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□ ORIGINAL ARTICLE □

Clinical Comparative Study of Sulbactam/Ampicillin and Imipenem/Cilastatin in Elderly Patients with Community-Acquired Pneumonia

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Abstract

Objective To evaluate the clinical usefulness of sulbactam/ampicillin therapy for community-acquired pneumonia in the elderly.

Methodology A randomized prospective clinical study was conducted in the elderly patients with moderate-to-severe community-acquired bacterial pneumonia.

Results Overall clinical efficacy of sulbactam/ampicillin therapy (6 g/day) in these patients (efficacy rate: 91.4%) was comparable to that of imipenem/cilastatin therapy (1 g/day; efficacy rate: 87.5%), when each therapy was administered intravenously twice daily for 7-14 days. With regard to clinical efficacy based on disease severity, bacteriological efficacy, improvement of chest X-ray findings and adverse reactions, the two therapies were comparable.

Conclusion These results suggest that sulbactam/ampicillin therapy has excellent efficacy and tolerability and that it may be highly effective, even in severe cases of pneumonia. This regimen may thus serve as first-line treatment for the treatment of community-acquired pneumonia in elderly patients.

Key words: community-acquired pneumonia, pulmonary infection, clinical trial, elderly patients, antibiotics

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Introduction

According to the Japanese Ministry of Health, Labour and Welfare (MHLW), pneumonia is the fourth leading cause of death in Japan. If deaths from pneumonia are analyzed by age, elderly patients (aged > 65 years) account for >90% of total deaths from pneumonia (1). The high death rate among elderly patients with pneumonia is primarily attributable to the following factors: 1) elderly individuals are prone to infection due to compromised immune function caused by underlying disease, malnutrition, etc.; and 2) occult misswallowing and reduced drug absorption due to cerebrovascular disease and dementia (2, 3). Because pneumonia in elderly individuals tends to follow severe courses under the influence of these factors, drugs with potent and broad-spectrum antimicrobial activity (e.g., cephalosporins, carbapenems) are often used to manage elderly patients with pneumonia. In recent years, however, narrow-spectrum antimicrobial agents have been recommended for more widespread use due to their improved medical economics and as a result of bacterial resistance to broad-spectrum antimicrobial agents (4). Under such circumstances, the clinical usefulness of the penicillins has been reviewed, and the use of ampicillin (ABPC) in combination with beta-lactamase inhibitors is considered to be highly effective, particularly considering

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that ABPC is even effective against some Gram-negative bacteria.

Community-acquired pneumonia (CAP) is an acute infection seen among humans participating in ordinary social interaction. The microorganisms responsible for this type of pneumonia are often highly toxic bacteria. The bacterium most frequently isolated from patients with CAP is *Streptococcus pneumoniae*, followed by *Haemophilus influenzae* (5-7). Guidelines for the diagnosis and treatment of CAP have been made public in Western countries (8, 9). In Japan, the Japanese Respiratory Society (JRS) proposed guidelines in 2000 (10).

The present study was undertaken in order to evaluate the usefulness of sulbactam (SBT), a beta-lactamase inhibitor, in combination with ABPC, an antimicrobial agent, in the treatment of CAP in elderly individuals. To this end, the efficacy and safety of SBT/ABPC therapy were compared with those of imipenem/cilastatin (IPM/CS) therapy.

Subjects and Methods

Participating facilities

This study was conducted at the Second Department of Internal Medicine of Nagasaki University Hospital, Nagasaki, and its 10 affiliated facilities between November 2002 and October 2003.

Patients

Subjects were > 65-year-old patients diagnosed at the participating facilities as having moderate-to-severe bacterial CAP according to the differential criteria in the JRS guidelines (including patients with cerebrovascular disease, but excluding patients with mild pneumonia according to the JRS criteria for CAP severity). The JRS guidelines define CAP as pneumonia seen in the general population that affects mostly healthy people living ordinary social lives, but also the elderly and those with various underlying diseases. Patients with a history of allergies to SBT/ABPC or IPM/CS, severely compromised renal or hepatic function, or successful therapeutic response to previous treatments, as well as those taking steroids (equivalent to >10 mg/day prednisolone), and those judged by the attending physician to be inappropriate for the study based on immune function or any other reason were excluded from the study. Prior to the start of the study, the patient or his/her legal agent was informed of the study design and consent was obtained in writing. This trial was approved by the institutional review board of Nagasaki University.

Dose level and administration method

Patients were randomized into two groups using sealed envelopes containing allocation of the groups: the SBT/ABPC group (treated intravenously with SBT/ABPC at 3 g twice daily) and the IPM/CS group (treated intravenously with IPM/CS at 0.5 g twice daily). In each group, treatment was performed for 7 days; however, the dosing period was extended (up to day 14), as needed. When fever subsided (to <37.5℃) or other systemic symptoms were alleviated, the attending physician discontinued treatment at his/her discretion. Cases showing no signs of improvement after 3 days of dosing were rated as non-responders to the therapy. Concomitant use of other antimicrobial agents (excluding macrolides and anti-tuberculosis agents started before the study) and gamma-globulin preparations was prohibited. Concomitant use of steroids, nonsteroidal anti-inflammatory analgesics, and anti-inflammatory enzyme preparations was also prohibited. Concomitant use of the following drugs was permitted (the dose used before the start of the study was left unchanged); granulocyte colony stimulating factor (G-CSF), expectorants, antitussives, bronchodilators, mucolytic agents without anti-inflammatory activity, and drugs for the treatment of complications and underlying diseases.

Discontinuation of treatment

Treatment was discontinued if underlying disease or infection was exacerbated, if efficacy of treatment was inadequate or condition was exacerbated, if complications were exacerbated, if incidental symptoms developed, if adverse reactions or laboratory abnormalities developed, if the patient or his/her proxy requested discontinuation, or if the attending physician considered discontinuation necessary for other reasons. Data from discontinued cases were included, if clinical evaluation was possible at the time of discontinuation.

Evaluation

Severity of pneumonia was rated based on the attending physician's subjective judgment, in addition to the Pneumonia Severity Index (PSI) prepared by the Infectious Disease Society of America (IDSA) (9) and the JRS classification of severity of CAP. Subjective and objective symptoms, chest X-ray findings, laboratory test data, and bacteriological test results were evaluated before, at 3 and 7 days after the start of dosing and at the end of dosing. Bacteriological tests included isolation and identification of bacteria from sputum and blood samples, evaluation of sensitivity of isolated bacteria to SBT/ABPC and IPM/CS, *Mycoplasma* and *Chlamydia* antibody test, urinary *Legionella* and pneumococcus antigen test, and observation of bacterial fate and changes in drug sensitivity following treatment.

Clinical efficacy judgment and analysis

Based on the time course of clinical symptoms from the start of dosing until days 3 and 7 (and on day 14) of dosing, the attending physician evaluated clinical efficacy of the therapy in individual cases using a four-category scale: cured (absence of fever >37.5℃, chill, chest pain, cough and difficulty breathing), improved (chill and fever absent but symptoms such as chest pain, cough and sputum persist), ineffective (all other cases) and unclassified (dropout). Chest X-ray findings were evaluated based on the time

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Table 1. Demographic and Clinical Characteristics of Patients

Characteristic	SBT/ABPC (n=35)	IPM/CS (n=32)	P value
Gender (Male/Female)	22/13	26/6	0.1624 a)
Mean (±SD) age (years)	78.5 ± 6.5	78.3 ± 6.5	0.8833 b)
Age range (years)	69–91	65–91	
Mean (±SD) body weight (kg)	50.26 ± 10.71	52.71 ± 8.95	0.3722 b)
JRS severity classification			0.8827 a)
Moderate	28	27	
Severe	7	5	
PSI severity classification			0.4521 a)
II	5	3	
III	11	8	
IV	18	17	
V	1	4	
Underlying disease (Yes/No)	31/4	29 /3	0.9003 a)
Complication (Yes/No)	6/29	5/27	0.8708 a)
Past illness (Yes/No)	27/8	29/3	0.2469 a)
Allergy (Yes/No)	4/31	2/30	0.7541 a)
Pneumococcal vaccine (Yes/No)	0/35	1/31	0.9640 a)

a) Fisher's exact test or r × 2 X^2-test

b) Student's t-test

JRS, Japanese Respiratory Society (10)

Table 2. Causative Bacteria and Bacteriological Efficacy of SBT/ABPC and IPM/CS

Causative bacteria	SBT/ABPC (n=35)		IPM/CS (n=32)	
	No. of isolates	Eradication (%)	No. of isolates	Eradication (%)
Streptococcus pneumoniae	11	11/11 (100)	8	8/8 (100)
MSSA	1	1/1 (100)	5	5/5 (100)
MRSA	0	—	2	1/2 (50)
Pseudomonas aeruginosa	3	0/3 (0)	4	2/4 (50)
Haemophilus influenzae	4	4/4 (100)	2	2/2 (100)
Moraxella catarrhalis	3	3/3 (100)	0	—
Klebsiella pneumoniae	0	—	1	0/1 (0)
α-Streptococcus	2	2/2 (100)	1	1/1 (100)
Enterobacter aerogenes	0	—	1	0/1 (0)
Haemophilus parainfluenzae	0	—	1	1/1 (100)
Streptococcus sanguis	1	1/1 (100)	0	—
Total	25	22/25 (84)	25	20/25 (80)

SBT/ABPC, sulbactam/ampicillin; IPM/CS, imipenem/cilastatin; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

course of X-ray findings after the start of dosing using a four-category scale (shadow disappearance, improvement, no change and deterioration). Bacteriological efficacy was evaluated based on the fate of bacteria after the start of dosing using a five-category scale: disappeared, reduced, replaced by other bacteria, unchanged and unclassified.

Adverse events (AEs)

For each accompanying symptom or laboratory abnormality appearing during the dosing period, the nature, severity, date of onset, treatment provided, and outcome were recorded. Causal relationships to the study drugs were rated as related, possibly related or not related.

Statistical analysis

Comparisons between treatment groups were carried out using a chi-square test. Additionally, 95% confidence intervals (CI) were calculated for the cure rate and pathogen eradication rate. The incidences of AEs were compared between treatment groups using a chi-square test. For clinical laboratory values and vital signs, the Student's paired t test was used to evaluate changes within treatment group over time. Mean changes from baseline were compared between treatment groups using a one-way analysis of variance (ANOVA). P values of <0.05 were considered statistically significant.

Results

Subjects

In a 1-year period beginning November 2002, 71 patients were enrolled in this study. All patients were included in the safety evaluation. Four cases were excluded by the Case Review Committee from efficacy evaluation, and thus a total of 67 patients were included in the efficacy evaluation. Of these, 35 received SBT/ABPC therapy and the remaining 32 received IPM/CS therapy. The four cases excluded from efficacy evaluation included one patient with interstitial pneumonia from the SBT/ABPC therapy group and 3 patients from the IPM/CS therapy group (one with acute exacerbation of chronic obstructive pulmonary disease, one with cardiac failure, and one with a disease not covered by this study). There was no significant difference between the SBT/ABPC therapy group and the IPM/CS therapy group with regard to background variables such as sex, age, JRS severity rating, PSI severity rating, underlying disease, complications, disease history, allergy or history of pneumococcal vaccination (Table 1). The most frequent underlying disease or complication was pulmonary emphysema (including chronic obstructive pulmonary disease), which was seen in 19 cases. Other frequent underlying diseases and complications were diabetes mellitus (11 cases), malignant diseases (malignant tumors, leukemia, etc.; 10 cases), pulmonary tuberculosis (including old tuberculosis; 7 cases), cardiac dis-

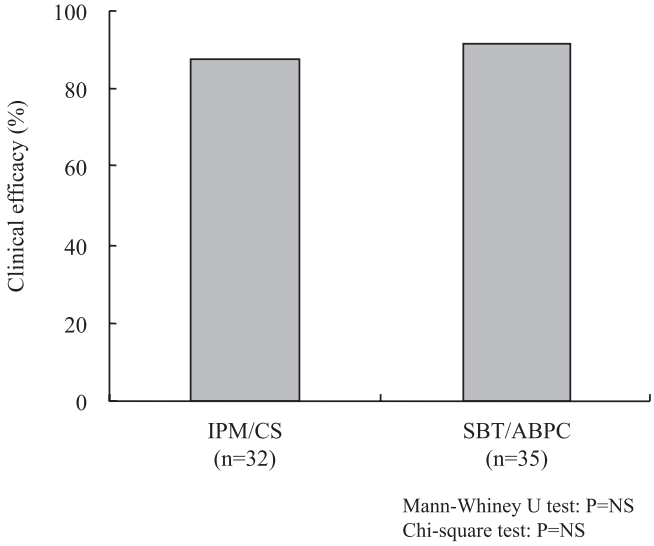

Figure 1. Overall clinical outcome after sulbactam/ampicillin (SBT/ABPC) or imipenem/cilastatin (IPM/CS) treatment. Efficacy rate (improvement + cure) was 91.4% in the SBT/ABPC-treated group and 87.5% in the IPM/CS-treated group.

eases (7 cases), cerebrovascular diseases (6 cases), dementia (3 cases), and others (43 cases). Some patients had two or more underlying diseases or complications. Six patients were free of underlying disease and complications. With regard to distribution of each underlying disease or complication, there were no significant differences between the SBT/ABPC and IPM/CS groups. The most frequent pathogen was *S. pneumoniae* (19 cases), followed by *Pseudomonas aeruginosa* (7 cases), methicillin-susceptible *Staphylococcus aureus* (MSSA; 6 cases) and *H. influenzae* (6 cases), as shown in Table 2.

Overall clinical efficacy

The efficacy rate was 91.4% (32/35) in the SBT/ABPC group and 87.5% (28/32) in the IPM/CS group, and did not differ significantly between the two groups (Fig. 1). When analyzed based on JRS severity rating, the efficacy rate in patients with moderate pneumonia did not differ significantly between the SBT/ABPC group (25/28; 89.3%) and IPM/CS group (23/27; 85.2%). Efficacy in patients with severe pneumonia also showed no significant differences between the SBT/ABPC group (7/7; 100%) and IPM/CS group (5/5; 100%). When efficacy was analyzed based on IDSA severity rating, the efficacy for class II, III, and IV cases did not differ significantly between the two groups.

Bacteriological efficacy

The eradication rate of *S. pneumoniae*, MSSA, and *H. influenzae* (three frequently isolated strains) was 100% in both the SBT/ABPC and IPM/CS groups (Table 2). The overall eradication rate for the pathogenic microorganism was 84% (22/25) in the SBT/ABPC group and 80% (20/25) in the IPM/CS group.

Bacteriological tests

Of the total 71 patients enrolled, bacteriological tests were undertaken as follows: *Mycoplasma* antibody test (IHA and/or CF tests) in 65 patients (91.5%), *Chlamydia* IgG antibody test in 56 patients (78.9%), *Chlamydia* IgA antibody test in 54 patients (76.0%), urinary *Legionella* antigen test in 46 patients (64.8%), and urinary pneumococcus antigen test in 47 patients (66.2%). The positive rate was 1 patient (1.5%) for *Mycoplasma* antibody, 1 patient (1.9%) for *Chlamydia* antibody, 2 patients (4.3%, including 1 quasi-positive patient) for urinary *Legionella* antigen, and 11 patients (23.4%, including 1 quasi-positive patient) for urinary pneumococcus antigen. A 4-fold rise in antibody titer between paired serum samples was considered positive for *Mycoplasma* and *Chlamydia*.

Adverse reactions

In the SBT/ABPC group, adverse reactions (adverse events whose causal relationship to the drug was not ruled out) were seen in 7 (19.4%) of 36 patients (8 reactions in total; 22.2%), with the major adverse reactions being hepatic dysfunction and eosinophilia. In the IPM/CS group, adverse reactions were seen in 11 (31.4%) of 35 patients (17 reactions in total; 48.9%), with the major adverse reactions being hepatic dysfunction, eosinophilia, and elevated serum potassium. All reactions were mild or moderate and transient.

Discussion

Pneumonia in elderly individuals involves multiple exacerbating factors (susceptibility to further infection, occult misswallowing, etc.). Furthermore, the symptoms of pneumonia in elderly patients are often masked by underlying disease. For these reasons, the detection of pneumonia in elderly patients tends to be delayed, often leading to severe courses of pneumonia (2, 11, 12). Hence, pneumonia is a life-threatening disease in elderly individuals. Despite development of various antimicrobial agents, pneumonia continues to have a high death rate among elderly patients. Appropriate diagnosis and treatment are therefore essential for pneumonia in elderly individuals. The JRS guidelines (10) recommend the combined use of a beta-lactamase inhibitor and penicillin for mild-to-moderate CAP with an unidentified pathogen. In Japan, Okimoto et al (13) reported the effectiveness of SBT/ABPC therapy for CAP among elderly individuals, while Wood et al (14) conducted a study comparing SBT/ABPC therapy with IPM/CS therapy in cases of ventilator-assisted pneumonia caused by *Acinetobacter*, and found that there was no significant inter-group differences in terms of efficacy, death rate, duration of mechanical ventilation, duration of ICU stay or duration of hospital stay.

The present study demonstrates that SBT/ABPC therapy has comparable clinical efficacy to IPM/CS therapy in elderly patients with moderate-to-severe CAP. The severity of

pneumonia was classified based on the criteria within the JRS and IDSA guidelines, and clinical efficacy, bacteriological efficacy, and improvement in chest X-ray findings were analyzed by severity and compared between the two groups. In this analysis, each parameter was comparable between the two groups. Furthermore, the efficacy for SBT/ABPC therapy was 100% in cases rated severe by the JRS and IDSA guidelines. These results indicate that SBT/ABPC therapy can be expected to exert excellent efficacy, even in cases of severe CAP. With regard to safety, no serious adverse reactions were observed in any patients in the SBT/ABPC group or in the IPM/CS group, thus indicating that SBT/ABPC therapy is highly tolerable in elderly patients.

It should be noted that the criteria for severity are slightly different between PSI and JRS guidelines. Severity in the latter guideline published in 2000 was based on evaluation criteria for efficacy of antimicrobial agents developed by the Japanese Society of Chemotherapy. Thus it provides sufficient evidence to evaluate efficacy of antimicrobial agents. However, subsequent analysis of data from many subjects in a prospective multicenter study revealed lack of correlation between individual indicators used for classification and mortality rate of pneumonia patients. Following this finding, the guidelines were modified in October 2005 (15). PSI, on the other hand, adopted criteria developed by PORT (9) involving quantitative analysis of short-term death rate of patients with community-acquired pneumonia.

Although carbapenems exert potent antimicrobial activity against a broad range of bacteria, including Gram-positive and Gram-negative microorganisms, it has recently been reported that metallo-β-lactamase-producing bacteria, which can degrade carbapenems, have become more widespread (4, 16) and that strains of *P. aeruginosa* resistant to carbapenems have been isolated (17). Thus, close attention is now being paid to the spread of drug-resistant bacterial strains caused by the careless and/or excessive use of broad-spectrum antimicrobial agents. Governmental intervention and controls against the use of broad-spectrum drugs and anti-MRSA drugs have also been instituted in recent years. The results of the present study indicate that under certain conditions (i.e., in elderly patients with CAP), SBT/ABPC can be used in place of carbapenems.

Briefly, the present comparison in elderly patients with moderate-to-severe pneumonia revealed that the efficacy of SBT/ABPC is comparable to that of IPM/CS and that SBT/ABPC is highly tolerable. SBT/ABPC is thus considered to be useful as a first-choice drug in the treatment of CAP in elderly individuals and is highly effective, even in severe cases.

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