Population pharmacokinetics of tazobactam/piperacillin in Japanese patients with community-acquired pneumonia

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The population pharmacokinetics on tazobactam/piperacillin (TAZ/PIPC; 1 : 8, 4.5 g× 3) was analyzed in Japanese patients with community-acquired pneumonia using the Nonlinear Mixed Effect Model version VI. Analysis by the one-compartment model yielded the following results for PIPC: total clearance (CL)＝8.22＋(Ccr－71.4)× 0.0561 (L/hr), distribution volume (Vd)＝13.7 (L). The pharmacokinetic parameters for TAZ were: CL＝8.67＋(Ccr－71.4)×0.0682 (L/hr), Vd＝14.4 (L). Of the pharmacokinetic parameters of PIPC, CL included Ccr as a variation factor, whereas the Vd included no variation factor. Because PIPC is excreted into the urine in the unchanged form, its pharmacokinetic factors seem to reflect the renal function status. In this study of patients with community-acquired pneumonia, the mean Vd per body weight was 0.26 L/kg, and the results suggested an increase of the Vd in patients with community-acquired pneumonia as compared with the value in healthy adults.

Introduction

Tazobactam/piperacillin (TAZ/PIPC) is a preparation of a penicillin family antimicrobial agent combined with a β-lactamase inhibitor and has been shown to have a broad antimicrobial spectrum. The 1 : 8 TAZ/PIPC combination has been approved in more than 90 countries in the

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world, including the USA and Europe, and has been extensively used in the treatment of severe or intractable infections. In Japan, a 1：4 TAZ/PIPC combination was initially marketed, the dose level of PIPC in this combination was lower than that in foreign countries, and the use of this formulation was restricted to a narrower spectrum of indications. In 2008, a 1：8 TAZ/PIPC combination, identical to the formulation approved overseas, was also approved in Japan, making it possible to administer PIPC at higher dose levels and expanding the available scope of antimicrobial agents for the treatment of intractable infections.

Recently, discussions have been held about the importance of efficacy/safety optimization from the viewpoint of ensuring proper use of antimicrobial agents, as well as about the importance of designing administration of antimicrobial agents based on the pharmacokinetic and pharmacodynamic (*i.e.*, PK-PD theory) profiles of the drugs to suppress the development of resistant strains of microorganisms. The antimicrobial activities of penicillins are time-dependent, and the time above the minimum inhibitory concentration (TAM) has been shown to serve as a useful pharmacokinetic-pharmacodynamic (PK-PD) parameter for appropriate use of the penicillins. It has been suggested that penicillins exert cytostatic activity when the TAM is over 30% and maximal cytocidal activity when the TAM is over 50%[1]. Thus, it is essential to take into account the TAM when considering treatment with the penicillins. Exploration and elucidation of the pharmacokinetics of TAZ/PIPC may be expected to allow optimum methods of treatment with this combination to be devised based on the PK-PD parameters. Under such circumstances, the present study was carried out to investigate the pharmacokinetics of TAZ/PIPC in Japanese patients with community-acquired pneumonia by analysis of the population pharmacokinetics.

Materials and Methods

Population

Referring to the data yielded by the clinical pharmacological study of patients with community-acquired pneumonia carried out by Watanabe *et al.*[2], we performed a population pharmacokinetic analysis in 53 patients, involving 157 points of blood sampling for PIPC and 146 for TAZ. TAZ/PIPC was administered three times a day (4.5 g×3) for all patient. It was carried out in accordance with the Ethical Guidelines on Epidemiological Studies (Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare of Japan) and the Law on Protection of Individual Information, as well as the Ethical Guidelines for Clinical studies of our hospital.

Pharmacokinetic model building

The analysis of the population pharmacokinetics was conducted using the Nonlinear Mixed Effect Model (NONMEM), version VI. The computer was used under the following settings:

CPU, Intel® Core™ i3 2.13 GHz; memory, 4.00 GB; OS, Windows®7 (Microsoft corporation). NONMEM was compiled with Digital Visual Fortran® 5.0A (Digital Equipment Corporation).

Algorithm for analysis

Analysis using NONMEM VI is based on 3 algorithms: first order (FO), first order conditional estimation (FOCE), and FOCE-interaction (FOCE-I). To determine then optimum algorithm for our analysis, we carried out analysis with the linear 1-compartment model, assuming an exponential error of total clearance (CL) for inter-individual variation and relative error for intra-individual variation, and compared the results on predictability obtained using the algorithms, using the scale of predicted error for the population.

Pharmacokinetic models

The predictability of the pharmacokinetic models was analyzed on the linear 1-compartment model (NONMEM sub-routine ADVAN1 TRANS2) not including covariates, and the 2-compartment model (ADVAN3 TRANS4). The 1-compartment model was adopted for both PIPC and TAZ, with the CL and distribution volume (Vd) serving as the PK parameters. Predictability was evaluated based on a general assessment of the Akaike Information Criteria (AIC)[3–5], root mean square error (RMSE).

Error models

Inter-individual variations were evaluated through analysis of objective function (OBJ), RMSE, to determine the exponential errors and absolute errors. Exponential errors were used for evaluation of the inter-individual variation of CL. No error model was assumed for determining the inter-individual variation of Vd. Inter-individual variation was defined as $CL_i = CL \times \exp(\eta i)$, where CL denotes a population parameter, CL_i denotes an individual's parameter, η is 0 on average, and ω^2 denotes variance.

For evaluation of intra-individual variation, the relative error model was selected on the basis of the results of evaluation of the predictability of the three models, *i.e.*, relative error model, absolute error model and absolute-exponential mixed error model. Intra-individual variation was defined as $Cp = F \times (1 + \varepsilon)$, where Cp denotes the observed blood drug level, F indicates the blood drug level predicted from the compartment model, ε averages 0, and σ^2 denotes variance.

Factors affecting the pharmacokinetics

Covariates were incorporated one by one into the basic model originally free of covariates, to evaluate the influence of these covariates on the pharmacokinetics. Of the variables, age, body weight, gender, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine (Scr) and creatinine clearance (Ccr) were incorporated into the model. The statistical signifi-

cance of the contribution of the covariates was judged on the basis of the likelihood ratio test comparing the variable in OBJ obtained from the NONMEM (−2 log likelihood difference; ΔOBJ) with the χ^2 value. Because ΔOBJ can be approximated with the χ^2 distribution, a 3.84 or greater change of the ΔOBJ associated with an increase of θ by 1 was regarded as significant ($p < 0.05$). Then, all covariates found to be significant were incorporated into the model, to obtain a full model. From this model, covariates were then eliminated one by one. A covariate whose removal resulted in a 6.63 or greater increase of the ΔOBJ was regarded as significant ($p < 0.01$). The covariates thus rated as insignificant were eliminated from the model one by one, beginning with the covariate whose elimination caused the smallest change of the ΔOBJ. In this way, a final model incorporating only significant covariates was constructed. Selection of covariates was based on a general assessment, covering not only the significance of each fixed effect, but also the accuracy of parameter estimation and the applicability.

Validity of the basic model

The validity of the basic model was evaluated in accordance with the European Medicines Evaluation Agency Guidelines through analysis of predictability, diagnosis of residuals, and assessment of the regularity of residuals on the GOF plots[6].

(1) Plasma drug level (Cp) *vs.* population predicted drug level (PRED)
(2) CP *vs.* individually predicted drug level (IPRED)
(3) Time after drug administration *vs.* weighted residual (weighted residual [WRES] or conditional weighted residual [CWRES])
(4) Population predicted drug level *vs.* weighted residual
(5) Population predicted drug level *vs.* absolute weighted residual

When the algorithm FO was used, WRES was adopted as the weighted residual. When the algorithm FOCE or FOCE-I was used, CWRES was adopted as the weighted residual[7].

Validation of the thus-developed population pharmacokinetic model

Bootstrap re-sampling is used for evaluation of the stability and robustness of the population pharmacokinetic model. Bootstrap re-sampling was carried out 200 times to compare the parameters of the final model with the average parameter values estimated with the bootstrap.

Results

Patients

Table 1 shows the blood sampling points for PIPC and TAZ and the variables of the 53 patients. Table 2 shows the Pearson's product-moment correlation coefficient (r) among the variables. The study involved adults (age over 16) ranging in age from 21 to 90 years. There were 39

Table 1. Patients' demographic data[a].

	Community-Acquired Pneumonia three times a day (4.5g×3) for all patients		
	Mean ± S.D.	Min-Max	Median
Gender (M/F)	53（39/14）		
Age (yr)	65 ± 17	21-90	69
HGT (cm)	160.1 ± 8.9	138.5-182.0	160
WGT (kg)	55.7 ± 11.9	38-112.6	55
AST (IU/L)	26.7 ± 15.2	10-84	20
ALT (IU/L)	22.7 ± 18.3	7-97	16
Scr (mg/dL)	0.76 ± 0.22	0.38-1.3	0.7
Ccr (ml/min)	81.4 ± 46.8	31.7-349.4	71.4

[a] M, male; F, female; HGT, height; WGT, weight; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Scr, serum creatinine; Ccr, creatinine clearance

Table 2. Relationships with the patients' demographic data[a,b].

	Age	HGT	WGT	AST	ALT	Scr
HGT	-0.341					
WGT	-0.184	0.544				
AST	0.146	0.007	0.171			
ALT	0.079	0.018	0.091	0.617		
Scr	0.349	0.115	0.191	0.119	0.130	
Ccr	-0.678	0.448	0.597	-0.082	-0.028	-0.513

[a] Pearson's product-moment correlation coefficient (r)

[b] HGT, height; WGT, weight; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Scr, serum creatinine; Ccr, creatinine clearance

males and 14 females, with body weights ranging from 38 to 112.6 kg. Creatinine clearance, as calculated using the Cockcroft-Gault equation[8], ranged from 31.7 to 349.4 mL/min. Correlation was noted between the age and Ccr (r＝－0.678), between the body weight and Ccr (r＝0.597),

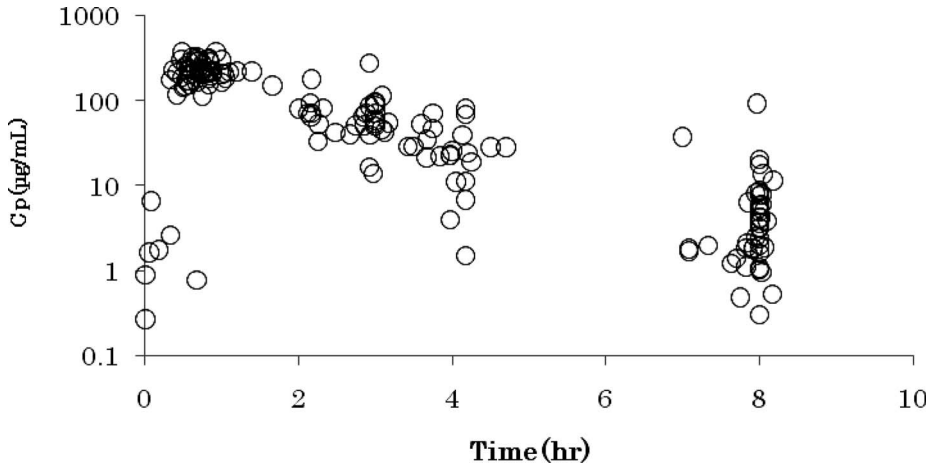
and between the Scr and Ccr (r=−0.513). The number of blood sampling points from 53 patients was 157 for PIPC and 146 for TAZ.

Population pharmacokinetic parameters

(1) PIPC

When the NONMEM sub-routine ADVAN1 TRANS2 1-compartment model was compared with the ADVAN3 TRANS4 2-compartment model, without incorporation of any covariate, the predictability did not differ significantly between the two models. For this reason, the 1-compartment model was adopted. The AIC was calculated to be 1086.654 for the 1-compartment model and 1063.06 for the 2-compartment model. When the blood drug level was plotted against time, a linear course of the blood drug level was obtained (Fig. 1). RMSE (root mean square error) did not differ significantly between the 1-compartment model (48.7 μg/mL) and the 2-compartment model (47.8 μg/mL). So, the 1-compartment model was adopted. The population predicted error assessment scale scores, calculated from the results of analysis with each algorithm, were as follows: FO (mean error (ME)=−0.43 μg/mL, mean absolute error (MAE)=34.06 μg/mL, RMSE =51.15 μg/mL), FOCE (ME=9.9 μg/mL, MAE=29.14 μg/mL, RMSE=49.2 μg/mL), FOCE-I (ME=6.8 μg/mL, MAE=29.41 μg/mL, RMSE=48.7 μg/mL). Thus, the obtained predictability was slightly better with algorithm FOCE-I. For inter-individual variation of the CL, the exponential error model was assumed. No improvement of the predictability of the inter-individual variations of Vd was noted even when the exponential error model was assumed. For this reason, the error model was not assumed for inter-individual variation of the Vd. For intra-individual variation, the relative error model was assumed. Comparison of the relative error model, absolute error model and absolute-relative mixed error model revealed that a greater OBJ was obtained with the absolute error model than with the other two models. OBJ did not differ between the relative

Fig. 1. Plot of observed concentration of PIPC *vs.* time



error model and the mixed error model, and no improvement was obtained with the mixed error model. For these reasons, the relative error model was adopted.

Table 3 shows the results of analysis with the covariate models, incorporating each variable. −2 log likelihood difference decreased significantly following incorporation of age, body weight, Scr or Ccr. Because these factors were correlated with each other, the Ccr causing the greatest decrease of the OBJ was incorporated into the full model. As only one variation factor was involved, no backward selection was performed. When a full model incorporating all of these factors was prepared and background selection was performed, the OBJ showed no significant increase following removal of age, body weight or Scr from the model, eventually resulting in the same model following removal of any of these factors. Vd was not analyzed because the inter-individual variation was very small and was scarcely influenced by the variation factors.

(2) TAZ

Like for the case of PIPC, the values of the parameters estimated using the FO algorithm differed markedly from those estimated using the FOCE or FOCE-I algorithm. The population-

Table 3. Hypothesis testing for fixed effects on the PIPC pharmacokinetics[a,b].

	OBJ	ΔOBJ	p value	θ1	θ2	θ3	ω^2	σ^2
Basic	1078.654			8.54	13.7		0.0765 (27.7%)	0.115 (33.9%)
CL = θ1 + θ3 × GEN Vd = θ2	1075.767	2.887	0.089	8.21	13.7	1.32	0.0709 (26.63%)	0.115 (33.9%)
CL = θ1 + θ3 × (AGE-69) Vd = θ2	1049.825	28.829	<0.001	8.23	13.7	-0.103	0.0421 (20.52%)	0.115 (33.9%)
CL = θ1 + θ3 × (WGT-55) Vd = θ2	1072.968	5.686	0.017	8.53	13.7	0.0702	0.0693 (26.33)	0.114 (33.7%)
CL = θ1 + θ3 × (AST-20) Vd = θ2	1078.115	0.539	0.463	8.65	13.7	-0.0155	0.0758 (26.0%)	0.115 (33.9%)
CL = θ1 + θ3 × (ALT-16) Vd = θ2	1078.625	0.029	0.865	8.52	13.7	0.00328	0.0765 (27.66%)	0.115 (33.9%)
CL = θ1 + θ3 × (Scr-0.7) Vd = θ2	1067.858	10.796	0.001	8.85	13.7	-4.45	0.0613 (24.7%)	0.115 (33.9%)
CL = θ1 + θ3 × (Ccr-71.4) Vd = θ2	1037.401	41.253	<0.001	8.22	13.7	0.0561	0.0319 (17.8%)	0.115 (33.9%)

[a] χ^2-test. OBJ ≥ 3.84 ($p < 0.05$), OBJ ≥ 6.64 ($p < 0.01$)

[b] OBJ, objective function; CL, total clearance; GEN, gender; Vd, distribution volume; AGE, age; WGT, weight; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Scr, serum creatinine; Ccr, creatinine clearance

predicted error assessment scale scores, calculated from the results of analysis with the FOCE and FOCE-I algorithms, were as follows: FOCE (ME＝1.36 μg/mL, MAE＝3.41 μg/mL, RMSE＝5.48 μg/mL), FOCE-I (ME＝1.00 μg/mL, MAE＝3.38 μg/mL, RMSE＝5.36 μg/mL). Thus, the predictability was slightly better with FOCE-I. For this reason, FOCE-I was used for the comparison between the 1-compartment analysis and 2-compartment analysis.

The obtained AIC was smaller by more than 100 with the 1-compartment model (455.222) than with the 2-compartment model (560.421). The predictability of each model was checked with DV-PRED plots, and the 1-compartment model was adopted. The inter-individual variations in the distribution volume were very small, like for the case of PIPC. For this reason, the exponential error model was not used, and the fixed effect model was not evaluated either. The intra-individual variation was similar to the results for PIPC. For this reason, the relative error was assumed for TAZ. With the basic model, the OBJ was 447.222 and the intra-individual variation was 31.8%. The estimated parameter value was 9.03 L/hr for CL and 14.6 L for Vd. Table 4 shows the results of analysis with the models incorporating each variable as a covariate. A tendency similar to that seen for PIPC was observed. The OBJ decreased following incorporation of each of

Table 4. Hypothesis testing for fixed effects on the TAZ pharmacokinetics[a,b].

	OBJ	ΔOBJ	p value	θ1	θ2	θ3	ω^2	σ^2
Basic	447.222			9.03	14.6		0.0914 (30.2%)	0.101 (31.8%)
CL = θ1 + θ3 × GEN Vd = θ2	445.501	1.721	0.189	8.72	14.6	1.21	0.0869 (29.5%)	0.101 (31.8%)
CL = θ1 + θ3 × (AGE-69) Vd = θ2	416.5	30.722	<0.001	8.68	14.4	-0.126	0.0496 (22.3%)	0.0987 (31.4%)
CL = θ1 + θ3 × (WGT-55) Vd = θ2	441.128	6.094	0.013	10.7	14.6	0.0838	0.0806 (28.3%)	0.101 (31.8%)
CL = θ1 + θ3 × (AST-20) Vd = θ2	446.314	0.908	0.341	9.21	14.6	-0.0261	0.0893 (29.9%)	0.101 (31.8%)
CL = θ1 + θ3 × (ALT-16) Vd = θ2	447.437	0.032	0.858	9.01	14.6	0.00448	0.0914 (30.2%)	0.101 (31.8%)
CL = θ1 + θ3 × (Scr-0.7) Vd = θ2	436.437	10.785	0.001	9.39	14.5	-5.1	0.0730 (27.0%)	0.101 (31.8%)
CL = θ1 + θ3 × (Ccr-71.4) Vd = θ2	402.838	44.384	<0.001	8.67	14.4	0.0682	0.0363 (19.1%)	0.0990 (31.5%)

[a] χ^2-test. OBJ ≥ 3.84 ($p < 0.05$), OBJ ≥ 6.64 ($p < 0.01$)

[b] OBJ, objective function; CL, total clearance; GEN, gender; Vd, distribution volume; AGE, age; WGT, weight; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Scr, serum creatinine; Ccr, creatinine clearance

age, body weight, Scr and Ccr. Finally, a model incorporating only Ccr was adopted.

PK model performance

(1) PIPC

Fig. 2 shows the goodness-of-fit plot for PIPC.

The Cp-PRED regression analysis revealed a relationship of R^2＝0.8382 (Fig. 2(A)). The Cp-IPRED regression analysis disclosed a relationship of R^2＝0.8531 (Fig. 2(B)). The distribution of CWRES plotted against PRED was almost homogeneous around the line CWRES＝0 (Fig. 2(C)). The distribution of CWRES relative to time was not biased (Fig. 2(D)). The success rate in bootstrap re-sampling was 99.5% (success in 199/200 points). The population pharmacokinetic parameters for the dataset were approximately identical to those for the final model (Table 5).

(2) TAZ

Fig. 3 illustrates the goodness-of-fit plot for TAZ.

The Cp-PRED regression analysis revealed a relationship of R^2＝0.8268 (Fig. 3(A)). Cp-IPRED regression analysis disclosed a relationship of R^2＝0.8749 (Fig. 3(B)). The distribution of CWRES plotted against PRED was almost homogeneous around the line CWRES＝0 (Fig. 3(C)). The distribution of CWRES relative to time was not biased (Fig. 3(D)). The success rate in bootstrap re-sampling was 99.5% (success at 199/200 points). The population pharmacokinetic parameters for the dataset were approximately identical to those for the final model (Table 6).

Final-model PK parameter

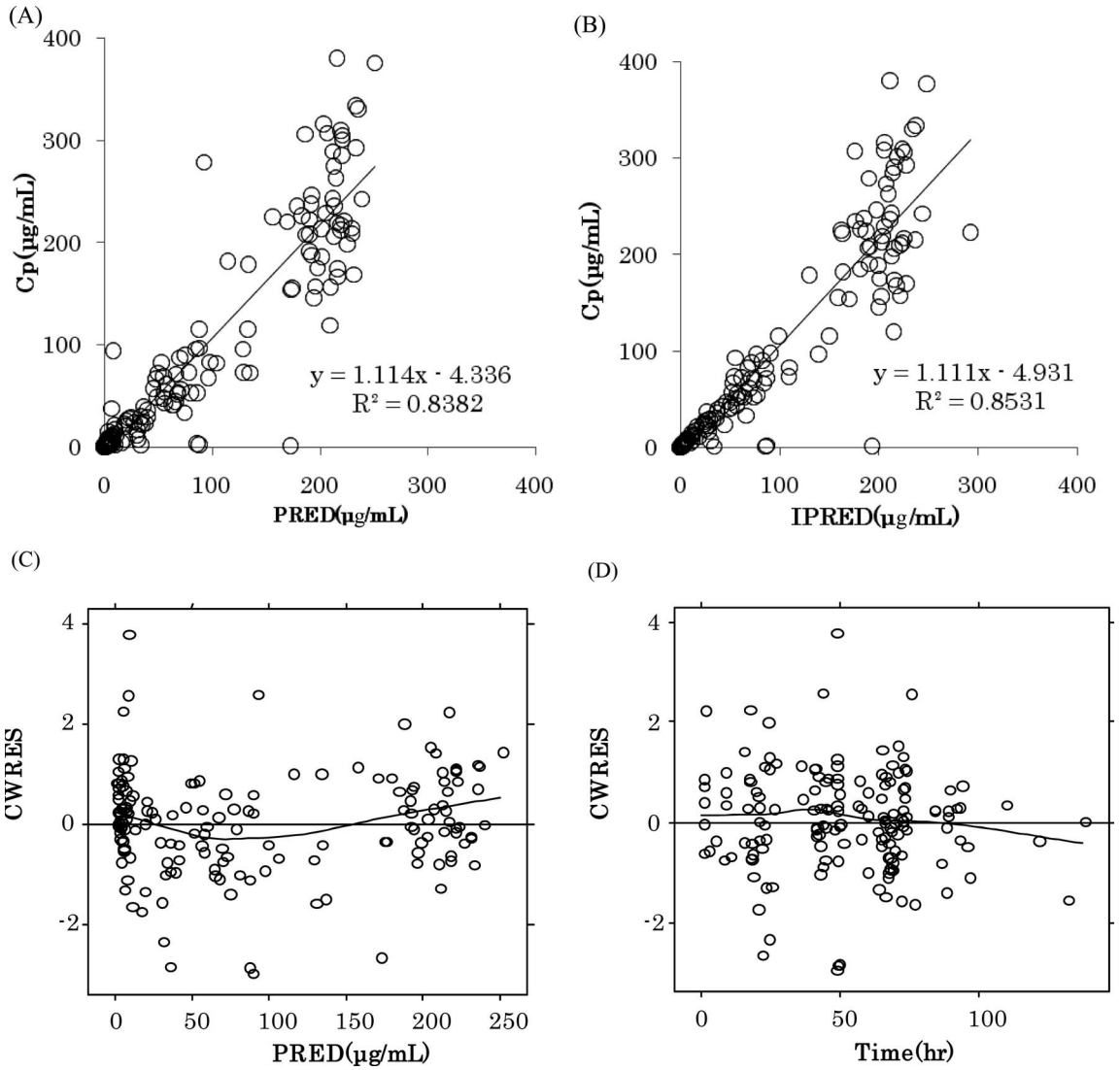
The calculation for PIPC yielded the following results: CL＝8.22＋(Ccr－71.4)×0.0561(L/hr), Vd＝13.7 (L); intra-individual variation, 33.9%. The OBJ decreased from 1078.654 to 1037.401 ($p<0.001$), while no change was revealed by analysis of intra-individual variation.

The calculation for TAZ yielded the following results: CL＝8.67＋(Ccr－71.4)×0.0682 (L/hr), Vd＝14.4 (L); intra-individual variation, 31.5%. The OBJ decreased from 447.222 to 402.838 ($p<0.001$), and the intra-individual variation changed from 31.8% to 31.5%.

Discussion

In regard to the pharmacokinetics of PIPC, some investigators have previously reported that non-linear pharmacokinetic profiles are noted following administration of this drug at extremely high dose levels[9]. In the present study, the drug was administered using the dosing method and dose level specified in the package insert, and the pharmacokinetic parameters measured were linear. Therefore, we assumed linearity in the present study. Although a report of analysis using a

Fig. 2. Goodness-of-fit for the PIPC final model (1-compartment model).



(A) Relationship between the observed PIPC plasma concentrations and the predicted values on the population mean parameters (PRED) determined using the final model.
(B) Relationship between the observed PIPC plasma concentrations and the predicted values after individual Bayesian fitting (IPRED) determined using the final model.
(C) Conditional weight residual (CWRES) between the observed PIPC plasma concentrations and the predicted values based on the population mean parameters (PRED) using the final model *vs.* predicted values based on the population mean parameters.
(D) Conditional weight residual (CWRES) between the observed PIPC plasma concentrations and the predicted values based on the population mean parameters (PRED) using the final model *vs.* time after PIPC administration.

Table 5. Final estimates for population pharmacokinetics parameters of PIPC in community-acquired pneumonia and bootstrap validation.

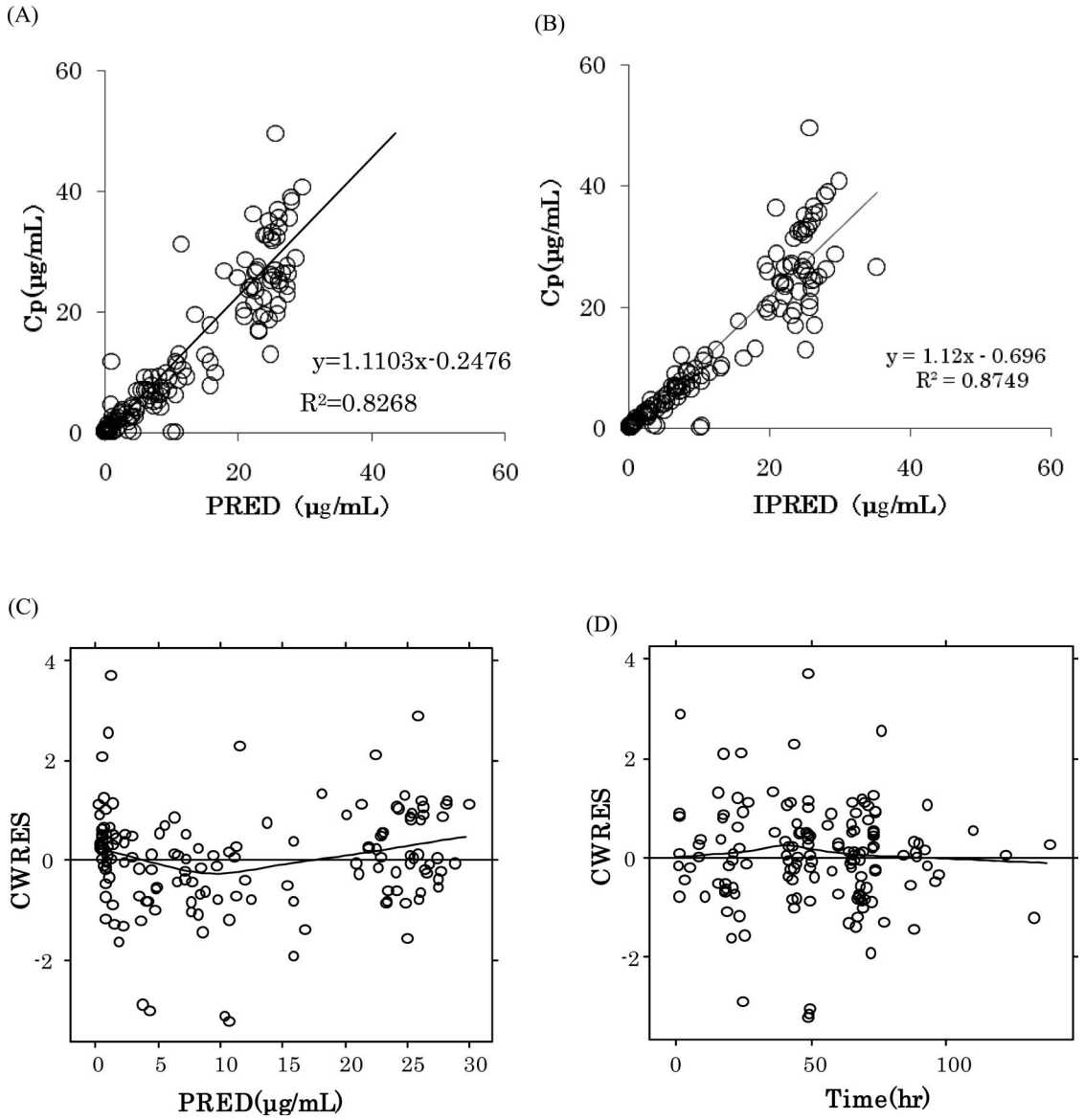
Parameter[a]	Population estimate	95%CI[b] (lower-upper)	% CV[c]	SE[d]	Bootstrap mean	Bootstrap 95%CI[b]
CL (L/hr) θ1	8.22	7.59-8.85		0.319	8.27	7.98-8.56
V (L) θ2	13.7	12.7-14.7		0.526	13.7	13.2-14.2
θ3	0.0561	0.0376-0.0746		0.00946	0.0578	0.048-0.068
$\eta(\omega^2)$[e]	0.0319	0.004-0.060	17.90	0.0141	0.17203	0.134-0.210
$\varepsilon(\sigma^2)$[f]	0.115	0.076-0.154	33.90	0.0197	0.338088	0.308-0.368

[a] Final model parameter (PIPC); CL = θ1 + (Ccr – 71.4) × θ3, Vd = θ2
[b] 95%CI, confidence interval (estimate ± 1.96 × standard error of the estimate)
[c] %CV, coefficient of variation
[d] SE, Standard error
[e] η is inter-individual error parameter ;η is 0 on average, and ω^2 denotes variance
[f] ε is intra-individual error parameter ; ε averages 0, and σ^2 denotes variance

2-compartment model has been published[10], there[11] was no marked difference between the *α* phase half-life and *β* phase half-life according to this report, and the *α* phase was also short. We therefore considered that analysis using the 1-compartment model would not be inferior in terms of predictability, as compared to analysis using the 2-compartment model.

In the present study, the influence of age, gender, physique and hepatic function on the pharmacokinetic parameters was evaluated. Of the PK parameters for PIPC, Ccr was identified as a variation factor for CL, while no variation factors were identified for Vd. Because PIPC is excreted into the urine in the unchanged form at a percentage of 46.0-52.9%[12], its PK factors seem to reflect the renal function status. AST and ALT were also analyzed, but neither was identified as a variation factor. The active metabolite of PIPC is desethyl piperacillin (DEt-PIPC), and no inactive metabolite is known. It has been estimated that CYP2C8, CYP2A6 and CYP2C9*1 are involved in the conversion of PIPC to DE-tPIPC, and that 5% of the PIPC administered is converted into this form, as judged from the plasma drug level and percent urinary excretion[10]. There was one point blank value, a patient calculated Ccr significantly high value of 349.4 mL/min by Cockcroft-Gault. However, it did not influence PPK regardless of input of the value or blank value. Metabolism in the liver affected the disappearance of PIPC little, and neither AST nor ALT was incorporated into the model equation. PIPC level in bile was high, and this drug is transferred well into bile. It has been reported that administration of PIPC to patients with jaundice resulted in lower bile PIPC levels[13], suggesting that disorders of the biliary tract can affect the

Fig. 3. Goodness-of-fit for the TAZ final model (1-compartment model).



(A) Relationship between the observed TAZ plasma concentrations and the predicted values on the population mean parameters (PRED) determined using the final model.
(B) Relationship between the observed TAZ plasma concentrations and the predicted values after individual Bayesian fitting (IPRED) determined using the final model.
(C) Conditional weight residual (CWRES) between the observed TAZ plasma concentrations and the predicted values based on the population mean parameters (PRED) using the final model *vs.* predicted values based on the population mean parameters.
(D) Conditional weight residual (CWRES) between the observed TAZ plasma concentrations and the predicted values based on the population mean parameters (PRED) using the final model *vs.* time after TAZ administration.

Table 6. Final estimates for population pharmacokinetics parameters of TAZ in community-acquired pneumonia and bootstrap validation.

Parameter[a]	Population estimate	95%CI[b] (lower-upper)	% CV[c]	SE[d]	Bootstrap mean	Bootstrap 95%CI[b]
CL (L/hr) θ1	8.67	8.02-9.33		0.334	8.7	8.4-9.0
V (L) θ2	14.4	13.3-15.5		0.562	14.5	13.9-15.0
θ3	0.0682	0.0413-0.0679		0.0137	0.07	0.056-0.084
$\eta(\omega^2)$[e]	0.0363	0.0047-0.0678	19.05	0.0161	0.179174	0.132-0.227
$\varepsilon(\sigma^2)$[f]	0.099	0.060-0.138	31.46	0.0199	0.315156	0.282-0.349

[a] Final model parameter(TAZ); CL = θ1 + (Ccr – 71.4) × θ3, Vd = θ2

[b] 95%CI, confidence interval (estimate ± 1.96 × standard error of the estimate)

[c] %CV, coefficient of variation

[d] SE, Standard error

[e] η is inter-individual error parameter ;η is 0 on average, and ω^2 denotes variance

[f] ε is intra-individual error parameter ; ε averages 0, and σ^2 denotes variance

pharmacokinetics of this drug.

Because inter-individual variation in Vd was small, no model of inter-individual variation was adopted in this study. This is probably because the variation in physique was smaller among the patients studied, except for the case of one patient who weighed 112 kg. The data on the Vd indicate that this drug is located in extracellular fluid and may be affected by the physique of individual patients. However, since the inter-individual variation was small in the present study, analysis of variation factors was not possible. Increase in the Vd of several drugs has been reported in infected patients[14]. In the present study of patients with community-acquired pneumonia, the mean Vd per body weight was calculated to be 0.26 L/kg. If this result is combined with the report that the Vd per body weight was 0.21 L/kg in healthy adults[13], it seems likely that the Vd of PIPC can increase in infected patients.

TAZ showed a tendency similar to that of PIPC in terms of the error models and PK parameters. For the same reason as that for PIPC, the 1-compartment model was adopted for TAZ. Considering that TAZ is excreted into the urine in the unchanged form at 63.5-71.2% of the administered dose, we may say that this model reflecting the renal function was valid for this drug, as for the case of PIPC. TAZ is degraded in the kidneys into inactive metabolites, and the liver is not involved in the metabolism or excretion of this drug. For this reason, neither AST nor ALT served as a variation factor. Vd seems to be confined to the extracellular fluid, but the inter-individual variation was small and no variation factor was identified, for similar reasons to those for PIPC.

The Vd of TAZ per unit body weight in healthy individuals has been reported to be 0.21 L/kg[13]. Thus, like PIPC, TAZ seems to show an increase of Vd in infected patients. When the final model was evaluated, homogeneous distribution along y＝x was noted with a high coefficient of regression between the predicted plasma drug level and the PRED, and the bias in the residual was also relatively small in the evaluation of CWRES. Furthermore, in the evaluation by the bootstrap method, the success rate was high, and the mean convergence rate was close to that of the final model, thus endorsing the internal validity of the population pharmacokinetic parameters measured in this study. We will be analyzed PK-PD modeling based on this PPK in Japanese.

Conflict of interest

This study was carried out without any financial support from any party. We have no conflict of interests to declare.

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