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Pharmacokinetics and pharmacodynamics of meropenem in children with severe infection

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ABSTRACT

This study aimed to describe the pharmacokinetic (PK) characteristics of meropenem in children with severe infections and to assess the pharmacokinetic/pharmacodynamic (PK/PD) profiles of various meropenem dosage regimens in these patients. Fourteen children with severe infections received intravenous (i.v.) bolus doses of meropenem (20 mg/kg/dose) every 8 h (q8h). Serum samples were obtained before and serially after the second dose of meropenem, and a population PK analysis was performed. The final model was used to simulate serum concentration–time profiles with various dosage regimens. The PK/PD target was to achieve a serum meropenem concentration higher than the minimum inhibitory concentration (MIC) of the causative organism (i.e. *Pseudomonas aeruginosa* and Enterobacteriaceae) for ≥40% of the dosing interval (40%$T_{>MIC}$). The median age and weight of the children were 6.0 years and 20.0 kg, respectively. Meropenem serum concentration–time profiles were best described by a two-compartmental model with first-order elimination. The simulations showed that the probabilities of target attainment (PTAs) for organisms with an MIC of 1 mg/L were 0.678 and 1.000 following i.v. bolus and 3-h infusion of meropenem (20 mg/kg/dose), respectively. Using a 3-h infusion of a 20 mg/kg/dose, the PTA was 0.999 and 0.765 for organisms with MICs of 4 mg/L and 8 mg/L, respectively. Meropenem given as i.v. bolus doses of 20 mg/kg/dose q8h appeared to be inadequate for PK/PD target attainment for organisms with an MIC of 1 mg/L. The simulations showed that meropenem administration via a 3-h infusion using the same dose improved the PTA.

1. Introduction

Meropenem is a carbapenem antibiotic characterised by time-dependent bactericidal activity [1–6]. It binds to penicillin-binding proteins and inhibits cell wall synthesis [2,7]. Meropenem is resistant to extended-spectrum β-lactamases and AmpC chromosomal β-lactamases. It is used for empirical and definitive therapy of serious and multidrug-resistant bacterial infections [2,3,5,6].

In severe infections, physiological changes may affect serum drug concentrations [6,8–10]. The effects of increased drug clearance (CL) and/or increased volume of distribution (V_d) may result in lower serum drug concentrations, which might result in a decrease in the time that the serum concentration is above the minimum inhibitory concentration ($T > MIC$) of the causative pathogen [6,8–10]. At the same time, an increase in V_d may result in an increased half-life ($t_{1/2}$) since $t_{1/2} = (0.693 \times V_d)/CL$, and this might be increase the $T > MIC$ [9,10]. Therefore it is difficult to predict drug concentration in patients with sepsis and in severely infected patients [9,10]. Studies in adults showed that drug concentrations might be insufficient in critically ill patients, therefore adjusting the dosage regimen may be important to maximise the efficacy of antibiotics [4–6,8–13].

A pharmacokinetic/pharmacodynamic (PK/PD) analysis study by Taccone et al of 80 patients (aged 18–85 years) in Belgian intensive care units (ICUs) who were treated with β-lactam antibiotics (meropenem, cefepime, ceftazidime and piperacillin/tazobactam) in the early phase of severe sepsis and septic shock showed that standard antibiotic regimens were inadequate at achieving the PK/PD target [time spent greater than four times the target MIC (%$T_{>4\times MIC}$), when MIC > 1 mg/L] for patients with *Pseudomonas aeruginosa* infection [13]. A study by Roberts et al among 10 critically ill patients (aged 48–63 years) found that administration of meropenem by infusion maintained higher concentrations in subcutaneous tissue and plasma and thus achieved a superior cumulative fraction of response (CFR) than administration by bolus injection against Gram-negative organisms [14]. However, a study in 40 children (aged 0.2–14.8 years) from Japan by Ikawa et al demonstrated adequate effects of antibiotics with standard regimens [20 mg/kg/dose every

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8 h (q8h)] [15]. Another study by Smith et al from the USA among neonates who were suspected to have or who had complicated intra-abdominal infections and received meropenem dosage strategies based on their gestational age showed that the given dosage regimens were able to achieve the target concentration in most of the children (96%) [16]. Pharmacokinetic (PK) data for meropenem in children with severe infection conditions remain unclear. Thus, the primary objective of this study was to characterise the PK characteristics of meropenem in children with severe infection or sepsis. Moreover, the secondary objective was to assess the PK/PD profile of various meropenem dosage regimens in these patients.

2. Materials and methods

2.1. Study design

This was an exploratory study to assess the pharmacokinetics of meropenem in paediatric patients with severe infection conducted at Chiang Mai University Hospital (CMUH) in Chiang Mai, Thailand. The Chiang Mai University Ethics Research Committee approved the study protocol. All patients and their parents or guardians provided written informed consent before participating in the study.

2.2. Study setting

The study was conducted in the general paediatric wards of CMUH between April and October 2012.

2.3. Inclusion criteria

Patients were considered for inclusion if they were aged 4–12 years and had been diagnosed with severe infection by a paediatrician. In this study, a severe infection was defined as a severe sepsis condition or sepsis that required treatment with meropenem as second-line therapy. Sepsis and severe sepsis were defined according to the criteria outlined in the '*International Pediatric Sepsis Consensus Conference: definitions for sepsis and organ dysfunction in pediatrics*' [17].

2.4. Exclusion criteria

Patients were excluded from the study if they had been diagnosed with cardiovascular dysfunction, renal dysfunction, hepatic dysfunction or heart failure. Organ dysfunction was defined according to the criteria outlined in the '*International Pediatric Sepsis Consensus Conference: definitions for sepsis and organ dysfunction in pediatrics*' [17].

2.5. Antibiotic treatment

All patients enrolled in the study received a 20 mg/kg/dose of meropenem (Mapenem® injection; Siam Pharmaceutical Co., Ltd., Bangkok, Thailand) q8h administered by an intravenous (i.v.) bolus injection (push over 15–20 s). Meropenem administrations were carried out by the research nurses.

2.6. Data collection

All patient information including demographics, pre-existing chronic diseases, admission diagnosis and biological data were collected from the patients' medical records. Information obtained during the study included patients' haemodynamic data, other concomitant antibiotics or medications and inotropic drugs, use of mechanical ventilation, length of hospital stay, mortality rate as well as adverse events observed during the study.

2.7. Sample size

All children, according to the inclusion and exclusion criteria, who were admitted to general paediatric wards of CMUH during April–October 2012 were recruited into the study.

2.8. Blood sampling

Blood samples were collected immediately before administration and serially after administration of the second dose of meropenem to avoid interference of the study processes with patient care during the initiation of treatment; however, the pharmacokinetics of the drug was still observed within 16 h of the diagnosis. Blood samples (5 mL) were collected via peripheral lines immediately before, immediately after, and at 1, 3, 5 and 7 h after drug administration. Normal saline was used to maintain the patency of venous access. The exact blood sampling times were recorded by research nurses. Blood samples were collected into non-heparinised evacuated blood collection tubes. They were allowed to clot for at least 15 min (but no longer than 30 min) and were subsequently centrifuged at 3000 rpm for 10 min. The serum was separated and was stored at –70 °C until analysis (no longer than 6 weeks) [18].

2.9. Drug assay

Meropenem plasma concentrations were determined by validated methods using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection at the Bioanalytical Development Department of Pharma Nueva Co., Ltd. (Bangkok, Thailand). The stationary phase was a HiQ Sil C18W column (5 µm, 250 × 4.6 mm) and the mobile phase was acetonitrile with 50 mm ammonium acetate (pH 5.0) (10:90, organic solvent:buffer). Meropenem and theophylline (internal standard) were detected by UV detection at 296 nm. The flow rate was 0.8 mL/min. The retention times of meropenem and theophylline were 7.2 min and 11.6 min, respectively. Standard curves were prepared in blank human plasma. The standard curve was linear between 0.100 mg/L and 50 mg/L. Meropenem in plasma samples was quantified using the peak area of standard samples for calibrations; the lower limit of quantification was 0.1 mg/L. This analytical method was validated for linearity ($r = 0.99$), accuracy (intraday assay, –2.44 to 6.55%, $n = 3$; interday assay, 2.64–5.96%, $n = 3$), precision (intraday, 3.66–4.78%, $n = 3$; interday, 2.51–5.84%, $n = 3$) and recovery (97.66–106.55% at 0.30, 25 and 45 mg/L).

2.10. Population pharmacokinetic analysis

The population PK analysis was performed using Phoenix® NLME 1.3 software (Certara USA, Inc., Princeton, NJ). One-, two- and three-compartmental models with first-order elimination were evaluated. First-order conditional estimation with extended least squares (FOCE-ELS) was used for all analyses. PK models were assessed using both statistical and graphical methods. Shrinkage of the individual random effects towards the population mean was computed to assess whether the final model provided reliable estimates of individual PK parameters. Smaller shrinkage <0.2 (<20%) indicates good individual estimates. The objective function value (OFV) (i.e. –2 × log-likelihood) was used as a cut-off criterion for model improvement and covariate effect(s) on PK parameter(s).

Individual patient characteristics that could potentially influence meropenem PK parameters were evaluated for inclusion in the model. Covariates tested were age, body weight, body mass index (BMI) and creatinine clearance (CL_{Cr}) using a stepwise forward inclusion ($P = 0.01$, λ^2, d.f. = 1) and backward elimination ($P = 0.001$, λ^2, d.f. = 1) model building procedure. The cut-off criterion was a difference of the OFV

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