Population Pharmacokinetic Analysis of Meropenem After Intravenous Infusion in Korean Patients With Acute Infections

Yong Kyun Kim, MD[1,*]; Dong-Hwan Lee, PhD[2,*]; Jaehyun Jeon, PhD[3]; Hang-Jea Jang, MD[4]; Hyeon-Kuk Kim, MD[4]; Kyubok Jin, PhD[5]; Sung-Nam Lim, PhD[6]; Sung Sook Lee, PhD[6]; Bong Soo Park, PhD[7]; Yang Wook Kim, PhD[7]; Jae-Gook Shin, PhD[8]; and Sungmin Kiem, PhD[1]

[1]Division of Infectious Diseases, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; [2]Hallym Institute for Clinical Medicine, Hallym University Medical Center, Anyang, Republic of Korea; [3]Department of Infectious Diseases, Division of Intensive Care Medicine, Sheikh Khalifa Specialty Hospital, North Ras Al Khaimah, United Arab Emirates; [4]Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; [5]Division of Nephrology, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [6]Division of Hemato-Oncology, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; [7]Division of Nephrology, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; and [8]Department of Clinical Pharmacology, Inje University College of Medicine, Busan, Republic of Korea

ABSTRACT

Purpose: The aim of this study was to investigate the population pharmacokinetic (PK) profile of meropenem in Korean patients with acute infections.

Methods: The study included 37 patients with a creatinine clearance ≤50 or >50 mL/min who received a 500- or 1000-mg dose of meropenem, respectively, infused intravenously over 1 hour every 8 hours. Blood samples were collected before and at 1, 1.5, and 5 hours after the start of the fourth infusion. The population PK analysis was conducted by using nonlinear mixed effect modeling software (NONMEM). Monte-Carlo simulations were performed to identify optimal dosing regimens.

Findings: Thirty-seven subjects completed the study. Meropenem PK variables were well described by using a one-compartment model. The typical values (relative SE) for weight-normalized clearance (CL) and V_d were 0.266 L/h/kg (12.29%) and 0.489 L/kg (11.01%), respectively. Meropenem CL was significantly influenced by the serum creatinine level, which explained 11% of the interindividual CK variability. The proposed equation to estimate meropenem CL in Korean patients was as follows: CL (L/h) = 0.266 × weight × [serum creatinine/0.74]$^{-1.017}$. The simulation results indicate that the current meropenem dosing regimen may be suboptimal in patients infected with normal or augmented renal function.

Implications: Prolonged infusions of meropenem over at least 2 hours should be considered, especially in patients with augmented renal function and those infected with pathogens for which the minimum inhibitory meropenem concentration is >1 μg/mL. Our results suggest an individualized meropenem dosing regimen for patients with abnormal renal function and those infected with pathogens with decreased in vitro susceptibility. (*Clin Ther*. 2018;■:1–12) © 2018 Published by Elsevier Inc.

Accepted for publication July 3, 2018.
https://doi.org/10.1016/j.clinthera.2018.07.001
0149-2918/$ - see front matter

* These authors contributed equally to this work.

Key Words: augmented renal function, meropenem, MIC, population pharmacokinetics, prolonged infusion, target attainment.

INTRODUCTION

The pharmacokinetic (PK) variables and pharmacodynamic (PD) targets of antimicrobial agents may differ according to patient characteristics, such as obesity or conditions such as burn injury.[1,2] In addition, the profound physiological changes associated with infection and sepsis may significantly alter the PK/PD profiles of antibiotics.[3] Thus, PK/PD optimization of antibiotic therapy could improve clinical outcomes through individualization of therapy. In this context, a recent guideline for the management of hospital-acquired pneumonia proposed using PK/PD–optimized dosing as opposed to the manufacturer's recommended dose.[4]

Meropenem is a broad-spectrum antimicrobial agent of the carbapenem class and is widely used as either empirical or definitive therapy in patients with sepsis.[5] In most previous PK/PD studies of meropenem in patients with infection, prolonged infusions for maximized time above the MIC for unbound fraction of the drug ($fT_{>MIC}$) improved PD targets.[6–8] However, previous studies have been performed in different geographic locations, and only one study evaluated the PK profile of meropenem in Korean patients with febrile neutropenia.[9] Because ethnic or racial differences in the PK/PD profile of antimicrobial agents may be clinically significant and influence patient outcomes,[10,11] physicians should not overlook the potential effect of ethnicity or race on PK/PD variables.

Our institution previously conducted PK/PD studies to evaluate the individualized dosing of important antibiotics in Korean patients with acute infections.[12–14] The goal of the present study was to determine the PK profile and clearance (CL) equations of meropenem in Korean patients with acute infections and to investigate appropriate dosage regimens for meropenem by using population PK analysis and a Monte-Carlo simulation for predicting PD parameters.

PATIENTS AND METHODS

Patients

From October 2013 to July 2015, adult patients (aged ≥20 years) with acute infections such as pneumonia, intra-abdominal infections, or bacteremia were eligible for this study. Patients were included if they had sepsis or severe sepsis as defined by the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[15]

The following exclusion criteria were used: any history of relevant allergy or hypersensitivity to β-lactam antibiotics, an estimated creatinine clearance (CL_{CR}) <10 mL/min (determined by using the Cockcroft-Gault method), any concomitant treatment that may cause drug–drug interactions (eg, valproic acid and probenecid), any infection of the central nervous system (eg, meningitis, brain abscess), any uncontrolled or severe cardiovascular disease (eg, myocardial infarction within 6 months before enrollment, New York Heart Association functional class III or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial diseases, any ECG evidence of acute ischemic or active conduction system abnormalities), severe hepatic disorders (eg, alanine or aspartate aminotransferase levels >3 times the upper limit of normal, total bilirubin levels >2 times the upper limit of normal), any psychiatric disorders that could prevent compliance with the study protocol, pregnancy/breastfeeding, or any findings in the medical examination deviating from normal and judged as clinically relevant by the investigators. Patients with septic shock or those receiving renal replacement therapy were also excluded.

The study protocol was reviewed and approved by the Institutional Review Board of Inje University Haeundae Paik Hospital (Busan, Republic of Korea). Informed consent was written and obtained from all patients or their legally authorized representative before study inclusion.

Study Design

Four consecutive 500- or 1000-mg doses of meropenem were intravenously (IV) infused over the course of 1 hour every 8 hours in patients with a CL_{CR} ≤50 or >50 mL/min, respectively. In patients with a CL_{CR} of 10 to 25 mL/min, we planned to administer 500-mg doses over the course of 1 hour every 12 hours; however, this dosage regimen was not used in any patients because none of those enrolled had CL_{CR} values 10 to 25 mL/min.

Forty patients were enrolled, and blood samples were collected before and at 1, 1.5, and 5 hours after the start of the fourth infusion; in patients with a CL_{CR}