Nephrotoxicity Induced by Piperacillin–Tazobactam in Late Elderly Japanese Patients with Nursing and Healthcare Associated Pneumonia

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This study aimed to clarify the efficacy, safety, and pharmacokinetics of piperacillin–tazobactam (PIPC–TAZ) in late elderly Japanese patients. This is the first antimicrobial pilot study in late elderly patients with nursing and healthcare associated pneumonia. After PIPC–TAZ administration, PIPC concentrations in plasma were measured chromatographically and the pharmacokinetic parameters were estimated. Efficacy, safety, and bacteriological evaluations were also carried out. The mean age was 85.0 years old and most of the patients were late elderly. Chest X-rays, body temperature, white blood cell count, and C reactive protein all improved significantly, and a high efficacy ratio of 90.9% was observed. Serious nephrotoxicity was observed in 4 cases (18.2%) after administration of PIPC–TAZ. Creatinine clearance (mean±S.D.) measured before PIPC–TAZ therapy was significantly lower in the nephrotoxicity group (32.5±4.4 mL/min) than in the non-nephrotoxicity group (46.1±16.7 mL/min), although the ages were not different between the 2 groups. In the pharmacokinetic parameters for PIPC, total clearance was slightly lower in the nephrotoxicity group than in the non-nephrotoxicity group. However, no significant difference was observed in plasma PIPC levels between the 2 groups. In patients with renal impairment, especially with a creatinine clearance of <40 mL/min, renal impairment was found to be an influencing factor for severe nephrotoxicity following PIPC–TAZ administration. In conclusion, the results suggest that physicians should pay close attention in order to avoid possible toxicity, and that deliberate administration planning and careful follow-up are required in late elderly patients with comprised organ dysfunction.

Key words piperacillin–tazobactam; Japanese late elderly patient; nephrotoxicity; nursing and healthcare associated pneumonia

Recently, changes in medical care environments have led to increasing numbers of community-acquired pneumonia (CAP) patients who are infected with multidrug-resistant pathogens and have a poor prognosis when coming into contact with hospitals. In 2005, American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) proposed a new category of pneumonia: healthcare-associated pneumonia (HCAP).[1] Guidelines for the management of nursing- and healthcare-associated pneumonia (NHCAP) were published by the Japanese Respiratory Society in August 2011.[2] NHCAP was defined by considering the characteristics of the Japanese healthcare system. Namely, NHCAP is a concept focusing on pneumonia onset in patients having backgrounds such as: (1) admitted to a long term care facility or a nursing home, (2) discharged from the hospital within 90 d, (3) elderly or paralyzed patients requiring nursing care, (4) receiving on-going endovascular repair treatment as an outpatient, with many cases falling under above definition being elderly patients. In Japan, most deaths caused by pneumonia are among elderly patients[3] so that the appropriate selection and use of antimicrobials against pneumonia is very important, particularly in late elderly patients. Piperacillin–tazobactam (PIPC–TAZ) is a beta-lactamase inhibitor combined penicillin with a maximum dose thereof set equivalent to that of overseas, and is mainly used for treatment against serious intractable infectious diseases. In the NHCAP guideline, PIPC–TAZ is rated as a first choice drug for in-hospital care patients with a risk of resistant bacteria in the same manner as fourth generation cephems, carbapenems and new quinolones.[2]

Although few epidemiological studies of this newly designated NHCAP in Japan have been reported so far, we previously reported that the frequency of nephrotoxicity caused by PIPC–TAZ therapy was significant higher than that by biapenem in patients with NHCAP.[4] However, there is no reports regarding to risk factors for nephrotoxicity induced by PIPC–TAZ therapy, so it is necessary to accumulate evidence on late elderly patients with NHCAP. In previous pharmacokinetic studies, it has been reported that the total body clearance, area under the drug concentration–time curve, and terminal elimination rate of PIPC–TAZ are correlated to renal function,[5] and moreover, simulation results of the optimal administration of PIPC–TAZ to renal impairment patients based on population pharmacokinetic analysis have been reported in Japan.[6,7]

The aim of this study is to clarify the efficacy and safety of PIPC–TAZ in late elderly patients with NHCAP. Additionally, we conducted a prospective pharmacokinetic study to ascertain risk factors for nephrotoxicity induced by PIPC–TAZ therapy in patients with NHCAP.

The authors declare no conflict of interest.

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PATIENTS AND METHODS

Subjects and Study Protocol This study was approved by "Ethics Committee of Shimane University Faculty of Medicine." The patients aged 65 years old or older, who were diagnosed with NHCAP in Shimane University Hospital, and satisfying the three items of: (1) body temperature of 37°C or more, (2) C-reactive protein (CRP) value of 1.0 mg/dL or more, and (3) clear pneumonia shadow observed upon chest X-ray or computed tomographic image within 2 d prior to commencing treatment. Furthermore, cases falling under any of the followings were excluded: (1) case with serious heart/liver/renal function failure, (2) case in which atypical pneumonia is strongly suspected, (3) case requiring concomitant use of antibacterial drugs excluding macrolide antibiotics, (4) case with a history of allergies to beta lactam antibiotics, (5) case determined as being unsuitable as a subject of this study by the doctor in charge. The severity of pneumonia in each patient was evaluated in accordance with the classification of the disease severity of pneumonia (A-DROP).[8] The cases were divided into: (1) mild, (2) moderate, (3) severe, and (4) very severe.

PIPC–TAZ (4.0 g/0.5 g) was dissolved in 100 mL saline and intravenous drip infusion was carried out for an hour each session three times a day. In patients with the estimated glomerular filtration rate (eGFR) of <50 mL/min, the dose was reduced to 2.25 g of PIPC–TAZ (2.0 g/0.25 g) each session three times a day in accordance with the Sanford guide to antimicrobial therapy.[9]

Venous blood samples (3 mL) were collected in heparinized tubes before (0) and 1, 1.5, 2, and 4 h after the beginning of the intravenous administration. Plasma was immediately separated from the blood samples by centrifugation at 3000 rotations/m for 10 min at 4°C, and store at −30°C until analysis. The plasma total concentration of PIPC was measured by using HPLC with UV detection in accordance with method reported previously.[10]

Evaluation of the Clinical Effect and Toxicity Clinical effects of PIPC–TAZ therapy was evaluated upon dividing the cases into: (1) effective: pneumonia symptoms, CRP, white blood cell (WBC) count, chest X-ray were all improved from the state prior to the therapy, (2) not effective: no improvement was observed in any of above items and (3) immeasurable: primary factors other than pneumonia were clearly involved; in accordance with the "Clinical evaluation methods for new antimicrobial agents to treat respiratory infections" of the Japan Society of Chemotherapy.[11] Assessment of nephrotoxicity began 24 h following the first order for PIPC–TAZ. The primary definition of nephrotoxicity used was at least a 100% (>2-fold) increase in creatinine clearance (CL_{cr}). An evaluation was carried out upon dividing the side effects into: (1) mild: side effects believed to be minor, (2) moderate: side effects that are not serious but not minor, (3) serious: serious side effects with a risk of death or permanent malfunction affecting the daily life of patients in accordance with the classification criteria of severity of adverse drug reactions by the Ministry of Health, Labour and Welfare of Japan.[12]

Pharmacokinetic Analysis PIPC plasma concentration–time data were individually fitted to a two-compartment model by employing the nonlinear least-squares regression program, WinNonlin (Ver. 3.0, Scientific Consulting, Mountain View, CA, U.S.A.). Pharmacokinetic parameters, total clearance (CL_{tot}), apparent distribution volume (V_d), area under the plasma concentration–time curve (AUC) from 0 h to infinity and elimination half-life ($t_{1/2\beta}$) of PIPC were calculated for the individual patients.

Statistical Analysis Statistical analysis was carried out using statistical analysis software SPSS ver. 20 (IBM Corporation). Differences in patient background between with and without nephrotoxicity patient groups were analysed using the paired t-test, Fisher's exact test and McNemar test. A p value <0.05 was determined as having statistical significance.

RESULTS

The patient characteristics are shown in Table 1. A total of 22 cases were investigated, with 17 males and 5 females. The mean age was 85 years old, with most of the patients were late elderly and 20 cases were over 80 years old.

The mean creatinine clearance was 44.4 mL/min. Total protein and serum albumin levels were 6.6 g/dL and 2.9 g/dL, respectively, and both values were relatively low in comparison with the reference range. Regarding the severity of pneumonia, there were 12 moderate and 10 severe cases upon A-DROP classification, and all 22 cases had underlying diseases. Treatment for pneumonia before admission was carried out on 6 patients (27.3%), and also 6 cases (27.3%) exhibited chronic respiratory disease.

Clinical efficacy and adverse effects after beginning the administration of PIPC–TAZ were summarised in Table 2, PIPC–TAZ was effective in 20 among 22 cases, yielding an efficacy ratio of 90.9%. On the other hand, regarding the tox-

Table 1. Characteristics of the Patients with Nursing and Healthcare Associated Pneumonia Treated with Piperacillin–Tazobactam

Characteristics	Number or mean±S.D.
Gender (No. of patient)	Male 17/Female 5
Age (years)	85.0±6.5
Body weight (kg)	42.8±8.0
Serum creatinine (mg/dL)	0.80±0.34
CL_{cr} (mL/min)[a]	44.4±16.1
Total protein (g/dL)	6.6±0.8
Serum albumin (g/dL)	2.9±0.6
Severity level (A-DROP)[b]	
Moderate	12
Severe	10
Underlying disease	
Yes/No (%)	22/0 (100)
Pretreatment	
Yes/No (%)	6/16 (27.3)
Chronic respiratory disease	
Yes/No (%)	6/16 (27.3)
Old tuberculosis	1
COPD	1
Interstitial pneumonia	1
Pneumoconiosis	1
Lung cancer	2

a) CL_{cr} (creatinine clearance) was estimated by using Cockcroft–Gault equation. *b*) Pneumonia severity classification from the Japanese Respiratory Society guidelines for the management of community acquired pneumonia in adults. CL_{cr}, estimated creatinine clearance according to the Cockcroft and Gault formula; COPD, chronic obstructive pulmonary disease.

icity, nephrotoxicity was observed in 4 cases (18.2%) at 4–7 d after the beginning of PIPC–TAZ administration. PIPC–TAZ was administered for 8.1±3.0 d (mean±S.D.). Regarding the PIPC–TAZ administration method, there were 18 cases of 4.5 g three times/d and 4 cases of 2.25 g three times/d. In the patients with nephrotoxicity, reduction of the dose in 1 case and discontinuation of administration in 3 cases were necessary. Hepatic toxicity was observed in 2 cases (9.1%), and pseudomembranous enterocolitis was observed in 1 case (4.6%).

A two-compartment model was found to describe the plasma PIPC concentration data after intravenous administration of PIPC–TAZ (4.0 g/0.5 g or 2.0 g/0.25 g) as shown in Fig. 1. No significant difference ($p=0.329$) in the peak plasma concentration of PIPC–TAZ was observed between patients with and without nephrotoxicity induced by PIPC–TAZ. While there was no significant difference in pharmacokinetic parameters, CL_{tot}, V_d, AUC and $t_{1/2\beta}$ of PIPC between both groups, in patients with nephrotoxicity induced by PIPC–TAZ therapy, 20% decrease in CL_{tot} and 1.5 fold increases in $t_{1/2\beta}$ were observed in comparison to patients without nephrotoxicity.

In the group expressing nephrotoxicity, the mean value CL_{cr} were significantly lower compared to those of the group without nephrotoxicity ($p<0.01$) in Table 3, although there was no significant difference in age, BMI, serum total protein, serum albumin between both groups.

As shown in Table 4, the low renal function ($CL_{cr}<40$ mL/min) was detected as a significant influencing factor on the nephrotoxicity induced by the treatment with PIPC–TAZ.

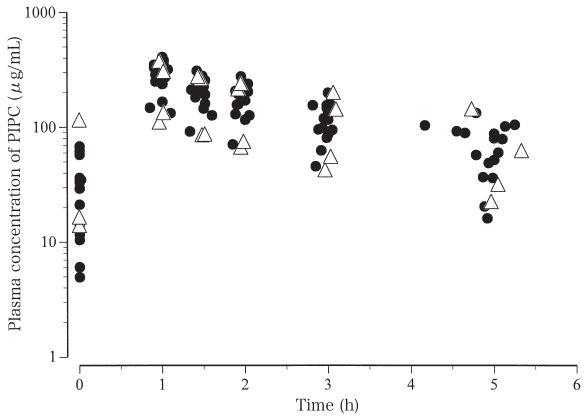

Fig. 1. Plasma PIPC Concentration–Time Curve after Administration of PIPC–TAZ in Patients with NHCAP

These data include 135 concentration points (total) from 22 patients. Close circle, patients without nephrotoxicity; open triangle, patients with nephrotoxicity.

Table 2. Clinical Efficacy and Toxicity after Beginning the Administration of PIPC–TAZ in Late Elderly Patients with NHCAP

Clinical effectiveness[a)]	Case (%)			
Effective	20 (90.9%)			
Not effective	2 (9.1%)			
Immeasurable	0 (0%)			
Toxicity[b)]		Severity	PIPC–TAZ administration	Outcome
Renal dysfunction	4 (18.2%)	Mild	Discontinuation	Recovering
		Moderate	Reduction	Recovering
			Discontinuation	Not recovered
			Discontinuation	Not recovered
Liver dysfunction	2 (9.1%)	Mild	Continuation	Recovering
		Moderate	Discontinuation	Not recovered
Pseudomembranous enterocolitis	1 (4.6%)	Moderate	Discontinuation	Recovering

a) Clinical effective was evaluated in accordance with the "Clinical evaluation methods for new antimicrobial agents to treat respiratory infections" of the Japan Society of Chemotherapy. *b*) Toxicity was evaluated in accordance with the classification criteria of severity of adverse drug reactions of the Ministry of Health, Labour and Welfare of Japan.

Table 3. Patient Backgrounds and Pharmacokinetic Parameters Associated with Nephrotoxicity after Administration of PIPC–TAZ

Factor	All patients ($n=22$)	Nephrotoxicity	
		Without ($n=18$)	With ($n=4$)
CL_{cr} (mL/min)	44.4±16.1	46.1±16.7	32.5±4.4*
Daily dose of PIPC–TAZ (g)	12.3±2.7	12.8±2.2	10.1±3.9
PIPC-CL_{tot} (L/h)	4.9±2.0	5.1±2.0	4.0±1.3
PIPC-V_d (L)	8.8±6.8	8.7±7.4	9.0±3.5
PIPC-$t_{1/2}$ (h)	1.3±0.8	1.2±0.7	1.7±1.1
PIPC-AUC (mg/L・h)	888.3±394.2	885.1±348.2	902.4±632.7

Each value represents the mean±S.D. CL_{cr}, creatinine clearance estimated by Cockcroft–Gault equation,; PIPC-CL_{tot}, total clearance of PIPC; PIPC-V_d, apparent distribution volume of PIPC; PIPC-$t_{1/2\beta}$, β-phase elimination half life of PIPC; PIPC-AUC, area under the concentration–time curve of PIPC. *$p<0.01$, *vs.* without nephrotoxicity by Student's *t*-test.

Table 4. Factor Analysis of Nephrotoxicity Induced by PIPC–TAZ Treatment

Risk factor	Nephrotoxicity		*p* Value
	Without (n=18)	With (n=4)	
Chronic respiratory disease			
Yes	5	1	1.000[c]
No	13	3	
Pre-treatment			
Yes	4	2	0.292[c]
No	14	2	
Severity level (A-DROP)[a]			
Moderate	10	2	1.000[c]
Severe	8	2	
Gender			
Male	14	3	1.000[c]
Female	4	1	
PIPC–TAZ dose (g)			
2.25	2	2	0.135[c]
4.50	16	2	
Liver dysfunction			
Yes	0	2	0.500[d]
No	18	2	
Pseudomembranous enterocolitis			
Yes	1	0	1.000[c]
No	17	4	
CL_{cr}[b] (mL/min) before PIPC–TAZ treatment			
>40	8	4	0.008[d]
≤40	10	0	

a) Pneumonia severity classification from the Japanese Respiratory Society guidelines for the management of community acquired pneumonia in adults. *b*) CL_{cr} (creatinine clearance) was estimated by using Cockcroft–Gault equation. *c*) Fisher's exact test. *d*) MacNemar test.

DISCUSSION

The broadest-spectrum antibiotics, such as fourth-generation cephalosporins, PIPC–TAZ, and carbapenems, play an important role in the empiric therapy of serious infections, pneumonia. Gram-negative nosocomial pneumonia, particularly that caused by *P. aeruginosa*, is a severe and often life-threatening infection in elderly patients.[13] This study was performed to evaluate the efficacy, safety, and pharmacokinetic analysis of PIPC–TAZ regarding Japanese late elderly pneumonia patients.

We observed a very high efficacy ratio of 90.9% by the antibiotic chemotherapy with PIPC–TAZ in the special population, (1) late elderly patients, (2) moderate and serious cases, (3) high risk patients with suffering from underlying and existing diseases. Upon previous clinical pharmacological studies with Japanese CAP as subjects, the efficacy ratio of PIPC–TAZ was 86.0%,[14] and was 91.3%[15] upon a phase III study. Moreover, the efficacy rate was 82.9% upon an investigation into administering PIPC–TAZ for moderate to severe aspiration pneumonitis,[16] and was 91.7% upon an investigation into aspiration pneumonitis due to *Klebsiella pneumoniae*.[17] Therefore, it was evaluated in the present study on late elderly NHCAP patients that satisfactory clinical response as well as previous clinical studies was observed. Additionally, the pharmacokinetic study was performed to investigate the influence of drug concentration on the efficacy of PIPC–TAZ therapy. The total clearance of PIPC in late elderly NHCAP patients (mean age: 85.0 years old) of this study was 30% lower than that of Japanese CAP patients (mean age: 63.7 years old) of previous study.[14] However, we did not find a significant relationship between the clinical response and pharmacokinetic parameters of PIPC. Since we did not determine the free concentration of PIPC in plasma, there is a limitation in evaluating the relationship between pharmacokinetics and pharmacodynamics of PIPC in the present study. It was suggested that in late elderly NHCAP patients, the delay of drug excretion could lead to the accumulation of drug in the body. Thus, enough plasma PIPC levels against the Gram-negative nosocomial pneumonia were maintained in therapeutic period, the resulting response rate was satisfactory in late elderly patients with NHCAP.

While a high efficacy ratio was observed in the late elderly patients with mean age of 85.0 years old, the serious nephrotoxicity was found in four out of 22 cases (18.8%) of patients. In the previous reports, dose adjustment of PIPC–TAZ in accordance with the CL_{cr} was recommended in patients with renal dysfunction.[6] However, there are few reports of nephrotoxicity induced by PIPC–TAZ so far. Wherein, we analysed influencing factors for nephrotoxicity induced by PIPC–TAZ in our special population. The CL_{cr} in the patients with nephrotoxicity were significantly lower than that of the patients without nephrotoxicity ($p<0.01$), although there was no significant difference in other factors between both groups

(Table 3). Otherwise in our patients with NHCAP (85 years old), CL_{tot} of PIPC showed a large reduction in comparison with previous reports (HCAP; 65 years old, healthy adults; 25 years old),[14] resulting in a prolonged elimination half-life of PIPC. There was no significant difference in pharmacokinetic parameters between both groups, but it was observed that 1.5 folds prolonged $t_{1/2}$ and 20% decline of CL_{tot} in patients with nephrotoxicity. This result indicates that the largely decrease of elimination clearance of PIPC was dependent on the relatively low renal clearance in late elderly patients. On the other hand, Shiba *et al.* recommended to decrease the dose of PIPC–TAZ in the patients with low CL_{cr} (<40 mL/min) upon pharmacokinetic–pharmacodynamic simulation in Japanese CAP patients.[6] The mean CL_{cr} of our patients was 44.4±16.1 mL/min, so that dose of PIPC–TAZ was reduced in patients with reduced renal function. Although there is no significantly difference in in total clearance of PIPC between the patients with CL_{cr}<40 mL/min and CL_{cr}≥40 mL/min, the low renal function (CL_{cr}<40 mL/min) was detected as a significant influencing factor on the nephrotoxicity induced by the treatment with PIPC–TAZ. From this result, we consider that existing renal impairment is a potential influencing factor for nephrotoxicity following PIPC–TAZ administration. Therefore, administration to the patients with CL_{cr}<40 mL/min is not recommended. Generally, interstitial nephritis due to allergic mechanisms is reported as nephrotoxicity due to antibiotic penicillin.[18] However, recently, Jensen *et al.* reported PIPC–TAZ was identified as a cause of delayed renal recovery in intensive care patients. They suggested that this impact on renal function was caused by toxic effect on the renal tubule.[19] Therefore, it is considered that amount of exposure to kidney of PIPC–TAZ could contribute the appearance of nephrotoxicity. Because we have many information of the pharmacokinetics–pharmacodynamics of PIPC, we evaluated the blood concentration of only PIPC in this study. Thus, it is not deniable that there is a possibility that the exposure to TAZ may effect on the nephrotoxicity induced by PIPC–TAZ. Although, Casu *et al.* suggested that the CL_{cr} was significantly correlated with concentrations and clearance of β-lactams including PIPC–TAZ, changes in elimination clearance did not reliably predict variations in drug pharmacokinetics–pharmacodynamics.[20]

Since the number of patients was small and special population as late elderly patients might effect on the renal dysfunction, there is a limitation in evaluating the relationship between the pharmacokinetics of PIPC and nephrotoxicity. Additionally, due to the special population as late elderly patients, their V_d of PIPC in this study was lower than those in previous reports. This resulted in a high PIPC concentration and a high *AUC* in some patients. Consequently, it is possible that a high PIPC exposure contributed to increasing the occurrence of the PIPC adverse effects, although we need to further examine other factors associated with nephrotoxicity induced by PIPC–TAZ. Therfore, when paying attention to the frequency of severe nephrotoxicity in this study, we should consider PIPC–TAZ dose adjustment for late elderly patients with NHCP.

In conclusion, although PIPC–TAZ was effective to elderly patients with NHCAP, the appearance of serious nephrotoxicity was relative high frequency. It is suggested that renal impairment, especially a creatinine clearance of <40 mL/min, could be an influencing factor for nephrotoxicity induced by PIPC–TAZ administration. In the PIPC–TAZ treatment of late elderly patients comprising impaired renal function, more deliberate administration planning and careful follow up are required from a safety perspective.

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