Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 1, 2012

Research Article

PHARMACODYNAMIC TARGET ASSOCIATED WITH CLINICAL OUTCOME OF HOSPITAL-ACQUIRED PNEUMONIA TREATMENT WITH CEFOPERAZONE/SULBACTAM

NARAWADEENIAMHUN[1], DUANGCHIT PANOMVANA[1*], PINTIP PONGPECH[2], ATHAVUDHDEESOMCHOK[3]

[1]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences , Chulalongkorn University, Bangkok ,Thailand, [2]Department of Biochemistry and Microbiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand, [3]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Email: duangchit.p@chula.ac.th

Received: 5 Nov 2011, Revised and Accepted: 23 Dec 2011

ABSTRACT

Background: For anti-infective agents, pharmacodynamics (PD) parameters have been proposed as predictors of clinical and microbiological success. Hospital-Acquired Pneumonia (HAP) patients have altered pharmacokinetics (PK) that needs to be considered when dosing antibiotics. We conducted a prospective study to assess (PK/PD) of cefoperazone/sulbactam treatment in HAP patients and to identify patient and PD indices associated with clinical response.

Methods: Patients with HAP were identified, and information related to patient demographics, clinical status, antibiotic treatment and clinical outcome were documented. Cefoperazone/Sulbactam plasma concentrations were analyzed by validated High-Performance Liquid Chromatography (HPLC).Patient characteristics and PK/PD related factors were tested for associations with clinical outcome.

Results: Twenty eight patients of hospital-acquired pneumonia patients were identified. 26 patients (93.1%) had *Acinetobacterbaumannii* infection and 2 patients (6.9%) had both of *Pseudomonas aeruginosa* and *Acinetobacterbaumannii* infection. At the end of treatment, clinical cure was note in 25 % of patients (7/28), improvement 46.4% (13/28) and 28.5% (8/28) had clinical failure. For microbiology outcome, microbiological eradication was note in 12 /28 (42.9%), 12/28 (42.9%) patients had organism persistence and 4 (14.3%) patients had new infection organism.The time which total cefoperazone concentration exceed the MIC (50% T>MIC) and age of the patient who was less than 60 years were significantly associated with clinical response ($p<0.05$)

Conclusion: The percent of a dosing interval in which thecefoperazone serum concentration is above the MIC (%T>MIC) is strongly associated with clinical outcomeand is essential to the appropriate management of *A.baumanii* and *P.aeruginosa* infections.

Keyword: Pharmacodynamics, Cefoperazone/Sulbactam, Hospital-Acquired Pneumonia

INTRODUCTION

Hospital-acquired pneumonia (HAP) is currently the second mostcommon nosocomial infection in the United States, remains important causes of mortality and morbidity despite advance in antimicrobial therapy. It is growing with an estimated incidence of 5-10 cases/10000 hospital admission with the incidence increasing by as much as 6-to20-fold in mechanically ventilated patients[1].HAP is also accounts for approximately one fourth of all infection in the intensive care unit[2].This infection is commonly caused by aerobic gram-negative organisms such as *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and Acinetobacter spp., and gram-positive cocci bacteria such as *S. aureus*[3]. In a recently, *P.aeruginosa* and *A.baumannii* are becoming a major cause of nosocomial infections, including hospital-acquired and ventilator-associated pneumonia[4]. It is also indicated that *P.aeruginosa* and *A.baumannii* pneumonia are associated with severe infection and higher mortality[5,6]. Isolates of *P. aeruginosa*or *Acinetobacter* species that are resistant to all, or almost all, β-lactam antibiotics, carbapenems, aminoglycosides, and fluoroquinolones are now prevalent worldwide[4,6]. Antimicrobial agents, treatment of these organisms are often challenging. It is important for these patients to receive an appropriate antimicrobial agent as early as possible and combination therapy might be needed when choosing empirical therapy for *P.aeruginosa*and *A.baumannii* HAP infections[1,3].

For anti-infective agents, PD parameters have been proposed as predictors of clinical and microbiological success. Cefoperazone is a third generation cephalosporin used in treatment of gram positive and negative organism. Sulbactam is an irreversible inhibitor of beta lactamase; it binds the enzymeand does not allow to interact with beta-lactam antibiotic[7]. The addition of sulbactam to cefoperazone, expands the spectrum of its activity for *P.aeruginosa*and *A.baumannii*. For cefoperazone, the exposure of unbound free drug in relation to the MIC (*f* T>MIC) has been shown to correlate well with efficacy and now contribute significantly to the establishment of MIC breakpoint[8].Just as a change in an organism MIC can affect PD ratios, changes in an individual patient's PK can also affect these PD ratios. For HAP patients with serious illness, PK parameter may be notably different and differ from non-serious patient or healthy individual.

We conducted a prospective study to assess PK/PD of cefoperazone/sulbactam treatment in HAP patients and to identify patient and PD indices associated with clinical and microbiological response.

MATERIALS AND METHODS

Study population

The protocol was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, Thailand. Twenty-eight adult hospital-acquired pneumonia patients who admitted to the internal medical department, Maharaj Nakorn Chiang Mai hospital were enrolled. HAP was diagnosed based on The American Thoracic Society (ATS) and the Infectious Disease Society (IDSA) criteria. Inclusion criteria for this study were following: age over 15 years old, admission for treatment of HAP with recent sputum culture being positive for *P.aeruginosa* or *A.baumannii*; were currently receiving cefoperazone/sulbactam and the regimen were stable for at least 3 days. Patients were excluded if they had either one of the following condition: were pregnant, possibly pregnant, or breastfeeding; had history of hypersensitivity reaction to any β-lactam antibiotics and β-lactamase inhibitor; received cefoperazone/sulbactam within 1 week before enrollment; had history of hepatic disease (AST and/or ALT > 3

times of the upper limit) ;had history of biliary obstruction; had severe renal insufficiency (CrCL<30 ml/min or renal dialysis); had immunologic or hematologic impairment. Before participation in the study, informed consent was obtained from each subject or his/her parents after explaining purpose of the study, the process and the risk-benefit of the study.

Cefoperazone/Sulbactam pharmacokinetics

Serial blood samples for determination of cefoperazone and sulbactam concentrations were collected after fifth dose from a forearm vein via an intravenous catheter at before the dose and 10 minutes, 2 and 4 hours after administration. Approximately five ml were collected into the heparined tube, chilled at 0°C. The blood samples were centrifuged at 3000 rpm for 15 minutes. Plasma were removed and placed in glass tubes. They were immediately frozen at -40°C until analysis.

The samples were assayed by a validated high-performance liquid chromatography. Cefoperazone and sulbactam were extracted from human plasma by liquid-liquid extraction method. The HPLC system consists of a C18 column (Hypersil, 250 x 4 mm, 5 μm; Agilent Teachnologies, USA) with column temperature of 25°C. Elutants were detected using UV detector where an emission wavelength was set at 220 nm. The isocratic mobile phase were acetonitrile: methanol: 5mM tetrabutylammomiumhydroxide (13:9:78), pH=6.4 for cefoperazone and acetonitrile: 5mM tetrabutylammomiumhydroxide (25:75) pH=6.5 for sulbactam.

The data on pharmacokinetic parameters of cefoperazone/sulbactam were analyzed by one-compartment pharmacokinetic model using the WinNonlin Professional (Ver. 3.2; Pharsight Corporation, USA). Log mean concentration-time profiles were graphed for each subject. The maximum concentration (Cmax) was obtained directly from a plot of concentration-time data. The terminal elimination rate constant (Ke) was obtained by least squares regression analysis of the terminal phase of the log-linear plot of concentration-time data. Individual half-life values were calculated as 0.693/ke. The Area under the concentration-time curve (AUC) was calculated using the linear-trapezoidal rule. Systemic clearance was estimated as dose/AUC.

Pharmacodynamic analysis

%T>MIC was estimated based on equation %T>MIC = ln (Dose*/(Vd*MIC))*($t_{1/2}$/0.693)*(100/DI)and %*f*T>MIC was estimated based on equation %*f*T>MIC = ln (Dose**f*u/(Vd*MIC))*($t_{1/2}$/0.693)*(100/DI)[9], where*f*u is a free fraction unbound, Vd is the apparent volume of distribution in the central compartment (L/kg),Ke is the elimination rate constant (h^{-1}), DI is the dosing interval (h), MIC is the minimum inhibitory concentration for the *A.baumannii* and *P.aeruginosa.* MICs were determined using E-test® (AB biodisk, Solna, Sweden).Bactericidal pharmacodynamic target was defined as 50% *f*T>MIC for cefoperazone/sulbactam[10].

Response

All eligible patients were assessed for a clinical and microbiological response. A clinical evaluation was performed on day 1, day 3, day 7 or the end of cefoperazone/sulbactam treatment.

Clinical responses were assessed as follow:

Cure: Suandok clinical points of cure were used to determine clinical cure of treatment. The criteria were: no fever (>37.3°C) more than 24 hours, absence or non-purulent sputum, no more vasoactive drug more than 24 hours, CPIS score<6, chest X-ray shows no progression/cavities/effusion.

Improved: The resolution of all signs and symptoms, continued stable signs upon discontinuation of antibiotic therapy, and no subsequent need of antibiotics for treatment of relapse with the follow-up period or decreased CPIS score.

Failure: Any of the following conditions: persistence or progression of signs and symptoms of infection, development of new active infection, or death because of infection or unchanged or increased CPIS

Microbiological outcome were assessed as follow:

Cure: Elimination of the *P.aeruginosa* or *A.baumannii* from the site of original isolation (sputum) during completion of therapy or absence of sputum for culture and evaluation.

Failure: Persistence of the organism, whether or not it had acquired resistance.

Stastistical Analysis

Continuous variables were given as mean ± S.D. Comparative analysis to identify variables associated with clinical response were done with λ^2 test or Fisher's exact test. All tests were two tailed; $p < 0.05$ were considered to be statistically significant.

RESULTS

Study population

There were 28 patients of hospital-acquired pneumonia patients enrolled in our study. 26 patients (93.1%) had *A.baumannii* infection and 2 patients (6.9%) had both of *P.aeruginosa* and *A.baumannii* infection. The characteristics of the 28 patients of HAP studied were presented in Table 1. The average age was 61.1(±15.9) years. The male to female ratio was 20:8. Seven patients who were admitted to general internal medical ward and twenty-one patients were admitted to medicine sub ICU and medicine ICU ward. 35.7% (10/28) of patients had cardiovascular disease, 32.1% (9/28) of patients had cerebrovascular disease and 28.6% (8/28) of patients had chronic lung disease. Most of patients, 26 of 28 patients had mechanical ventilator. 14 patients had co-infection with HAP, which were urinary tract infection and septicemia 20.7 % and 13.8%, respectively.

Pharmacokinetic/Pharmacodynamic analysis

Antibiotic pharmacokinetic parameters, MIC data and pharmacodynamic indices are summarized in Table 2.Wide inter-subject variability was seen with coefficients of variationfrom 32.64-41.07% for Vd of cefoperazone, 38.89-45.83% for T1/2 of cefoperazone and 34.90-42.00% for Vd of sulbactam, 40.93-72.50% T1/2 of sulbactam. As predicted from laboratory abnormalities and the greater physiologic variability by these HAP patient compared with normal subjects, several observations are supportive of greater inter-subject pharmacokinetic variability in patients as well. The Coefficient variation for CL in these patients was approximately double for cefoperazone (CL = 1.82±0.81 L/h) and sulbactam (6.80±4.30) compared with that previously reported normal subjects (CL= 4.55±0.79, CL =18.07±2.75, respectively)[11].Therefore, the physiologic alteration and variability imposed by serious infection patients may be manifested, as well as altered mean pharmacokinetic parameter values.

Following dose 1 g I.V. q 12 h, 2 g I.V q 12 h and 2 g I.V. q 8 h, the mean terminal eliminate half-life was 5.04, 6.64, and 7.72 h, respectively for cefoperazone and 2.62, 2.64, and 2.32 h, respectively for sulbactam. The volume of distribution was 10.44, 15.94, and 18.97 L, respectively for cefoperazone and 21.45, 25.25, and 22.39 L, respectively for sulbactam. Both of cefoperazone and sulbactam, the pharmacokinetic parameters, CL, Vd, Ke, T1/2 were not significant different when comparing between dosing regimens.

Response to treatment

The average length of treatment with cefoperazone/sulbactam treatment was 11.38 days (±3.58 days). At the end of treatment, clinical cure was note in 7 (25.0%), improvement in 13 (46.4%), and 8 patients (28.5%) had clinical failure.The results are shown in Table 2. During the treatment, Microbiology outcome, microbiological

eradication was note in 12 (42.9%) of the patient, while 12 (42.9%) of the patient had the organism persistence in their sputum, however, these patients had either clinical improvement or clinical failure. 4 patients (14.3%) had the new infection organism or superinfection with *P.aeruginosa, K.pneumoniae,* MRSA.

Univariate analyses are presented in Table 3, total cefoperazone/sulbactam concentration exceed the MIC more than 50% of the dosing interval (50% T>MIC) and age less than 60 year old were significantly associated with clinical response (p=0.038, and p= 0.038, respectively).

Table 1: Patient demographics for 28 cases of *A.buamanni* and *P.aeruginosa* hospital-acquired pneumonia

Characteristic	Mean ± S.D. or No. (%) patients
Age (years)	61.1±15.9 (17-82)
Gender (male)	20 (69%)
Weight (kg)	53.13±74.15
Ward of admission	
General medical ward	7(24.1%)
Medical sub ICU or ICU ward	21(62.1%)
Co-morbidity	
Cardiovascular disease	10(35.7%)
Cerebrovascular disease	9(32.1%)
Chronic lung disease	8(28.6%)
Diabetes	2(7.1%)
Malignancy	2(7.1%)
Co-infection	
Urinary tract infection	6(20.7%)
Septicemia	4(13.8%)
Vascular catheter/skin infection	4(13.8%)
Antibiotic combination	
Single antibiotic	11(39.3%)
Co-administration	17(60.7%)
Inotropes	3(10.3%)
Mechanical ventilation	26(92.6%)
Duration of cefoperazone/sulbactam treatment (days)	11.38(±3.58)
CPIS score (day 1)	6.83(±1.39)

Table 2: Antibiotic pharmacokinetic parameters and pharmacodynamic indices of cefoperazone in patients with *A.baumannii* and *P.aeruginosa* hospital acquired pneumonia

Pt.	regimen	Vd (L)	T1/2 (h)	MIC (µg/ml)	50% T>MIC	Clinical outcome	Microbiological outcome
1	2 g q 12h	16.0	7.73	16	Y	Improve	Eradicate
2	2 g q 12h	15.25	10.82	12	Y	Improve	New infection
3	2 g q 12h	16.44	4.91	12	Y	Cure	Eradicate
4	2 g q 12h	21.40	5.29	16	Y	Cure	Eradicate
5	2 g q 8h	19.47	7.00	16	Y	Cure	Persistent
6	2 g q 12h	13.88	4.45	12	Y	Cure	Eradicate
7	1 g q 12h	9.18	4.14	32	N	Failure	New infection
8	1 g q 12h	5.19	2.44	64	N	Failure	Eradicate
9	2 g q 12h	17.04	6.02	16	Y	Improve	New infection
10	2 g q 12h	19.13	4.35	16	N	Cure	Persistent
11	2 g q 12h	15.67	6.78	32	Y	Improve	Eradicate
12	2 g q 8h	21.75	7.69	12	Y	Failure	Eradicate
13	2 g q 12h	13.54	6.52	32	Y	Improve	Eradicate
14	1 g q 12h	15.46	6.08	12	Y	Improve	Persistent
15	2 g q 12h	9.12	3.61	32	N	Failure	Persistent
16	2 g q 12h	10.71	4.23	16	N	Improve	Persistent
17	2 g q 12h	11.81	5.23	12	Y	Improve	Persistent
18	2 g q 12h	12.59	12.99	4	Y	Improve	Eradicate
19	2 g q 12h	11.50	7.51	24	Y	Failure	Persistent
20	2 g q 12h	15.41	5.50	24	Y	Improve	Persistent
21	2 g q 8h	15.07	11.46	24	Y	Cure	Persistent
22	1 g q 12h	8.17	8.46	32	Y	Failure	New infection
23	1 g q 12h	14.18	4.06	32	N	Improve	Persistent
24	2 g q 12h	32.32	5.01	16	Y	Cure	Eradicate
25	2 g q 8h	27.51	9.21	48	N	Failure	Persistent
26	2 g q 12h	15.04	8.01	32	Y	Failure	Persistent
27	2 g q 12h	20.07	10.59	12	Y	Improve	Eradicate
28	2 g q 8h	11.07	3.25	8	Y	Improve	Eradicate

Y as achieved pharmacodynamic target at 50%T>MIC, and N as not achieved pharmacodynamic target at 50% T>MIC

Table 3: **Factor associated with clinical response in patients with *A.baumannii* and *P.aeruginosa* hospital acquired pneumonia**

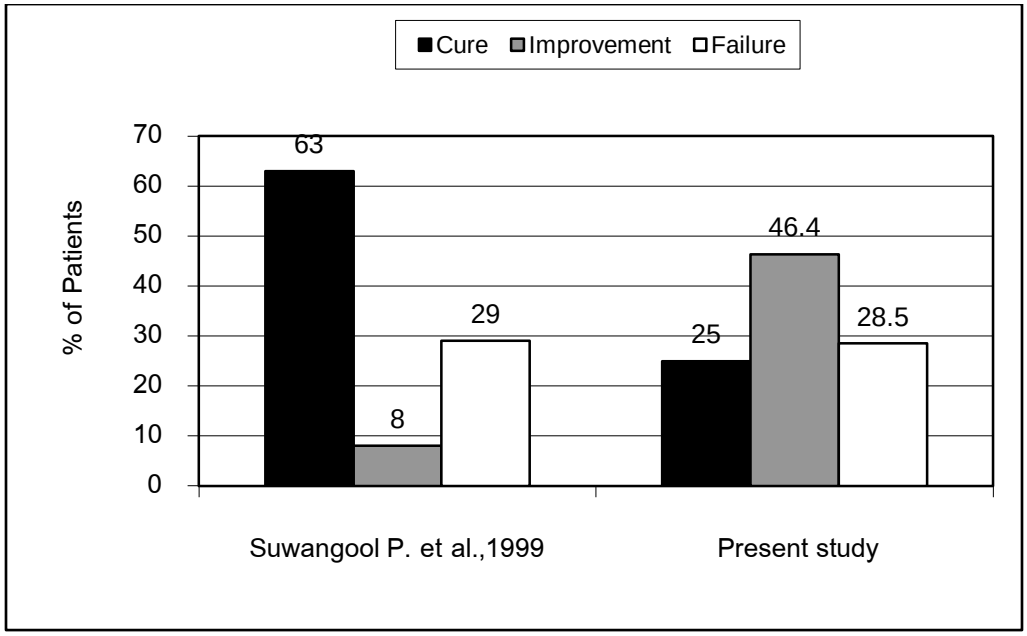
Variable	No.(%) patient, mean ± S.D.		
	Clinical cure/improvement (n=20)	Clinical failure (n=8)	*P* value
Age less than 60 years	12	1	0.038[a]
Chronic lung disease	4	4	0.172
Cardiovascular disease	7	3	0.669
Cerebrovascular disease	8	2	0.063
Diabetes mellitus	1	1	1.000
Malignancy	1	1	0.497
Co-infection	10	4	1.000
Mechanical ventilation	18	8	1.000
Use of combination antibiotics	12	5	0.657
Achieved 50% T>MIC for cefoperazone/sulbactam	18	4	0.038 [a]
Achieved 50%*f*T>MIC for cefoperazone/sulbactam	1	0	1.000

[a] significantly difference $p < 0.05$

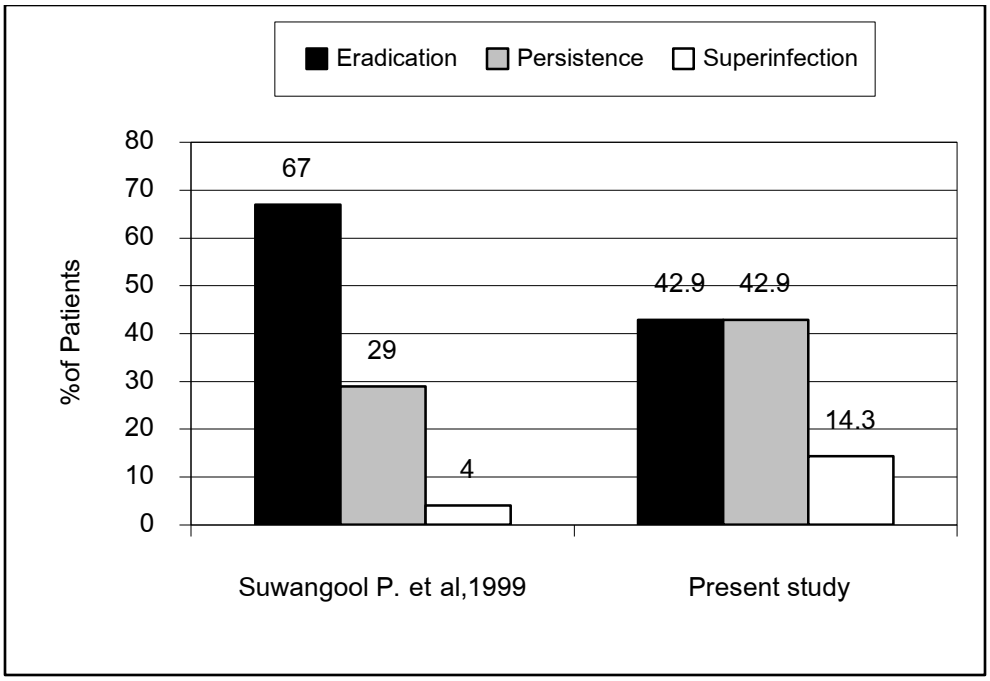
DISCUSSIONS

This study identified factors associated with clinical outcome of HAP treatment with cefoperazone/sulbactam and we have detected significant relationship between cefoperazone concentrations, organism susceptibility and therapeutic response. There were no difference in treatment outcome between patients who received monotherapy and those who were given a combination of antibiotics. ATS and IDSA guidelines[1], for treatment of patients with HAP plus risk factors for MDR pathogens, recommended the combined therapy of an antipseudomonalβ-lactam, or β-lactam/β-lactamase inhibitor, plus an antipseudomonalfluoroquinolone or aminoglycoside. However, in our hospital, the fluoroquinolones and aminoglycosides were only approximately 50% of *P.aeruginosa* and lesser than 30% of *A.baumannii*were susceptible to fluoroquinolones and aminoglycosides, that might explain why combination the therapy in our study did not show significant advantage over monotherapy.

At the end of treatment, clinical cure was note in 7 patients (25.0%), improvement in 13patients (46.4%), while 8 patients (28.5%) had clinical failure. Microbiology outcome were observed during the treatment, microbiological eradication was note in 12 patients (42.9%), while 12 patients (42.9%) had persistent organism in their sputum; the clinical outcome of these patients could be either clinical improvement or clinical failure. The rest 4 patients (14.3%) had new infection organism or superinfection with *P.aeruginosa, K.pneumoniae,*MRSA. In 1999, SuwangoolPet.al.[12], performed a study in three hospital in Thailand to assess the activity of cefoperazone/sulbactam treatment in 24 patients with nosocomial pneumonia which showed similar results. The most common causative agent was *P.aeruginosa* (37.5% of cases), followed by *K.pneumoniae* and *A.baumannii* (16.7% each). The patients were treated with cefoperazone/sulbactam 1-2 g twice daily for mean duration of 13 days. Results of the therapy were encouraging, with response being seen in 71% of patients (63% cure, 8% improvement) The microbiologic response showed eradication in 67% of the patients, persistence in 29% and superinfection in only one patient. Our study, showed lower success rate of treatment compared to aforementioned study. The drug resistance may subsequently become a problem after a number of years of use. Comparisons the results between the two studies are shown in Figure 1



(A) Clinical outcome



(B) Microbiology outcome

Fig. 1: Efficacy of cefoperazone/sulbactam in the treatment of nosocomial pneumonia.

In this study, we examined the pharmacokinetics of cefoperazone/sulbactam in HAP patients. Population of ill patient always has lower drug clearance, larger volume of distribution, and longer terminal half-life than those seen in healthy volunteer population[13].Pharmacokinetics parameter of cefoperazone and sulbactamwere estimated after multiple intravenousinjections. Wide inter-subject variability was seen with coefficients of variation ranged from32.64-45.83% for pharmacokinetic parameters of cefoperazone and 34.90-72.50% for sulbactam. As could be predicted from laboratory abnormalities greater physiologic variabilities of these HAP patients as compared with normal subjects were noticed. Several previous observations also supported greater inter-subject pharmacokinetic variabilities in patients as compared to healthy volunteers as well. Therefore, the physiologic alteration and variability imposed by serious infection patients may be manifested, as well as altered mean pharmacokinetic parameter values.

Fromchi-square analyze, at least 50% of the time during a dose interval in which the total cefoperazone/sulbactam concentration was exceed the MIC (50% T>MIC) and age of the patient which was less than 60 year old were significantly associated with clinical response. Even though many previous studies, demonstrated that %*f*T>MIC is the best predictor for outcome of β-lactams treatment,the present study indicated that 50% free T>MIC was not significantly associated with clinical response. Protein binding is a rapid process that it is produces a reversible interaction process between antibiotic and protein. In HAP patients, protein binding could be altered by several conditions, such as, elderly patients, hypoalbuminemia, stress, infection, etc. Effect of protein binding depends upon the extent of plasma protein binding and the relative affinity to plasma protein and bacterial receptor sites. The unboundfree fraction of 0.1 for cefoperazonemay not suitable to put directly in the equation used to calculates the %*f* T>MIC. This same situation may also be used to explain why ceftriaxone (95% protein bound) provides activity at below its MIC, even though failure would be predicted. The effect of protein binding required much further investigations for better understanding the pharmacodynamics of β-lactams. If an optimal PD index could not be achieved with a single agent, a second drug should be added.

In conclusion, By considering PK of cefoperazonevariability and the MIC of the organism, PD models can be estimated to help us optimize cefoperazone/sulbactam dosing in HAP patients.

ACKNOWLEDGEMENT

This study was supported by a research grant from THE 90TH ANNIVERSARY OF CHULALONGKORN UNIVERSITY FUND (Ratchadaphiseksomphot Endowment Fund).

REFERENCES

1. American Thoracic Society (ATS). Guideline for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J RespirCrit Care Med 2005; 171: 388-416.
2. Beardsley JR, Williamson JC, Johnson JW, Ohl CA, Karchmer TB, Bowton DL. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. Chest 2006; 130:787-793.
3. Bakry MM, Mustafa S, Omar MS, Antimicrobial therapy in critically ill patients with nosocomial infections. Int J Pharm PharmSci 2011; 3: 340-342.
4. Paterson DL. The Epidemiological Profile of Infections with Multidrug-Resistant *Pseudomonas aeruginosa* and *Acinetobacter* Species. ClinInfect Dis 2006;43 Suppl2: S43-48.
5. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluation attributable mortality and hospital stay. Am J Med1993; 94: 281-288.
6. Arora D, Jindal N, Romit RK, Emerging antibiotic resistance in pseudomonas-a challenge.Int J Pharm PharmSci 2001; 3: 82-84.
7. Palanikumar BP, Thenmozhi A, Sridharan D. An RP-HPLC Method for simultaneous estimation of ceftriaxone sodium and sulbactam

sodium in injection dosage form. Int J Pharm PharmSci 2010; 2: 34-36.

8. Higgins PG, Wisplinghoff H, Stefanik D, Seifert H. In vitro activities of the β-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with β-lactams against epidemiologically characterized multidrug-resistant *Acinetobacterbaumannii* strains. Antimicrob Agents Chemother 2004; 48:1586-1592.
9. Turnidge J. What can be done about resistance to antibiotics? BMJ. 1998; 317:645-647.
10. Wang H, Zhang B, Ni Y, Kuti JL, Chen B, Chen M, Nicolau DP.Pharmacodynamic Target Attainment of Seven Antimicrobials against GramnegativeBacteria collected from China in 2003 and 2004. Int J of AntimicrobAgents 2007; 30:452-457.
11. Reitberg DP, Whall TJ, Chung M, Blickens D, Swarz H, Arnold J. Multiple dose pharmacokinetics and toleration of intravenously administered cefoperazone and sulbactam when given as single agents or in combination. AntimicrobAgents and Chemother1988; 32: 42-46.
12. Suwangool P, Leelasupasri S, Chuchottaworn C. Treatment of nosocomial pneumonia with cefoperazones/sulbactam. J Infect Dis Antimicrob Agents1999; 16: 65-8.
13. Reitberg DP, Marble DA, Schultz RW, Whall TJ, Schentag JJ, Pharmacokinetics of cefoperazone (2.0g) and sulbactam (1.0g) coadministered to subjects with normal renal function, patients with decreased renal function, and patients with end-stage renal disease on hemodialysis. Antimicrob Agents and Chemother1988; 32: 503-509.