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Original article

The efficacy, safety, and pharmacokinetics of biapenem administered thrice daily for the treatment of pneumonia in the elderly

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ABSTRACT

Biapenem has been widely used to treat bacterial pneumonia; however, there is little information concerning its efficacy and safety in elderly patients. Based on pharmacokinetic–pharmacodynamic theory, administration of biapenem thrice rather than twice daily would be expected to be more effective because of longer time above the minimum inhibitory concentration. In this study, we aimed to evaluate the efficacy, safety, and pharmacokinetics of biapenem (300 mg) administered thrice daily in pneumonic patients aged 65 years or older. Biapenem was effective in 22 of 25 patients, as assessed by the improvement in clinical symptoms and/or the eradication of the causative organisms, and caused no serious adverse events. The pharmacokinetic profile was established based on simulations using a modeling program. Among 17 patients whose causative organisms were detected, time above the minimum inhibitory concentration was estimated to be 100% in 16 patients, all of whom showed clinical improvement. The results of this study confirmed the efficacy and safety of 300 mg of biapenem administered thrice daily for the treatment of pneumonia in elderly patients.

1. Introduction

Pneumonia is the third leading cause of death in Japan. As the number of elderly patients increases, the frequency of fatal pneumonia is expected to increase. Therefore, development of better treatments against pneumonia in elderly patients is necessary. The guidelines set forth by the Japanese Respiratory Society (JRS) for the treatment of community- or hospital-acquired pneumonia recommend carbapenems as the first-line treatment for elderly patients [1].

Biapenem (BPM), the fourth member of the carbapenem class, was launched in Japan in 2002 [2]. Similar to other carbapenems, BPM is a broad-spectrum antibiotic effective against gram-positive, gram-negative, and anaerobic bacteria, including β-lactamase-producing strains. BPM is also more stable than other carbapenems, including imipenem and meropenem, escaping inactivation by human dehydropeptitase-1 (DHP-1) [3].

The therapeutic efficacy of any drug is intimately related to its pharmacokinetic–pharmacodynamic (PK–PD) profile. Therefore, based on the PK–PD theory, it is reasonable to propose that the efficacy of BPM could be dependent on the time above the minimum inhibitory concentration (TAM). For this reason, BPM administration thrice daily to yield a longer TAM would be expected to be more effective than twice-daily dosing [4]. However, little is known about the efficacy and safety of BPM (300 mg)

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administered thrice daily compared to twice-daily dosing. Therefore, the aim of this study was to evaluate the efficacy, safety, and PK–PD profile of 300 mg of BPM administered thrice daily in elderly patients.

2. Patients and methods

2.1. Patients

This study was performed with the approval of the Ethics Committee of the Ashikaga Red Cross Hospital and the Fuji Heavy Industries Health Insurance Society Ota Memorial Hospital in April 2002. Written informed consent was obtained from all patients. Current protocol and analysis was performed under the approval of the Ethics Committee of the Keio University School of Medicine in November 2013.

Newly admitted pneumonia patients aged over 65 years were enrolled from either one of two participating institutions, Ashikaga Red Cross Hospital and Fuji Heavy Industries Health Insurance Society Ota Memorial Hospital, between January 2011 and December 2012. A diagnosis of pneumonia was made on the basis of clinical features and radiological findings by pulmonary experts when the following 3 conditions were met [1]: body temperature at or above 37 °C [2]; infiltrate shadow on chest X-ray or computed tomography imaging, suggesting bacterial pneumonia; and [3] expectoration of purulent sputum before treatment commencement. The severity of pneumonia was judged using the A-DROP system according to the JRS guidelines [1].

Exclusion criteria included [1]: serious cardiac, hepatic, and/or renal dysfunction (patients receiving renal replacement therapy) [2]; a history of hypersensitivity to β-lactam antibiotics [3]; a predisposition to BPM-related allergies [4]; potential infections with BPM-resistant causative organisms [5]; convulsive disorders, e.g., epilepsy [6]; a history of treatment with valproic acid [7]; a history of other antibiotic administration before BPM; and [8] unsuitability for the study based on the judgment of the attending physician.

2.2. Dosage and administration

BPM (Meiji Seika Pharma Co., Ltd, Tokyo, Japan) was administered at a dose of 0.9 g/day in 3 divided doses, each given by intravenous drip infusion over 60 min.

2.3. Efficacy criteria

On the seventh day of BPM treatment, clinical efficacy was evaluated subjectively and objectively according to symptomatic improvement and clinical effectiveness judgment criteria, respectively [5]. Efficacy was evaluated on the following 4 parameters [1]: reduction in body temperature to <37 °C [2], reduction in C-reactive protein (CRP) level to <30% of the initial level [3], reduction in the area of the infiltrate shadow on chest X-ray to <70% of that observed before treatment, and [4] reduction in white blood cell count (WBC) to <9000/mm^3. Radiological improvements on chest X-ray were assessed by 2 pulmonary experts independently. When more than three of the four conditions mentioned above were met, treatment was considered effective; if not, treatment was considered ineffective. Toxicity was evaluated on the basis of suspected treatment-related adverse events.

2.4. Criteria for bacteriological response

Bacteriological response was reported as eradicated, decreased, persisted, or unknown, based on the following criteria.

1) Eradicated: The causative organism (including suspected causative organisms) was eradicated or a marked symptomatic improvement was noted at the conclusion of the study, such that specimen collection was not necessary.
2) Decreased: The causative organism (including suspected causative organisms) was significantly diminished in infection density or there was evidence of partial elimination of a plurality of causative organisms.
3) Persisted: There was either no change or an increase in infection density of the causative organisms (including suspected causative organisms).
4) Unknown: No causative organism could be identified or changes in infection density of the causative organism over time remained unclear.

2.5. Pharmacokinetic study

The plasma concentrations of BPM were measured 15 min and 6 h after administration on day 2 by using high-performance liquid chromatography (HPLC) as previously described [6]. The system composition and conditions were as follows: pump, LC-10ATvp; column oven, CTO-20A; ultraviolet spectrophotometric detector, SPD-10Avp (Shimadzu, Kyoto, Japan); precolumn, TSK GUARDGEL ODS-80TM (7 μM; Toso, Tokyo, Japan); analysis column, Luna 5u C18(2)100 A (250 × 4.6 mm; Phenomenex, USA); column temperature, 30 °C; mobile phase, a mixture of 0.1 M phosphate buffer adjusted to 7.8; and buffer/methanol ratio in the mobile phase, 98:2. The velocity was 1 mL/min, and wavelength was 300 nm. A 300-μL aliquot consisting of 30 μL of control (pooled) serum and 270 μL of the mobile phase, which contained 1 μg/mL of BPM, was ultrafiltered using Microcon® Ultracel YM-10 (Millipore, Billerica, MA, USA) by centrifugation at 14,000 × *g* for 20 min at 4 °C. Twenty microliters of the filtrate was injected into the HPLC system. After the plasma concentrations were measured, PK–PD parameters were predicted by using PK–PD software developed by Ikawa et al. [7].

2.6. Statistical analysis

Data are presented as mean ± SD. Statistical comparisons were performed using Fisher's exact test or Wilcoxon signed-rank test. *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population

Table 1 shows the patient characteristics. Of the 32 patients who met the clinical inclusion criteria, 25 were enrolled. Four patients were excluded because they received other antibiotics before BPM, 2 were excluded because they received BPM twice, not thrice daily, and 1 was excluded due to insufficient data. As for smoking history, 8 patients were current smokers, 10 patients were ex-smokers, and 10 patients were never smokers. Most patients (64%) were classified as having severe pneumonia, according to the A-DROP system, while 20% and 16% were classified as having moderate and ultra-severe pneumonia, respectively.

3.2. Clinical efficacy

We administered BPM for 11.4 ± 4.9 (mean ± SD) days. Clinical responses were evaluated in all 25 patients. Therapeutic responses were classified as effective in 22 and ineffective in 3; thus, the response rate was 88%. Most patients (20/25) showed radiological