of age [20], and that CSF volume in children aged 5–13 years [34] is less than in adults [38]. In addition, inflammation in bacterial meningitis enhances the permeability of the BBB [2–4]. On the basis of these anatomical and pathological perspectives, meropenem permeability to CSF was investigated using clinical laboratory data. The reason for the absence of clear differences in total protein, WBC and glucose in CSF between the three age groups (Fig. 4) is probably that the kinetics of those components do not depend to a great extent on the immaturity of the BBB, but on changes in permeability of the BBB due to inflammation. In addition, marked variability might mask the clear relationship with the clinical laboratory data in this study.

On the other hand, the AUC ratio of meropenem under the threshold (<0.4) of the glucose ratio for bacterial meningitis (Fig. 4D) was significantly greater than that over the threshold, and all patients aged <6 months were under the threshold with high meropenem AUC ratios, suggesting that meropenem is delivered to the inflamed site in CSF more efficiently in the case of bacterial meningitis. Once a diagnosis of bacterial meningitis has been established by CSF analysis in a paediatric patient

[3], antimicrobial susceptibility profiles of the assumed pathogens, antimicrobial resistance, and treatment with drugs delivered to the target site (e.g. meropenem) should be considered for initial therapy.

There has been no clinical evidence for the meropenem PD target for achieving a good therapeutic outcome in paediatric patients with bacterial meningitis, as highlighted in recent studies [17–18]. In the present study, 36 patients showed satisfactory clinical responses and the $T_{>MIC}$(CSF) achieved was equivalent to 75.3% or higher. This result could become an index for the PD target with bacterial meningitis.

According to a recent white paper [39], the following are recommended: (1) effect site PK studies; (2) PK/PD-based dosing regimen selection; and (3) combination with clinical data as substantial evidence for efficacy. Additionally, Drusano referred to use of Monte Carlo simulation [40]. The present analysis responds to these issues. The model developed for this study suggested the possibility to predict penetration (AUC) and $T_{>MIC}$ at the infected site [$T_{>MIC}$(CSF)] using the plasma data for meropenem, although further investigations with larger sample sizes are necessary.

In conclusion, this study is the first report of a cerebrospinal PK and PD analysis performed to integrate $T_{>MIC}$ with clinical responses of paediatric patients with inflamed central nervous system disease (bacterial meningitis) under adjunctive dexamethasone therapy. The results indicate that meropenem 40 mg/kg q8h is necessary to achieve clinical efficacy in paediatric patients with bacterial meningitis. Thirty-six patients who achieved satisfactory clinical cure showed at least 75.3%$T_{>MIC}$(CSF).

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Competing interests

YO and Y. Tomita are employees of Sumitomo Dainippon Pharma Co., Ltd. KS and Y. Tanigawara have received consultancy fees from Sumitomo Dainippon Pharma Co., Ltd.

Ethical approval

Not required.

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