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Original Article

Pediatric community-acquired pneumonia treated with a three-day course of tebipenem pivoxil

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ABSTRACT

We evaluated the efficacy and safety of a 3-day treatment regimen of tebipenem pivoxil for pediatric community-acquired pneumonia. Tebipenem pivoxil was administered to 49 patients, and its effectiveness was evaluated in 36 patients 2–4 days after initiation of treatment. Thirty-two patients were cured 7–15 days after initiation of treatment. Body temperature was significantly lower on the day following initial administration (median 38.8 to 37.0 °C, n = 33). Leukocyte counts and C-reactive protein levels were significantly reduced by Day 2–4 of treatment (median 16,100 to 7800 white blood cells/μL, and 5.6 to 1.5 mg/dL, respectively; n = 28). Six of the 49 patients had mild diarrhea. Thus, we concluded that 3-day treatment with tebipenem pivoxil was safe and efficacious for treating pediatric community-acquired pneumonia.

1. Introduction

Streptococcus pneumoniae is a frequent pathogen in pneumonia, meningitis, septicemia, and other lethal infections [1,2]. The global use of conjugate vaccines has dramatically decreased the incidence of invasive infections such as meningitis and septicemia, but non-vaccine type *S. pneumoniae* infections have become a more significant problem, particularly infections with *S. pneumoniae* resistant to penicillin and macrolide antibiotics [3–6]. Tebipenem pivoxil is a tebipenem prodrug with superior antimicrobial and bactericidal activity against *S. pneumoniae* that shows good absorption via transporters in addition to passive diffusion [7–9]. Tebipenem pivoxil, an oral carbapenem antibiotic, was introduced in Japan in 2009 and was approved for the treatment of pediatric pneumonia, otitis media, and sinusitis [10]. Based on clinical research in young children, tebipenem pivoxil has shown superior efficacy in the treatment of community-acquired pneumonia [11–13]. Cures for suspected community-acquired bacterial pediatric pneumonia are based on the causative pathogen, the patient age, and the clinical findings. *S. pneumoniae* is the most frequent pathogen causing pneumonia in children aged <5 years, and for children that do not require hospitalization, amoxicillin is recommended. Alternative antibiotic therapies includes clavulanate/amoxicillin and broad-spectrum cephalosporins [14–16]. In Japan, penicillin and macrolide-resistant *S. pneumoniae* and β-lactamase non-producing ampicillin-resistant *Haemophilus influenzae* are often isolated. Because they are also resistant to clavulanic acid/amoxicillin and cephalosporins, tebipenem pivoxil is the drug of choice for infections caused by these bacteria [16]. Since the excessive use of antibiotics increases the appearance of resistant bacteria, optimal antibiotic selection, based on the likely causative pathogen and its drug sensitivities, is recommended. On the other hand, the optimal duration of antibiotic therapy in bacterial pneumonia has not been established. Therefore, we prospectively evaluated the efficacy and safety of a 3-day course of tebipenem pivoxil for the treatment of pediatric community-acquired pneumonia of suspected bacterial origin.

Abbreviations: CRP, C-reactive protein level; MIC, minimum inhibitory concentration; WBC, white blood cells.

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2. Materials and methods

This study was approved by the institutional ethics review boards of the participating facilities. In clinics that had no institutional ethics review boards, the review was carried out by the ethics committee of Hakujikai Memorial Hospital, from which approval was received. The children who were enrolled in our study consisted only of pediatric patients whose legal guardians provided written consent.

From May 2013 to April 2014, 50 children (aged 8 months to 15 years and 8 months, 27 boys and 23 girls) were diagnosed with community-acquired pneumonia of bacterial origin in 12 pediatric facilities in Japan (Table 1). In all cases, tebipenem pivoxil 12 mg/kg/d was orally administered in two divided doses for 3 d. The diagnostic criteria for bacterial pneumonia included the presence of all of the following: 1) fever ≥37.5 °C with coughing, phlegm production, or other respiratory symptoms, 2) an acute infiltration on chest radiograph, and 3) a leukocyte count of ≥15,000 white blood cells (WBC)/μL or a C-reactive protein level (CRP) of ≥4 mg/dL. The inclusion criteria were as follows: patients suspected of resistant bacterial infection or hospitalized patients with moderately severe pneumonia who were indicated for treatment with injectable medication according to the Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2011 [16]. Safety was evaluated in 49 cases; a 9-month-old boy who could not ingest the drug was excluded. Body temperatures were measured in the morning, at noon, and in the evening (for example, at 7:00, 13:00, and 19:00). Efficacy was assessed at 2–4 d by the resolution or improvement of clinical symptoms (cough, phlegm, labored respiration, fever, respiratory rate, oxygen saturation, chest auscultation, chest pain, general appearance, interference with normal activities, leukocyte count, and CRP level) and at 7–15 d by clinical cure. To estimate the causative microorganism, nasopharyngeal swabs were collected and cultured before tebipenem pivoxil was administered.

3. Results

A total of 36 patients (19 boys and 17 girls) were evaluated for clinical efficacy (Fig. 1). Three cases of drug non-compliance, 9 cases of antibiotic therapy for ≥4 d, and 1 case of no examination 2–4 days after the start of the antibiotic treatment were excluded. For the 36 patients included in the efficacy evaluation, the median age was 29.5 months (interquartile range, 17.8–43.5 months) and the median body weight was 11.6 kg (interquartile range, 10.0–14.6 kg). Based on the Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2011, 23 patients had mild cases of suspected resistant bacterial infections, and 13 patients had moderate cases for which injectable antibiotics were recommended (including 10 cases of suspected resistant bacterial infection). The median number of days from the onset of fever or flu-like symptoms until the start of tebipenem pivoxil administration was 3 d (interquartile range, 2–4 d).

In 13 cases, other antibiotics had been administered within the previous two weeks. Third-generation oral cephems accounted for 6 cases; macrolides accounted for 3 cases; high-dose penicillins, penems, and fluoroquinolones accounted for one case each; and details were unclear in 1 case. Underlying diseases were found in 8 cases, including 4 cases of asthma and allergic rhinitis, and 1 case each of a chromosome abnormality complicated by an atrial septal defect, hypothyroidism, IgG subclass deficiency, congenital heart disease, and bronchopulmonary dysplasia. In addition, 4 cases with acute otitis complications were seen. At the start of tebipenem pivoxil administration, the median values (interquartile range) of body temperature, leukocyte count, and CRP levels were 38.8 °C (38.1–39.3 °C), 15,900 WBC/μL (9400–17,500 WBC/μL), and 5.2 mg/dL (4.4–8.4 mg/dL), respectively. Nasopharyngeal swabs were cultured, and the findings showed that *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis* were isolated from 30 of the 36 patients who were subjected to a treatment efficacy assessment (Fig. 2). In the remaining 6 patients, indigenous oral cavity bacteria were isolated, including *Staphylococcus epidermidis*, Corynebacterium, and α-Streptococcus.

Trends in body temperature (33 cases), leukocyte counts (28 cases), and CRP levels (28 cases) after the initiation of antibiotic therapy are shown in Fig. 3. Body temperature was significantly decreased by the day following the initiation of antibiotic therapy. The median value (interquartile range) decreased from 38.8 °C (38.1–39.3 °C) to 37.0 °C (36.7–37.4 °C; $p < 0.0001$, paired t test). Twenty-three cases had a temperature of <37.5 °C within 24 h of tebipenem pivoxil administration, 29 cases had a temperature of <37.5 °C within 48 h of drug administration, and 31 cases had a temperature of <37.5 °C within 72 h of drug administration. In the remaining patient, fever decreased one day after administration of treatment, and although a body temperature of 38.9 °C was recorded on day 4, the fever disappeared the next morning. The median time from antibiotic administration to a decrease in body temperature was 12 h (interquartile range, 6–24 h). The leukocyte counts and CRP levels were significantly decreased by 2–4 d after administration. The median value (interquartile range) decreased from 16,100 WBC/μL (9200 to 17,500 WBC/μL) to 7800 WBC/μL (6600 to 10,100 WBC/μL), and from 5.6 mg/dL (4.4–9.0 mg/dL) to 1.5 mg/dL (0.8–2.9 mg/dL), respectively ($p < 0.0001$ for both, paired t test). Coughing and sputum excretion, along with chest auscultation findings, also quickly improved. At the final evaluation, 7–15 d after starting tebipenem pivoxil, pneumonia symptoms had completely disappeared in 32 cases and the patients were considered cured. Three patients who did not present for follow-up 7–15 d after the start of therapy were excluded as was 1 patient who developed acute otitis media after resolution of the pneumonia symptoms.

Of the 9 cases that were excluded from the efficacy evaluation because antibiotic administration exceeded 3 d, 7 cases involved infants <1 year old with underlying diseases or complications such as trisomy 21, mental retardation, tracheal stenosis, and asthma. Two of these cases required continued treatment for complications arising from otitis media. In all 9 cases, the pneumonia symptoms were confirmed to have improved within 3 d of the initiation of tebipenem pivoxil treatment. In the 49 cases evaluated for adverse events, diarrhea and soft stool were observed in 6 cases. Gastrointestinal symptoms were mild and resolved after the completion of therapy.

Table 1
The 12 cooperative pediatric facilities in Japan.

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Sotobo Children's Clinic, Medical Corporation Shigyo-no-kai
Department of Pediatrics, Kawasaki Medical School
Department of Pediatrics, Hakujikai Memorial Hospital
Department of Pediatrics, National Hospital Organization Tokyo Medical Center
Department of Pediatrics, Yokosuka Kyosai Hospital
Department of Pediatrics and Child Health, Kurume University School of Medicine
Department of Pediatrics, Fuji Heavy Industries Ltd., Health Insurance Society General Ota Hospital
Department of Pediatrics, Hiroshima Prefectural Hospital
Department of Pediatrics, Osaka Rosai Hospital
Department of Pediatrics, Yokohama Minami Kyosai Hospital
Nagai Pediatric Clinic