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Original Article

The exploration of population pharmacokinetic model for meropenem in augmented renal clearance and investigation of optimum setting of dose☆

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ABSTRACT

In recent years, augmented renal clearance (ARC), in which renal function is excessively enhanced, has been reported, and its influence on β-lactam antibiotics has been investigated. In this study, we aimed to determine the optimum population pharmacokinetic model of meropenem in patients with sepsis with ARC, and evaluated dosing regimens based on renal function. Seventeen subjects (6 with ARC and 11 without) were enrolled in this study. Predicted meropenem concentrations were evaluated for bias and precision using the Bland–Altman method. To examine the dosing regimen, Monte Carlo simulation was performed to calculate the cumulative fraction of response (CFR). In patients with ARC, the bias (average of the predicted value and measured value residuals) of models constructed by Crandon et al. (2011), Roberts et al. (2009), and Jaruratanasirikul et al. (2015) were 5.96 μg/mL, 10.91 μg/mL, and 4.41 μg/mL, respectively. Following 2 g meropenem every 8 h (180 min infusion), CFR ≥ 90%, a criterion of success for empirical therapy, was achieved, even with creatinine clearance of 130–250 mL/min. For patients with sepsis and ARC, the model of Jaruratanasirikul et al. showed the highest degree of accuracy and precision and confirmed the efficacy of the meropenem dosing regimen in this patient population.

1. Introduction

In 2016 in Japan, approximately 11,510 fatalities among the whole population were the result of sepsis [1]. Treatment for sepsis generally involves the early administration of an antimicrobial agent. Where *Pseudomonas aeruginosa* is presumed to be involved in the nosocomial onset, or where the patient's background is unknown for community-acquired onset, meropenem (MEPM), a broad spectrum carbapenem antibiotic, is one pharmacotherapeutic option. For these indications, the approved standard dosing regimens for adults include 500 mg or 1000 mg MEPM administered as a short-term infusion every 8 h (q8h); in the case of bacterial meningitis, doses up to 2000 mg are recommended [2].

Renal insufficiency should be considered when determining the dose of MEPM, as this compound is excreted primarily via the kidney [3,4]. In recent years, augmented renal clearance (ARC), a condition in which renal function is excessively enhanced, has been reported in intensive care [5]. Furthermore, a reduction in the levels of β-lactam antibiotics in the blood has been shown to be associated with ARC and is therefore of clinical interest [6,7] because of the importance of maintaining the level of MEPM in the blood to

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ensure the effectiveness of antimicrobial treatment and prevent bacterial resistance.

To date, the optimum MEPM dose adjustment in patients with ARC has not been established, although therapeutic drug monitoring (TDM) [8], prolonged infusion [9], and population pharmacokinetic modeling [10] may be considered. Population pharmacokinetic models are used to facilitate dose adjustment according to renal function in many clinical settings. Several population pharmacokinetic models of MEPM have been reported for patients with sepsis [11–13], although the accuracy of these models for predicting MEPM blood levels in patients with ARC remains unclear. Therefore, in this study, we aimed to determine the optimum model for MEPM dose adjustment in septic patients with ARC. We also evaluated a specific dosing regimen for high PK/PD target attainment according to renal function using Monte Carlo simulation.

2. Patients and methods

2.1. Study protocol

We included patients aged 18 years or older who were receiving MEPM for sepsis in the intensive care unit (ICU) of Showa University Hospital emergency center. The following patients were excluded: (1) patients receiving hemodialysis, (2) patients with burns, (3) patients with massive bleeding, and (4) cancer patients. The examination period was from April 8, 2016 to June 30, 2017. For the diagnosis of sepsis, systemic inflammatory response syndrome (SIRS) criteria were adopted [14]. ARC was defined as creatinine clearance (CrCl) $\geq$ 130 mL/min/1.73 m^2 calculated by 8-h urine collection [15]. Blood samples (approximately 2 mL) were collected immediately prior to MEPM administration and 2 h after the start of infusion as a point of the elimination phase. For patients with ARC, blood samples were also collected after the second and subsequent doses of MEPM, and for patients without ARC, a blood sample was drawn after the third dose of MEPM. Age, sex, height, weight, serum creatinine value, measured CrCl, acute physiology and chronic health evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, information on MEPM administration method and concomitant medication was collected.

In the model of Crandon et al. [11], CrCl was estimated by the Cockcroft–Gault formula using estimated ideal body weight (IBW) (0.9 mg/dL was used for calculation when serum creatinine was $\leq$0.9 mg/dL in patients $\geq$65 years).

IBW = 50 kg + 2.3 kg for each inch over 5 feet (males)
IBW = 45.5 kg + 2.3 kg for each inch over 5 feet (females)

In addition, adjusted body weight (AdjBW) was used when the actual body weight exceeded IBW by 20% or more.

$$AdjBW = IBW + 0.4\,(actual\ body\ weight - IBW)$$

In the model of Roberts et al. [12], CrCl was calculated by the Cockcroft–Gault equation using actual body weight, and by the modification of diet in renal disease (MDRD) method in the model of Jaruratanasirikul et al. [13].

This study was approved by the Showa University Ethics Committee (no. 1966). All patients provided signed informed consent prior to participation in this study.

2.2. Measurement of plasma MEPM level

The MEPM level in plasma was measured using high-performance liquid chromatography as described previously [16], with minor modifications. Cefotaxime was used as the internal standard (final concentration 2.0 μg/mL). Samples were separated on a CAPCELL PAK C18 UG120 5 μm (4.6 mm × 150 mm) column (SHISEIDO, Kyoto, Japan). The mobile phase was a mixture of 10 mM phosphate buffer (pH 7.4) and acetonitrile (94.5:5.5, v/v). The injection volume was 100 μL. The calibration curve of MEPM in human plasma was linear from 0.064 to 81.9 μg/mL. The limit of quantitation was 0.064 μg/mL. For measurements, the interday and intraday accuracy of the absolute values (relative errors of the mean) and precision (as coefficient of variation) were within 10%.

2.3. Evaluation of population pharmacokinetic models

Three population pharmacokinetic models were used to predict free-form MEPM plasma level [11–13]. Blood MEPM levels were calculated based on one- or two-compartment models using reported population pharmacokinetic parameters (drug clearance, volume of distribution, and intercompartmental transfer rate constant). Predictions were evaluated for bias and precision using the Bland–Altman method [17]. The difference between the predicted value and the measured value was plotted against the average of the two values. Bias and precision were evaluated from the average of the difference between the predicted value and the measured value and the 95% confidence interval, respectively.

2.4. Evaluation of MEPM dosing regimen by Monte Carlo simulation

The achievement of 40% $fT_{>MIC}$, the time point when free drug blood level exceeds the minimum inhibitory concentration (MIC) of the causative bacteria, was evaluated by Monte Carlo simulation using population pharmacokinetic parameters and bacterial MIC data [18,19]. Monte Carlo simulation (n = 10,000) was performed using Oracle Crystal Ball software (Kozo Keikaku Engineering Inc., Tokyo, Japan).

The definitive dosing regimen was judged to be efficacious by the probability of target attainment (PTA). The PTA is the likelihood that the dosing regimen will meet or exceed the predefined pharmacodynamic target at a specific MIC.

The level of free MEPM was calculated with the assumption that the protein binding rate was 2% [3]. PTA $\geq$ 90% was defined as effective.

Conversely, because the MIC is difficult to determine in empirical therapy, the dosing regimen for which the MIC distribution is taken into account should be sought. To determine the effectiveness of empirical therapy, the cumulative fraction of response (CFR) was used [20], with a value $\geq$ 90% defined as effective [21]. The CFR was calculated as the summation of $PTA_i \times F_i$, with the subscript i indicating the MIC category ranked from lowest to highest MIC of a population of microorganisms, PTA_i indicating the PTA of each MIC category for that drug regimen, and F_i indicating the fraction of the population of microorganisms at each MIC category. The MIC distribution for the calculation of CFR used data from a surveillance study conducted in Japan (MIC $\geq$ 0.06 μg/mL) [22]. *P. aeruginosa* was selected for this evaluation because of the treatment difficulties it presents. The MIC value of 2 μg/mL for determining PTA was taken from the Clinical and Laboratory Standards Institute (CLSI) and corresponded to the drug susceptibility breakpoint of *P. aeruginosa* [23].

2.5. Statistical analysis

Continuous variables were evaluated by a Wilcoxon rank sum test using JMP Pro 13 software (SAS Institute Japan, Tokyo). Data are listed as median and interquartile ranges unless otherwise noted.

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