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Original article

Clinical efficacy and safety of high-dose doripenem in Japanese patients with pneumonia

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ABSTRACT

Background: Pneumonia is now the third leading cause of death in Japan, and the number of patients with pneumonia is expected to increase with the progression of aging of the country. Higher dosage of antibiotics has recently been used, and high-dose doripenem (DRPM; 3 g daily) was approved for use in Japan in April 2011. However, there is a lack of data regarding the efficacy and safety of high-dose DRPM in Japan. This study prospectively assessed the clinical efficacy and safety of high-dose DRPM in Japanese patients with refractory pneumonia.
Methods: This study was performed at University of Occupational and Environmental Health, Japan and affiliated hospitals. The efficacy and safety of DRPM in patients with pneumonia treated with 3 g daily of DRPM, including those in whom DRPM dosage was increased from 1.5 g to 3 g daily, were evaluated.
Results: The safety evaluations included 56 patients, and the efficacy was evaluated in 51 patients. DRPM (3 g daily) treatment showed the response rate of 92.2% (47/51). Adverse effects of DRPM (3 g daily) were observed in 11 of 56 patients (19.7%), and all of these patients improved after DRPM cessation. Two patients had to stop DRPM administration due to elevated aminotransferase levels. The efficacy of DRPM in patients with pneumonia in whom DRPM was increased from 1.5 g daily to 3 g daily was 84.6% (11/13).
Conclusions: High-dose DRPM (3 g daily) treatment is effective and relatively safe in Japanese patients with pneumonia.

1. Introduction

Pneumonia is the third leading mortality cause in Japan, and most cases were of elderly patients over 65 years of age [1]. Aging of the population and an increase in the number of patients with pneumonia is predicted in Japan.

Doripenem (DRPM) is a carbapenem antibiotic with broad-spectrum and high bactericidal activity against Gram-positive and -negative bacteria including anaerobes. DRPM is also active against multi-resistant Gram-negative bacilli such as extended-spectrum beta-lactamase-producing (ESBL) Gram-negative *Enterobacteriaceae* and non-fermentative Gram-negative bacilli. Similar to the other beta-lactam antibiotics, DRPM exhibits bactericidal effects to inhibit bacterial cell wall biosynthesis by inactivating penicillin-binding proteins (PBP) [2].

According to the Japanese guidelines for pneumonia, carbapenem antibiotics including DRPM have been recommended for patients with moderate, severe and extremely severe community-acquired pneumonia (CAP) [3], hospitalized nursing and healthcare-associated pneumonia (NHCAP) patients with risk factors for multidrug-resistant pathogens [4] and moderate to severe hospital-acquired pneumonia (HAP) patients, including those with ventilator-associated pneumonia (VAP) [5].

The maximum dosage of DRPM for infectious diseases had been 1.5 g daily in Japan compared with 3 g daily outside Japan. In 2011, the administration of DRPM at 3 g daily was approved in Japan for

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treating refractory infections including pneumonia. However, the efficacy and safety of high-dose DRPM (3 g daily) for treating infectious diseases in Japanese patients have been unclear so far, and a clinical validation is important.

In this study, we evaluated the clinical efficacy and safety of high-dose of DRPM (3 g daily; 1 h intravenous administration of DRPM 1 g for three times daily) in Japanese patients with pneumonia.

2. Patients and methods

2.1. Study design

This was a prospective, open-label, multicenter study conducted in the University of Occupational and Environmental Health, Japan and its affiliated community hospitals from December 2013 to April 2015. The study was approved by the ethics committee of each participating institutions and was registered on a clinical trial registry (UMIN 000012685). Written informed consent was obtained from each patient.

2.2. Definitions

Pneumonia was diagnosed fulfilling all three criteria: (1) positive findings of at least one of following symptoms; fever, cough, purulent sputum, moist rales, pleural pain, dyspnea, tachypnea; (2) new pulmonary infiltrates on chest radiology and (3) positive findings of inflammation at least one sign of the followings; a white blood cell (WBC) count > 10,000/mm^3 or < 4500/mm^3, an elevated serum level of C-reactive protein (CRP), body temperature $\geq$ 37 °C.

Definition of CAP was as follows; pneumonia acquired in the community with no risk factors for NHCAP. NHCAP was defined as pneumonia acquired in the community with at least one of the following risk factors: (1) resident of an extended care facility or nursing home, (2) discharged from a hospital within the preceding 90 days, (3) an elderly or disabled person receiving nursing care, or (4) receiving regular outpatient endovascular treatment [4]. Definition of HAP was pneumonia acquired $\geq$48 h after admission to the hospital.

The inclusion criteria were: (1) CAP or NHCAP patients with a mild, moderate, severe or extremely severe grade according to the A-DROP system [3,4]; (2) HAP patients with a moderate or severe grade according to the I-ROAD system [5]; and (3) patients older than 20 years of age. The exclusion criteria were: (1) having contraindications for DRPM administration; (2) liver insufficiency such as elevated levels more than five times of the upper limit of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT); (3) renal insufficiency such as elevated levels more than two times the upper limit of serum blood urea nitrogen (BUN) and/or creatinine; (4) febrile patients due to noninfectious causes; (5) patients with convulsive disorders; and (6) patients receiving valproic acid therapy.

2.3. Dosage and administration of DRPM

DRPM (1 g) was intravenously administered for 1 h every 8 h, and the treatment period ranged from three to 14 days. In addition to high dose DRPM (3 g daily) used from the beginning, treatment with DRPM (3 g daily) was applied in patients initially treated with DRPM (1.5 g daily, 0.5 g for 1 h every 8 h) or other antibiotics except carbapenems when the patient did not satisfy the criteria of "effective" according to the clinical evaluation methods for new antimicrobial agents to treat respiratory infections [6] three days after starting DRPM (1.5 g daily) or other antibiotics. The concomitant use of antimicrobials, including macrolides and corticosteroids, was not allowed during the study.

2.4. Evaluation of the clinical efficacy

The clinical efficacy at the end of treatment (EOT) determined by the changes in the clinical symptoms and laboratory and chest radiographical findings [6] was the primary endpoint. Clinically "effective" was considered in cases which satisfied more than three of the followings: (1) the clinical symptoms showed an improvement or complete resolution, (2) the body temperature was improved to $\leq$37 °C, (3) a chest radiography score was improved to $\leq$70% of the previous value, (4) WBC count was decreased to $\leq$9000/mm^3 and (5) CRP level was decreased to $\leq$30% of the previous value. When the efficacy criteria were not satisfied or were indeterminate for any reason, "ineffective" was considered.

2.5. Evaluation of adverse reactions of DRPM

The evaluation of adverse reactions was recorded from the start of therapy until three days after the discontinuation of DRPM according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [7].

2.6. Bacteriological evaluation

Before the start of DRPM administration, sputum, bronchoalveolar lavage fluid (BALF) and blood samples were collected for Gram staining and culturing when possible.

2.7. Statistical analysis

All statistical analyses were performed using the SPSS software package (version 19), and a value of $p < 0.05$ was considered to be statistically significant. Categorical variables were compared using Fisher's exact test (2 × 2).

3. Results

3.1. Patient enrollment and characteristics

A total of 59 patients were enrolled, and three of them were excluded from this study due to pulmonary mycosis (n = 1) and noninfectious causes (n = 2) (Fig. 1). The characteristics of enrolled 56 patients (42 males, 14 females) are summarized in Table 1. The average age was 79.2 ± 10.6 years, and 42 of 56 patients (75.0%) had at least one comorbid illness, including 12 patients (21.5%) with chronic respiratory disorders: chronic obstructive pulmonary disease (COPD) (n = 7), nontuberculous mycobacteriosis (n = 2), COPD with old tuberculosis (n = 1), bronchiectasis (n = 1) and old tuberculosis (n = 1). Antimicrobial agents other than DRPM before starting 3 g daily of DRPM were used in 14 (25.0%) patients, and the dosage of DRPM was increased from 1.5 g to 3 g daily in 13 (23.2%) patients. The types of pneumonia consisted of patients with CAP (n = 13, 23.2%), NHCAP (n = 30, 53.6%) and HAP (n = 13, 23.2%) (Table 1).

3.2. Clinical efficacy

As shown in Fig. 1, 51 patients were enrolled in the efficacy evaluation, and the clinical efficacy of treatment with 3 g daily of DRPM is shown in Table 2. Treatment with DRPM (3 g daily) was effective in 92.2% (47/51) of patients, including 95.8% (23/24) of patients in whom 3 g daily DRPM was administered from the beginning, 92.9% (13/14) patients who changed from other