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Effects of Ampicillin/Sulbactam Dose and Dosing Frequency in Elderly Patients with Nursing- and Healthcare-Associated Pneumonia (Nhcap)

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Abstract

Japan has the most rapidly aging population in the world. This study aimed to examine the differences in the efficacy of ampicillin/sulbactam (ABPC/SBT) alone under different daily doses and daily dosing frequencies in elderly patients receiving healthcare at home and in elderly nursing home residents with pneumonia onset requiring hospitalization for treatment. By applying the Clinical Practice Guidelines for Nursing- and Healthcare-associated Pneumonia (NHCAP) of the Japanese Respiratory Society (JRS), we retrospectively analyzed clinical data, dose, dosing period, and the efficacy of antimicrobial agents, as well as outcomes of patients with NHCAP or community acquired pneumonia (CAP) who had been hospitalized at our department during the 3-year period of 2009 through 2011. The mean age of NHCAP patients (n=587) was 85 ± 9 years, significantly higher than the 77 ± 16 years of CAP patients (n=319). The serum albumin level in NHCAP patients was significantly lower than that in CAP patients. Among NHCAP patients, 82.5% received ABPC/SBT alone as the first-line therapy, with 50.7% receiving 1.5 g three times daily and 22.8% receiving 3 g twice daily. The mortality rate during hospitalization in the 1.5-g three-times-daily group was 12.4%, resulting in a significantly decrease as compared with the 3-g twice-daily group of 20.9% ($p<0.01$). In our study, which targeted the elderly in Japan, it was revealed that ABPC/SBT is an appropriate first choice of antibiotics in treating NHCAP and that administering 1.5 g three times daily is a suitable way of administration.

Keywords: Aspiration pneumonia; Mortality rate; Anaerobic bacteria; PK/PD

Introduction

According to World Health Statistics 2014, Japan has the longest life expectancy in the world, with a mean of 84 years for men and women combined [1]. Due to the rapid increase in the elderly population, pneumonia became the third leading cause of death following malignancy and heart disease in 2011, and further growth is anticipated. Therefore, for the increasing number of people receiving <cared> healthcare at home or as nursing home residents, Japanese Respiratory Society (JRS) issued the Clinical Practice Guidelines for Nursing- and Healthcare-associated Pneumonia (NHCAP) [2]. The guideline described the diagnosis, the conditions under which hospitalization can be applied and treatment.

Aspiration pneumonia is the main cause for the hospitalization of the elderly patients with pneumonia [3-7]. The frequent pathogen bacteria of aspiration pneumonia include intraoral anaerobes [8-10], which is covered by empiric antibiotic therapy. The US guidelines of heatlth care acquired pneumonia (HCAP) [11] and NHCAP [2] state that patients with aspiration pneumonia should receive β-lactams such as ampicillin/sulbactam (ABPC/SBT) when they must be admitted to hospitals and have no risk of multidrug resistant pathogens [2,11]. In NHCAP, however, the dose and frequency of ABPC/SBT have not been examined.

Based on the theory of pharmacokinetics (PK) and pharmacodynamics (PD), the percentage of time when the blood concentration of an microbial agent during a 24-hour period is above the minimum inhibitor concentration (MIC) of pathogenic bacteria (% time above MIC [%T>MIC]) is the indicator for β-lactam antimicrobial agents such as ABPC/SBT; efficacy increases along with dosing frequency [12,13].

To our knowledge, no study has been conducted on the frequency of APBC/STB administration per day, its dose per administration and its treatment effects on patients with NHCAP. In this study, we retrospectively examined the effects of ABPC/SBT doses and dosing frequencies on the outcomes of NHCAP during a 3-year period.

Subjects and Methods

Patients with pneumonia

Ours is an acute-phase hospital with 300 beds in a community. We extracted patients 16 years of age or older hospitalized at our facility during the period from April 2009 through March 2012 who had pneumonia (including the bacterial, aspiration, and Streptococcus pneumoniae pneumonia) based on the name of the primary disease and retrospectively analyzed those who showed infiltration on chest images (chest X ray, chest computed tomography). The following data were collected from medical charts: age, sex, residence immediately before admission (e.g., home, hospital, nursing home, group home),

comorbidity, past history, lifestyle history, blood test results, bacteriological test, the antimicrobial agent used in the initial treatment, outcome at the time of admission, or death (death within 30 days or termination of hospitalization due to death). Patients were classified into two groups, those with NHCAP [2] and those with CAP [14], according to the definitions of the JRS. A patient with NHCAP is defined as 1) an extended care unit resident or a nursing home resident; 2) a patient who was discharged from a hospital within 90 days; 3) an elderly patient or one with physical disabilities requiring nursing care; or 4) a patient who continues to receive endovascular treatment (treatments involving blood dialysis, antimicrobial agents, chemotherapy, or immunosuppressive agents) on an outpatient basis. "Nursing care" is defined as performance status (PS) 3 or higher (a patient who can perform limited self-care only and spends 50% or more of daytime hours in a bed or on a chair). Patients with hospital acquired pneumonia (HAP) or interstitial pneumonia which had occurred within 48 hours after hospitalization were excluded. For CAP, pneumonias caused by Mycoplasma pneumoniae, Legionella and atypical pneumonias, such as that due to Chlamydophila, were excluded. The antimicrobial agents were selected by primary physicians. At our hospital, antimicrobial agents are administered at 10:00 and 20:00, in a twice-daily regimen, and at 06:00, 14:00, and 22:00 in a three-times-daily regimen. We ensure that the dosing intervals on the day of admission are not longer than 12 hours and 8 hours, respectively. Death was evaluated as being at the time of discharge or during the 30-day period after admission.

Analysis of NHCAP

The data with NHCAP were extracted. The antimicrobial agents are administered at daily dose, dosing frequency, and dosing period of the antimicrobial agent used in the initial treatment and daily dose, dosing frequency, and dosing period of antimicrobial agents after a switch in regimen. Patients who improved without changing the dose or dosing frequency of the first antimicrobial drug were regarded as "treatment successes," and those in whom the first antimicrobial agent was switched to a different drug or who died were taken to be "treatment failures." We calculated the dosing periods of the first antimicrobial agent and those after switching agents (more than one) for both groups of patients.

Statistical analysis

Intergroup age comparisons were conducted using Student's t-test. Intergroup comparisons of the number of patients were conducted employing the chi-square test, and Fisher's extract test was used for test numbers below 10. Cox Proportional Hazard Model Analysis of the status data was conducted by using the number of days of hospitalization and deaths as indexesage, sex, oxygenWBC, CRP, Alb, BUN, Cr, survivaldeath. A P value <0.05 was considered to indicate a statistically significant difference.

Results

Patients

During the 3-year period from 2009 through 2011, 587 patients with NHCAP and 319 with CAP were admitted to our hospital. The mean age of NHCAP patients was 85.0 ± 8.59 years, significantly higher than the 77.0 ± 15.5 years of the CAP patients. As to concurrent underlying diseases, dementia and sequelae of cerebrovascular disease were significantly more common in NHCAP than in CAP patients (Table 1). The serum albumin levels were 3.16 ± 1.42 mg/dL in NHCAP patients and 3.44 ± 0.54 mg/dL in CAP patients, significantly lower in those with NHCAP. The mortality rates while hospitalized during the 3-year period were 16.9% in NHCAP patients and 5.3% in CAP patients, being lower in those with NHCAP. Sputum examinations on admission revealed the frequencies of isolating *Staphylococcus aureus*, MRSA, *Streptococcus agalactiae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* to be significantly higher in NHCAP than in CAP cases. The frequency of *S. pneumoniae* isolation was, however, significantly higher in CAP than in NHCAP cases (Table 2).

	NHCAP	CAP	p-value
Number of patients (n)	587	319	
Men	297 (51%)	211 (66%)	0.0001
age (mean ± SD)	85.0 ± 8.59**	77.0 ± 15.5	<0.0001
(range)	17 - 99	46 - 104	
Comorbidity			
hypertension	222	103	0.0973
dementia	219*	18	<0.0001
sequela stroke	174*	19	<0.0001
Diabetes mellitus	88	43	0.5365
COPD	48	49	0.0008
First antimicrobial agent			
ABPC/SBT	48081.8%	257 (80.6%)	0.6559
Ceftriaxone	45 (7.7%)	32 (10.0%)	0.2227
Results of laboratory examination			
WBC mL	10,900 ± 7,358	11,460 ± 5,110	0.0888
CRP mg/dL	9.03 ± 7.28*	15.0 ± 57.3	0.0337
Albumin g/dL	3.16 ± 1.42**	3.44 ± 0.54	0.0001
BUN mg/dL	26.7 ± 23.9	24.0 ± 15.5	0.0682
Cre mg/dL	0.98 ± 1.50	1.14 ± 1.12	0.0724
Number of death%	9916.9%	175.3%	<0.0001
Date are mean±SD. *p<0.05, **p<0.001, significant compared to community acquired pneumonia (CAP).			

Table 1: Patients background.

Dosage regimen of ABPC/SBT as the first-line therapy in NHCAP patients and comparison of clinical outcomes (Table 3). The mortality rate during hospitalization in the ABPC/SBT 1.5-g three-times-daily group was significantly lower than those in the 1.5-g twice-daily (P<0.001) and the 3-g twice-daily (P<0.01) groups. The mortality rate within 30 days was significantly higher in the ABPC/SBT 1.5-g twice-daily group than in either the 1.5-g three-times-daily (P<0.01) or the 3-g twice-daily group (P<0.05) group. Age was higher and the blood urea nitrogen (BUN) and creatinine (Cre) levels were significantly elevated in the ABPC/SBT 1.5-g twice-daily group as compared with the 3-g twice-daily-group and the 1.5-g three-times-daily group.

The number of patients successfully treated with ABPC/SBT alone was highest in the 1.5-g three-times-daily group, but there was no significant difference associated with dosing periods. The results of COX proportional hazards model are below: oxygen use (p=0.0167, Hazard ratio 2.4929 [95%CI:1.1797-2.4929]), WBC (p=0.0272, Hazard ratio 0.9940 [95%CI: 0.9887-0.9940]), Alb (p=0.0000, Hazard ratio 0.3501, [95%CI: 0.2136-0.5737], sex (p=0.1817, Hazard ratio 1.48084, [95%CI: 0.8520-0.2.3282], 3-g twice-daily-group and the 1.5-g three-times-daily group (p=0.0986, Hazard ratio 1.5235, [95%CI: 0.9245-2.5108].

	NHCAP (n=375)	CAP (n=207)
Gram positive		
α-Streptococcus	267	155
Corynebacterium species	86	62
Sta.aureus (MRSA)	82	7
Sta.aureus (MSSA)	80	26
Streptococcus spp.	70	41
CN Staphylococcus	64	26
Streptococcus agalactiae	46	1
Streptococcus pneumoniae	28	37
Gram positive		
Neisseria spp.	160	128
Klebsiella pneumoniae	47	10
Pseudomonas aeruginosa	42	4
Escherichia coli	33	11
Haemophilus sp	24	11
Fungus		
Candida albicans	148	72
Candida glabrata	83	44

Table 2: The results of sputum cultures in patients treated with ampicillin/sulbactam ABPC/SBT.

Discussion

Based on the PK/PD theory, the clinical efficacy of β-lactam antimicrobial agents reportedly increases along with the dosing frequency [12,13]. In this study, higher dosing frequency of antimicrobial agents were associated with lower mortality rates, clinically supporting the PK/PD theory as it pertains to the treatment of NHCAP. NHCAP patients were older and had a lower serum albumin level than CAP patients, which would presumably be associated with the results obtained. In general, the serum albumin level is a representative marker of nutritional status; nutritional status deteriorates with swallowing disturbance and dementia in the elderly, resulting in a low albumin level. Moreover, albumin correlates with the mortality rate of patients with pneumonia [15-18]. In this study, serum albumin concentration was associated with survivals in patients with NHCAP in COX models.

In general, drugs such as ABPC/SBT excreted by the kidney have an extended blood T1/2, resulting in an increase in the area under the curve and a reduction in the urinary excretion rate. In the determination of antimicrobial agent dosing, the doses need to be adjusted based on the renal functions of patients [12]. Among the three groups initially treated with ABPC/SBT in this study, the 1.5-g twice-daily group showed the poorest outcomes. It had the most elderly patients with the highest BUN and serum Cre levels among the three groups, and it is likely that the dose was set too low. It would be difficult to improve the outcomes of patients in this group.

	1.5 g × 2	3 g × 2	1.5 g × 3
Number of patients	48	134	298
Average age	89.0 ± 8.7$^{\alpha 2, \beta 2}$	85.0 ± 7.8	85.0 ± 8.6
menwomen	20:28	74 : 60	138 : 160
Oxygen use on admission	33 (68.8%)	87 (64.9%)	202 (67.8%)
Results of laboratory examination			
Albumin g/dL	3.17 ± 0.54	3.16 ± 0.51	3.20 ± 1.92
WBC /mL	10570 ± 4755	11060 ± 5780	11080 ± 7900
CRP mg/dL	7.37 ± 6.42 $^{\alpha 1}$	8.50 ± 7.08	9.13 ± 7.20
BUN mg/dL	41.3 ± 37.3 $^{\alpha 2, \beta 2}$	23.0 ± 19.6	25.9 ± 23.6
Cre mg/dL	1.92 ± 3.91 $^{\alpha 1, \beta 1}$	0.79 ± 0.53	0.91 ± 1.22
First ABPC/SBT			
treatment successes	27 (56.3%) $^{\beta 1}$	8966.4%	21371.5%
treatment days	9.3 ± 4.6	9.0 ± 4.2	9.3 ± 4.4
total death%	16 (33.3%)$^{\beta 3}$	2820.9%$^{\beta 2}$	3712.4%
30-day death%	10 (20.8%)$^{\alpha 1, \beta 2}$	139.7%	217.0%
$^{\alpha 1}$p<0.05, $^{\alpha 2}$p<0.01, $^{\alpha 3}$p<0.001 significant compared to 3 g × 2 group $^{\beta 1}$p<0.05, $^{\beta 2}$p<0.01, $^{\beta 3}$p<0.001, significant compared to 1.5 g × 3 group			

Table 3: The characteristics and prognosis of ampicillin/sulbactam dose and dosing frequency in patients with nursing- and healthcare-associated pneumonia (NHCAP).

Ishida et al. reported 451 NHCAP patients with a mean age of 82 years; the mortality rate during hospitalization was 13.1%; and the percentage of patients given penicillin antimicrobial agents containing a β-lactam inhibitor was 74% in a community hospital in Japan [19]. Oshitani et al. reported 477 NHCAP patients with a mean age of 84 years; the mortality rate during hospitalization was 24.7%; and the percentage of patients initially treated with ABPC/SBT was 64.6% [20]. Similar to the present study, the percentages of patients initially receiving ABPC/SBT were high, and the mortality rates during hospitalization were comparable. Shindo et al. reported 141 patients with health care-associated pneumonia who had a mean age of 81.3 years and the mortality rate during hospitalization was 21.3% at a university hospital, though the percentage of patients receiving β-lactam antimicrobial agents alone was low at just 39.7%, with many patients being given two or more antimicrobial agents concurrently [21]. Medical institutions providing advanced medical care such as

university hospitals have more patients with severe symptoms and patients treated previously than community hospitals; therefore, broad-spectrum antimicrobial agents are selected as the initial treatment.

On the recent reports, mortality in HCAP does not appear to be due to a higher frequency of multidrug resistant pathogens, such as methicillin resistant Staphylococcus aureus or Pseudomonas aeruginosa [3,15,22]. The risk factors for bacteria becoming multidrug resistant in HCAP include prior hospitalization, immunosuppression, previous antibiotic use, use of gastric acid-suppressive agents, and tube feeding [22]. The Guidelines for NHCAP of the JRS recommend that antimicrobial agents be selected for patients requiring hospitalization for treatment, in consideration of the risk of the emergence of resistant bacteria. When there is no risk of such emergence, ABPC/SBT, CTRX, panipenem/betamipron (PAPM/BP), and levofloxacin (LVFX) infusion are recommended [2]. In order to treat aspiration pneumonia, ABPC/SBT is an appropriate choice of bacteriocin for oral anaerobic species (e.g., Prevotella, Micromonas), aerobes such as Streptococcus anginosus Group and *S. pneumoniae*. On the other hand, the effects of ABPC/SBT on enterobacteriaceae such as *Klebsiella pneumoniae* are insufficent. Tsukada et al. studied inpatients with *K. pneumoniae* pneumonia, reporting that that the survival rate within 30 days was lower with ABPC/SBT (58.3%) than with PIPC/TAZ (91.7%) [23]. Since *K. pneumoniae* shows resistance to ABPC/SBT, a third or fourth generation cephem, PIPC/TAZ, or carbapenem antimicrobial agents need to be selected. In cases where the result of the phlegm examination that has been submitted on the day of hospitalization proves to be multidrug resistant pathogens a few days later, it is recommended that the treatment effects and sensitivity results of the initially-administered antibiotics should be evaluated and that their administration should be reconsidered. In this study, ABPC/SBT was used as the first-line therapy for many inpatients with NHCAP at a community hospital. It is appropriate for first choice with the APBC/SBT can be widely recommended for the treatment of NHCAP. And increased dose frequency is well efficacy for patients with NHCAP.

References

1. World Health Organization (2015) World Health Statistics 2014.
2. Kohno S, Imamura Y, Shindo Y, Seki M, Ishida T, et al. (2013) Clinical Practice Guidelines for Nursing- and Healthcare-associated Pneumonia (NHCAP). Respir Investiq 51: 103-126.
3. Chalmers JD, Rother C, Salih W, Ewig S (2014) Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. Clin Infect Dis 58: 330-339.
4. Carratala J, Mykietiuk A, Fernández-Sabé N, Suárez C, Dorca J, et al. (2007) Health care-associated pneumonia requiring hospital admission: epidemiology antibiotic therapy, and clinical outcomes. Arc Intern Med 167: 1393-1399.
5. Ewig S, Welte T, Chastre J, Torres A (2010) Rethinking the concepts of community-acquired and health-care-associated pneumonia. Lancet Infect Dis 10: 279-287.
6. Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, et al. (2008) High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. J Am Geriatr Soc 56: 577-579.
7. Teramoto S (2014) Clinical Significance of Aspiration Pneumonia and Diffuse Aspiration Bronchiolitis in the Elderly. J Gerontol Geriat Res 3: 142.
8. Bartlett JG, Gorbach SL, Finegold SM (1974) The bacteriology of aspiration pneumonia. Am J Med: 202-207.
9. Lode H (1988) Microbiological and clinical aspects of aspiration pneumonia. J Antimicrob Chemother 21 Suppl C: 83-90.
10. El-Solh AA, Pietrantoni C, Bhat A, Aquilina AT, Okada M, et al. (2003) Microbiology of severe aspiration pneumonia in institutionalized elderly. Am J Respir Crit Care Med 167: 1650-1654.
11. American Thoracic Society, Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Rrespir Crit Care Med 171: 388-416.
12. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26: 1-10.
13. Dagan R, Klugman KP, Craig WA, Baquero F (2001) Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy. J Antimicrob Chemother 47: 129-140.
14. Kohno S, Seki M, Watanabe A, CAP Study Group (2011) Evaluation of an assessment system for the JRS 2005: A-DROP for the management of CAP in adults. Intern Med 50: 1183-1191.
15. Shindo Y, Ito R, Kobayashi M, Ando M, Ichikawa M, et al. (2015) Risk factors for 30-day mortality in patients with pneumonia who receive appropriate initial antibiotics: an observational cohort study. Lancet Infect Dis 15: 1055-1065.
16. Chalmers JD, Taylor JK, Singanayagam A, Fleming GB, Akram AR, et al. (2011) Epidemiology, antibiotic therapy, and clinical outcomes in health care-associated pneumonia: a UK cohort study. Clin Infect Dis 53: 107-113.
17. Riquelme R, Torres A, El-Ebiary M, de la Bellacasa JP, Estruch R, et al. (1996) Community-acquired pneumonia in the elderly:a multivariate analysis of risk and prognostic factors. Am J Respir Crit Care Med 154: 1450-1455.
18. Hedlund J, Hansson LO, Ortqvist A (1995) Short- and long-term prognosis for middle-aged and elderly patients hospitalized with community-acquired pneumonia: impact of nutritional and inflammatory factors. Scand J Infect Dis 27: 32-37.
19. Ishida T, Tachibana H, Ito A, Yoshioka H, Arita M, et al. (2012) Clinical characteristics of nursing and healthcare-associated pneumonia: a Japanese variant of healthcare-associated pneumonia. Intern Med 51: 2537-2544.
20. Oshitani Y, Nagai H, Matsui H, Aoshima M (2013) Reevaluation of the Japanese guideline for healthcare-assocaited pneumonia in a medium-sized community hospital in Japan. J Infect Chemother 19: 579-587.
21. Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, et al. (2009) Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. Chest 135: 633-640.
22. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, et al. (2013) Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med 188: 985-995.
23. Tsukada H, Sakai K, Cho H, Kimura Y, Tetsuka T, et al. (2012) Retrospective investigation of the clinical effects of tazobactam/piperacillin and sulbactam/ampicillin on aspiration pneumonia caused by Klebsiella pneumoniae. J Infect Chemother 18: 715-721.