J Infect Chemother (2007) 13:224–229
DOI 10.1007/s10156-007-0529-4

ORIGINAL ARTICLE

Minako Aoki · Toshiyuki Fukao · Hideo Kaneko
Shingo Mizunaga · Junichi Mitsuyama · Haruki Sawamura
Mitsuru Seishima · Naomi Kondo

Clinical and bacteriological evaluation of the efficacy of piperacillin in children with pneumonia

Received: December 25, 2006 / Accepted: April 14, 2007

Abstract We aimed to prospectively evaluate the clinical and bacteriological effects of piperacillin in children with pneumonia. Twenty-eight patients (6 months to 5 years of age) with pneumonia were treated with piperacillin. In the same period, 95 strains of *Haemophilus influenzae* and 41 strains of *Streptococcus pneumoniae* were isolated in our department and the minimum inhibitory concentration (MIC) of piperacillin was determined. The clinical efficacy of piperacillin was excellent in 4 cases, good in 23, and fair in 1; the response rate was 96.4% (27/28). Among the isolates from our department, there were 4 strains (9.8%) of penicillin-susceptible *S. pneumoniae* (PSSP), 32 strains (78.0%) of penicillin-intermediate-resistant *S. pneumoniae* (PISP), and 5 strains (12.2%) of penicillin-resistant *S. pneumoniae* (PRSP). Against *S. pneumoniae*, the MIC_{50} and MIC_{90} for piperacillin were 0.5 μg/ml and 2 μg/ml, respectively. Panipenem showed the best results, followed by piperacillin, ampicillin, and flomoxef. Among the isolates from our department, there were 51 strains (53.7%) of β-lactamase-negative ampicillin-susceptible *H. influenzae*, 42 strains (44.2%) of β-lactamase-negative ampicillin-resistant *H. influenzae*, 1 strain (1.1%) of β-lactamase-positive ampicillin-resistant *H. influenzae*, and 1 strain (1.1%) of β-lactamase-positive amoxicillin-clavulanic acid-resistant *H. influenzae*. The MIC_{50} and MIC_{90} for piperacillin against *H. influenzae* were 0.0625 μg/ml and 0.125 μg/ml, respectively. Tazobactam/piperacillin and piperacillin showed the best results, followed by panipenem, ampicillin, and flomoxef. Piperacillin proved to be very useful for the treatment of pneumonia in children.

Key words Child · Pneumonia · Piperacillin · *Haemophilus influenzae* · *Streptococcus pneumoniae*

Introduction

Haemophilus influenzae and *Streptococcus pneumoniae* are the main causative bacteria of respiratory tract infections in children. In recent years, β-lactamase-negative ampicillin-resistant *H. influenzae* (BLNAR) and penicillin-resistant *S. pneumoniae* (PRSP) strains have been detected with increasing frequency, leading to an increase in the number of patients refractory to these antibiotics. Piperacillin is an antibiotic that shows a good antibacterial effect on *S. pneumoniae* and has greater effect on *H. influenzae*, especially on BLNAR, compared to other β-lactam antibiotics. In this study, we evaluated the efficacy of piperacillin in children with pneumonia, from the viewpoints of clinical and bacteriological efficacy and safety.

Patients and methods

The subjects were children with pneumonia who were admitted to the pediatric ward of Gifu University Hospital between June 2004 and May 2005. Based on radiological (infiltrative shadow on chest X-rays) and clinical findings (acute inflammation evidenced by neutrophilia and C-reactive protein [CRP] elevation, and respiratory symptoms including fever and cough), it was determined that antimicrobial infusion therapy was needed. Patients with a severe underlying disease or complication were excluded from the study. Further, mycoplasmal antibody and viral antigen tests were performed to exclude patients with mycoplasma or viral pneumonia from this study. Pharyngeal specimens were collected whenever possible for the identification

M. Aoki (✉) · T. Fukao · H. Kaneko · N. Kondo
Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido, Gifu 501-1194, Japan
Tel. +81-58-230-6386; Fax +81-58-230-6387
e-mail: mina@gifu-u.ac.jp

S. Mizunaga · J. Mitsuyama
Research Laboratories, Toyama Chemical Co. Ltd., Toyama, Japan

H. Sawamura
Clinical Laboratory, Gifu University Hospital, Gifu, Japan

M. Seishima
Department of Informative Clinical Medicine, Graduate School of Medicine, Gifu University, Yanagido, Gifu, Japan

of infecting bacteria. Piperacillin 100 mg/kg per day was administered in three divided doses by intravenous drip infusion over 1 h. The clinical characteristics of the patients, clinical efficacy, occurrence of adverse drug reactions, and antimicrobial susceptibility of the isolated bacteria were evaluated. Prior to the initiation of treatment, informed consent was obtained from the person with parental authority over each patient.

Clinical efficacy was evaluated using a four-category scale according to the judgment criteria in clinical tests for antibacterial agents used in pediatrics.[1] Clinical efficacy was based on the improvements in the major symptoms of pneumonia (observed items were body temperature, dyspnea, and cough; tested items were inflammatory response, chest X-ray, and bacteriological examination), as follows:

Excellent: major symptoms started to obviously improve within 1 day from the start of the medication (day 0), and most of the symptoms resolved within 3 days.
Good: major symptoms started to obviously improve within 3 days from the start of the medication (day 0), and most of the symptoms resolved within 5 days.
Fair: major symptoms improved after a period that exceeded the number of days defined for good efficacy.
Poor: major symptoms did not improve or were exacerbated after the start of the medication.

To assess the antibacterial activity of piperacillin, the minimal inhibitory concentration (MIC) was determined by broth microdilution test, according to the Clinical and Laboratory Standards Institute (CLSI) method, in the bacterial strains isolated from respiratory tract secretions obtained during the same period in our department.[2] The drugs tested were piperacillin, tazobactam/piperacillin, ampicillin, flomoxef, and panipenem. β-Lactamase production was determined by the nitrocefin method.

S. pneumoniae strains were classified based on the MIC of penicillin G (PCG); MIC of PCG ≦0.06 μg/ml, penicillin-susceptible *S. pneumoniae* (PSSP); MIC of PCG 0.12 μg/ml to 1 μg/ml, penicillin-intermediate-resistant *S. pneumoniae* (PISP); MIC of PCG ≧2 μg/ml, penicillin-resistant *S. pneumoniae* (PRSP).

H. influenzae strains were classified based on the presence/absence of β-lactamase production and the MIC of ampicillin (ABPC): non-β-lactamase-producing and MIC of ABPC <2 μg/ml, β-lactamase-negative and ampicillin-susceptible *H. influenzae* (BLNAS); non-β-lactamase-producing and MIC of ABPC ≧2 μg/ml, β-lactamase-negative and ampicillin-resistant *H. influenzae* (BLNAR); β-lactamase-producing and MIC of ABPC ≧2 μg/ml, β-lactamase-positive and ampicillin-resistant *H. influenzae* (BLPAR); β-lactamase-producing and resistant to clavulanic acid (CVA)/amoxicilin (AMPC), β-lactamase-positive and amoxicillin/clavulanic acid-resistant *H. influenzae* (BLPACR).

Based on the blood kinetics of piperacillin measured by Shishido et al.,[3] we calculated pharmacokinetic parameters and simulated the concentration of piperacillin in the blood when dosing at 33.3 mg/kg (100 mg/kg per day divided into three doses). We also calculated the time above MIC (TAM) of the simulated blood piperacillin concentration, as well as its percentage in 24 h. The pharmacokinetic analysis software, WinNonlin Standard (Japanese Edition version 4.1; Pharsight, CA, USA), was used to calculate pharmacokinetic parameters. The one-compartment model was adopted, the simplex method was used as the algorithm of the nonlinear least-squares method, and the results were weighted $1/y^2$. Other calculations were performed using Excel (Microsoft, WA, USA).

Results

Eighty-four patients with pneumonia, consisting of 37 with bacterial pneumonia, 31 with viral pneumonia and 16 with mycoplasma pneumonia, were hospitalized and treated at our hospital between June 2004 and May 2005. Six patients with bacterial pneumonia were excluded because of serious underlying diseases, and of the remaining 31, 28 were treated with piperacillin, 2 were treated with flomoxef, and 1 was treated with cefpirome.

Patient information is summarized in Table 1. There were 16 male and 12 female infants/children, aged 6 months to 5 years of (mean age, 2 years and 1 month) with pneumonia. Regarding underlying diseases, there was no notable disease except for asthma, in 6 patients. After treatment, the efficacy of piperacillin was considered excellent in 4 patients, good in 23, and fair in 1. The efficacy of piperacillin was judged as fair in patient 20, because an extended period of time was needed for a clear improvement of major symptoms. Patient 20, with underlying asthma and interstitial pneumonia, presented with hypoxia, and had to be treated with steroid therapy. There were 5 patients with asthma in whom the efficacy of the drug was judged to be good, according to the same criteria as those employed in patients without underlying diseases. As for bacteria isolated from pharyngeal specimens, eight strains of *H. influenzae* (BLNAS, five strains; BLNAR, three strains, two strains of *S. pneumoniae* (PISP), and one strain of *Pseudomonas aeruginosa* were isolated. Ten children were negative for infecting bacteria, probably because all of them had been treated with oral antibiotics (cephems, 5 patients; macrolides, 4 patients; penicillin, 1 patient) before their admission to our hospital. Resident bacteria were isolated only from 7 patients. No significant adverse event was observed during the administration of piperacillin.

Meanwhile, we isolated *S. pneumoniae* from respiratory tract secretions in our department in 1 year and examined the susceptibility of the isolates to penicillin G. As the result, 4 strains (9.8%) were PSSP, 32 strains (78.0%) were PISP, and 5 strains (12.2%) were PRSP (Table 2). The cumulative MIC distribution of four antibacterial agents for *S. pneumoniae* is shown in Fig. 1. The MIC_{50} and MIC_{90} for the antimicrobial agents were: 0.5 μg/ml and 2 μg/ml for piperacillin, 0.5 μg/ml and 2 μg/ml for ampicillin, 1 μg/ml and 4 μg/ml for flomoxef, and ≦0.12 μg/ml and ≦0.12 μg/ml for panipenem, respectively. Panipenem showed the best results, followed by piperacillin, ampicillin, and flomoxef.