Original Article

เภสัชจลนศาสตร์และชีวสมมูลของยาฉีดซื่อสามัญเซโฟเปอราโซน/ ซัลแบคแทม ในอาสาสมัครคนไทยสุขภาพดี

เชิดชัย สุนทรภาส[1]*, จุฬาภรณ์ ลิมวัฒนานนท์[1], บังอร ศรีพานิชกุลชัย[2], ธานี เทศศิริ[1], ภิรุญ มุตสิกพันธุ์[3]

บทคัดย่อ

เภสัชจลนศาสตร์และชีวสมมูลของยาฉีดซื่อสามัญเซโฟเปอราโซน/ ซัลแบคแทมในอาสาสมัครคนไทยสุขภาพดี

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บทนำ : สำนักงานคณะกรรมการอาหารและยามีข้อกำหนดให้ผลิตภัณฑ์ยาซื่อสามัญต้องมีข้อมูลการทดสอบชีวสมมูลประกอบการขึ้นทะเบียนยา การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาชีวสมมูลของยาสูตรผสม cefoperazone/sulbactam (1/0.5 กรัม) ระหว่างผลิตภัณฑ์ยาซื่อสามัญและผลิตภัณฑ์ต้นแบบโดยการฉีดเข้ากล้ามเนื้อ **วัสดุและวิธีการ :** การศึกษาเป็นแบบการให้ยาเพียงครั้งเดียว สองช่วง โดยเว้นระยะห่างกัน 1 สัปดาห์ สองลำดับ สุ่มสลับ ปกปิดสองด้าน ในอาสาสมัครคนไทยสุขภาพดี 20 คน เก็บตัวอย่างเลือดของอาสาสมัครก่อนให้ยาและที่เวลา 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 และ 12 ชั่วโมง หลังให้ยาฉีด cefoperazone/sulbactam (1/0.5 กรัม) โดยการฉีดเข้ากล้ามเนื้อ วิเคราะห์หาความเข้มข้นของยาในพลาสมาโดยวิธีไฮเพอฟอร์มานลิควิดโครมาโตกราฟี และวิเคราะห์ค่าตัวแปรทางเภสัชจลนศาสตร์โดยใช้แบบจำลอง non-compartment และวิเคราะห์ค่าทางสถิติโดยใช้ Wilcoxon Signed Rank test และ ANOVA **ผลการศึกษา :** เวลาที่ได้ความเข้มข้นสูงสุดในพลาสมาของยา cefoperazone และ sulbactam ทั้งผลิตภัณฑ์ซื่อสามัญและผลิตภัณฑ์ยาต้นแบบไม่แตกต่างกันอย่างมีนัยสำคัญ ($p > 0.05$) ค่าความเข้มข้นสูงสุดของยาในพลาสมา พื้นที่ใต้เส้นโค้งของกราฟความสัมพันธ์ระหว่างความเข้มข้นของยาในพลาสมากับเวลาถึงเวลาที่เก็บตัวอย่างครั้งสุดท้าย และพื้นที่ใต้เส้นโค้งของกราฟความสัมพันธ์ระหว่างความเข้มข้นของยาในพลาสมากับเวลาถึงเวลาอนันต์ของยา cefoperazone/sulbactam ของผลิตภัณฑ์ยาซื่อสามัญมีค่าเท่ากับ 61.9 ± 20.3/25.5 ± 10.4 มคก./มล. 247.4 ± 63.7/64.2 ± 21.3 มคก.ชม./มล. และ 264.8 ± 64.7/69.2 ± 24.0 มคก.ชม./มล. ตามลำดับ ส่วนค่าพารามิเตอร์ของ cefoperazone/sulbactam ของผลิตภัณฑ์ยาต้นแบบมีค่าเท่ากับ 59.4 ± 17.7/25.5 ± 8.0 มคก./มล. 245.0 ± 66.5/65.4 ± 22.4 มคก.ชม./มล. และ 258.8 ± 67.4/70.6 ± 24.8 มคก.ชม./มล. ตามลำดับ **สรุปผล :** ยาฉีด cefoperazone/sulbactam (1.0/0.5 g) ผลิตภัณฑ์ยาซื่อสามัญและผลิตภัณฑ์ยาต้นแบบในการศึกษาครั้งนี้มีชีวสมมูลกัน โดยมีช่วงความเชื่อมั่นที่ 90% ของอัตราส่วนของความเข้มข้นสูงสุดของยาในพลาสมา หรือพื้นที่ใต้เส้นโค้งของกราฟความสัมพันธ์ระหว่างความเข้มข้นของยาในพลาสมากับเวลาถึงเวลาที่เก็บตัวอย่างครั้งสุดท้าย หรือถึงเวลาอนันต์ในรูปลอการิทึมระหว่างแบบผลิตภัณฑ์ยาซื่อสามัญและผลิตภัณฑ์ต้นแบบอยู่ในช่วงที่กำหนดว่าเท่าเทียมกัน (0.80-1.25) และไม่พบความแตกต่างระหว่างค่าพารามิเตอร์ทางเภสัชจลนศาสตร์อื่นๆ

คำสำคัญ: ชีวสมมูล, cefoperazone, sulbactam

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Abstract

Pharmacokinetic and bioequivalence of cefoperazone/sulbactam injection in healthy Thai volunteers

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Introduction : Bioequivalence study of a generic drug is a registration requirement regulated by the Thai Food and Drug Administration. The present study was performed to assess the bioequivalence of a generic formulation of cefoperazone/sulbactam (1.0/0.5 g) compared with an innovator's formulation both by intramuscular injection. **Material and method :** A single dose, two period, two sequence, double blind, randomized cross-over with a one-week washout period was used. Twenty healthy Thai volunteers were recruited into the present study. All subjects were intramuscularly injected with a single dose of cefoperazone/sulbactam (1.0/0.5 g). Blood samples were collected before injection and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after injection. Plasma concentrations of cefoperazone and sulbactam were assayed by a validated HPLC method. The pharmacokinetic parameters were calculated using a non-compartmental model and Wilcoxon Signed Rank test and ANOVA were used for statistical testing. **Results :** Time to reach the peak concentration of cefoperazone and sulbactam in all volunteers who were injected with either generic or innovator's product were not significantly different ($p > 0.05$). Maximum concentration, area under the concentration time curve from time 0 to time t and area under the concentration time curve from time 0 to time infinity of cefoperazone/sulbactam were 61.9 ± 20.3/25.5 ± 10.4 µg/mL, 247.4 ± 63.7/64.2 ± 21.3 µg.h/mL and 264.8 ± 64.7/69.2 ± 24.1 µg.h/mL, respectively, for the generic pro duct and 59.4 ± 17.7/25.5 ± 8.0 µg/mL, 245.0 ± 66.5/65.3 ± 22.4 µg.h/mL and 258.8 ± 67.4/70.6 ± 24.8 µg.h/mL, respectively for the innovator's product. **Conclusion :** The generic and innovator's product of cefoperazone/sulbactam (1.0/0.5 g) injections used in the present study were bioequivalent. The 90% confidence intervals of the log transformed data of ratio of Cmax, AUC0-12h or AUC0-∞ between generic and innovator's product, both cefoperazone and sulbactam, were within the bioequivalence range of 0.80-1.25. Other pharmacokinetic parameters of both products were not significantly different.

Keyword: bioequivalence, cefoperazone, sulbactam

Introduction

Cefoperazone is a parenteral third generation cephalosporin with a broad antibacterial spectrum including *Pseudomonas aeruginosa*. As the prevalence of multidrug resistant microorganisms has been increasing, various methods have been offered to overcome this problem. Sulbactam, a beta-lactamase inhibitor, is combined with cefoperazone for synergistic effect and it expands the spectrum of activity of cefoperazone against many beta-lactamase-producing bacteria (Munoz *et al.*, 1996). This combination has been very useful for treating several types of infection such as skin, intra-abdominal, urinary tract and respiratory tract infections as well as gynecological infection (including pelvic inflammatory disease and endometriosis), and septicemia caused by susceptible microorganism (Killion *et al.*, 2003; McEvoy, 2002; Munoz *et al.*, 1996)

In Thailand, the combinations of cefoperazone sodium and sulbactam sodium have been commercially available for parenteral administration as sterile powder containing cefoperazone/sulbactam 500/500 mg or 1.0/0.5 g. There are many preparations of cefoperazone and sulbactam injections available on the market including Sulperazon® injection, the innovator's product, and many generic products without well-defined bioequivalence. As the bioequivalence study of generic drugs are a registration requirement regulated by both

the US and Thai Food and Drug Administration (CDER, 2001; DCD, 2007), the objective of the present study was to conduct a bioequivalence study between a generic and an innovator's product of cefoperazone/sulbactam. If the test products are bioequivalent, physicians can have an alternative choice for treating infection in patients with cheaper in drug cost and more confidence in therapeutic efficacy.

Material and method

Subjects

Twenty healthy Thai volunteers, 14 male and 6 female, aged between 21-28 years old with body mass indexes within 19-25 kg/m2 participated in the present study. Volunteers were in good health based on their medical histories, physical examinations, routine blood tests including complete blood count with differential count and blood chemistry profiles as well as having a negative screening test for hepatitis B surface antigen and anti-HIV. Volunteers with known contraindication or hypersensitivity to either cefoperazone or sulbactam were excluded as well as those with a known history of alcohol consumption or cigarette smoking. Drug and caffeine beverage were not allowed 1 week before the study period to avoid the effects of inducing or inhibiting hepatic metabolizing enzyme and the risk of drug interactions. The protocol of the present study was approved by the Ethical Committee for Human Research, Faculty of Medicine, Khon Kaen University (Reference number HE490141) and the Drug Control Division, Thai Food and Drug Administration, Ministry of Public Health, Thailand (Reference number 38/49). All volunteers signed an informed consent form prior to participating in the present study.

Study drug

The test product was a generic product (cefoperazone/sulbactam injection, Lot No. RDSC 09, MFD. 06/10/2007, Utopian Co., Ltd., Thailand) in the dosage of 1.5 g (cefoperazone 1 g/sulbactam 0.5 g). The reference product was an innovator's product (Sulperazon® injection, Reg No. 2C1/47 (N), Lot No. 739094, MFD. 11-2006, EXPD.11-2008, Pfizer Italia, Italy) in the dosage of 1.5 g (cefoperazone 1 g/ sulbactam 0.5 g).

Method of drug administration

A single dose, two treatment, two period, two sequence, double blind, randomized cross-over with one-week washout period was used. Subjects were admitted at Queen Sirikit Heart Center of the Northeast, Khon Kaen University on the study day. After an over night fast, each volunteer received a single gluteal intramuscular injection of either generic or innovator's product of cefoperazone/sulbactam (1/0.5 g). Blood samples were collected via an intravenous catheter with saline lock at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug administration. Then, the plasma was separated immediately by centrifugation and stored at -80°C until analysis for cefoperazone and sulbactam content.

Determination of the plasma cefoperazone and sulbactam concentrations

Plasma samples were prepared by liquid-liquid extraction. The concentrations of cefoperazone and sulbactam in plasma were analyzed using a validated High Performance Liquid Chromatography adapted from previous studies (Muder *et al.*, 1982; Reitberg *et al.*, 1988; Rogers *et al.*, 1983). The HPLC system consisted of a C18 column (Nova-pack C18 3.9 x 150 mm, 5 µm, Water Technologies, USA) with column temperature of 25°C. The isocratic mobile phases were 0.02 M tetrabutylammonium hydroxide and 0.01 M tribasic sodium phosphate adjusted to pH 3.5 : acetonitrile (23:77) for cefoperazone, and 5 mM tetrabutylam monium hydroxide and 1 mM disodium hydrogen phosphate and 1 mM sodium dihydrogen phosphate solution : acetonitrile (75:25) for sulbactam. Column elutes were monitored at wavelength 205 nm for cefoperazone and wavelength 320 nm for sulbactam.

The validations of the analysis method e.g. specificity, accuracy, precision, lower limit of quantification (LLOQ), linearity, extraction recovery, were performed before drug analysis. Standard curves were performed every day of analysis.

Pharmacokinetic parameters and statistical analysis

Plasma concentration-time course profiles were plotted and pharmacokinetic parameters were determined. Maximum plasma concentration (C_{max}) which represented the maximum extent of the drug entry into the blood circulation and time to reach the peak concentration (T_{max}) which represented the rate of the drug entry into the blood circulation were taken from the raw data. Area under the concentration time curve from time 0 to last measuring point (AUC_{0-t}), which represented the extent of the drug entry into the blood circulation, were determined using the trapezoidal rule. The area under the concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-\infty} = AUC_{0-t} + Ct/ke$, where Ct is the last measurable drug concentration and ke is the elimination rate constant calculated by linear regression of at least the last three data points. Elimination half-life (t1/2) was calculated as $t1/2 = 0.693/ke$. Mean residence time (MRT) was calculated as $MRT = AUMC_{0-\infty}/AUC_{0-\infty}$, where $AUMC_{0-\infty}$ equal to area under the moment curve from time 0 to infinity. The 90% confidence interval of log transformed pharmacokinetic parameters (C_{max} or AUC) was

$$90\%\ CI = \Delta + t_{0.10,df}\sqrt{MSE\ (2/n)}$$

calculated as follows (Bolton, 1997).

where Δ is a difference in means of log transformed pharmacokinetic parameters (Cmax or AUC) between the test and the reference product, t0.10,df is the tabulated two-tailed t value for a 90% CI, df is the degree of freedom of the mean square error obtained from the ANOVA table, MSE is the mean square error from the ANOVA table, and n is the number of subjects. The antilogarithm of the calculated confidence interval will yield an exact confidence interval for the ratio. Bioequivalence between the test and reference products would be concluded if the 90% CI of the ratios of the pharmacokinetic parameters, i.e. Cmax and AUC, were in the acceptable range of 0.80 –1.25 (Bolton, 1997; USPC, 2005).

Results

Analytical method validation

For the HPLC analysis of cefoperazone, the retention time of cefoperazone and salicylic acid (internal standard) were about 14 and 19 minutes, respectively. Accuracy and precision of the method was validated with cefoperazone concentrations of 6, 24 and 48 µg/mL. Accuracy and extraction recovery were 100.48-104.49% and 97.71-100.67%, respectively. The %CV of within-run and between-run variations were 0.33-7.25 and 2.96-8.33, respectively. The standard curve was linear over the concentration ranges of 3-48 µg/mL with a mean correlation coefficient of 0.9997. The lower limit of quantification (LLOQ) of cefoperazone in plasma was 3.0 µg/mL.

For the HPLC analysis of sulbactam, the retention times of sulbactam and ranitidine (internal standard) were about 7 and 3 minutes, respectively. Accuracy and precision of the method was validated with sulbactam concentrations of 3, 18 and 36 µg/mL. Accuracy and extraction recovery were 91.99-99.38% and 97.82-99.15%, respectively. The %CV of within-run and between-run variations were 1.87-2.40 and 5.49-9.42, respectively. The standard curve was linear over the concentration ranges of 1-40 µg/mL with a mean correlation coefficient of 0.9998. The lower limit of quantification of sulbactam in plasma was 1.0 µg/mL.

Pharmacokinetic analysis

The average cefoperazone concentration–time curves and the average sulbactam concentration-time curves are shown in Fig. 1 and 2, respectively.

Pharmacokinetic parameters, i.e. AUC_{0-12h}, $AUC_{0-\infty}$, C_{max}, T_{max} of cefoperazone and sulbactam are collated in Table 1. For cefoperazone, Tmax were 1.9 h and 1.8 h, AUC_{0-12h} were 247.4 and 245.0 μg.h/mL and $AUC_{0-\infty}$ were 264.8 and 258.8 μg.h/mL and Cmax were 61.9 and 59.4 μg/mL for the generic and the innovator's product, respectively. All of these pharmacokinetic parameters were not significantly different ($p > 0.05$).

For sulbactam, T_{max} were 0.8 h and 0.9 h, AUC_{0-12h} were 64.2 and 65.4 μg.h/mL and $AUC_{0-\infty}$ were 69.2 and 70.6 μg.h/mL, C_{max} were 25.5 and 25.5 μg/mL for the generic and the innovator's product, respectively. All of these pharmacokinetic parameters were not sig-

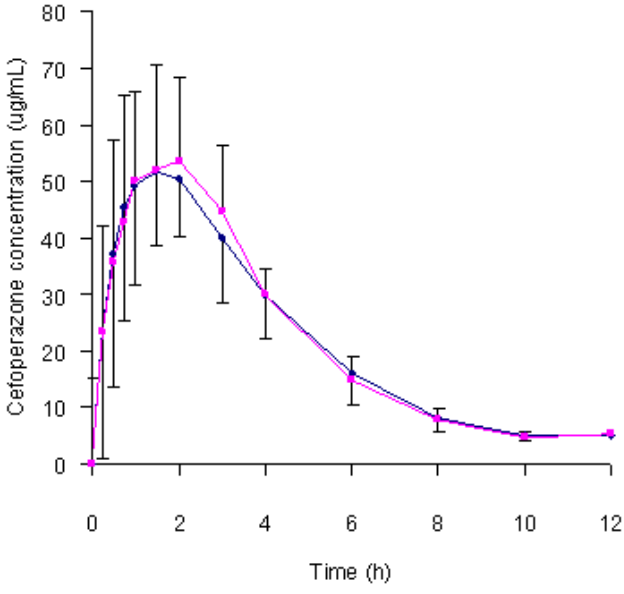

Figure 1 Average (and SD) of cefoperazone plasma concentrations at various sampling times of all volunteers after cefoperazone/sulbactam (1.0/0.5 g) IM injection. (◆) generic product (■) innovator's product (n = 20)

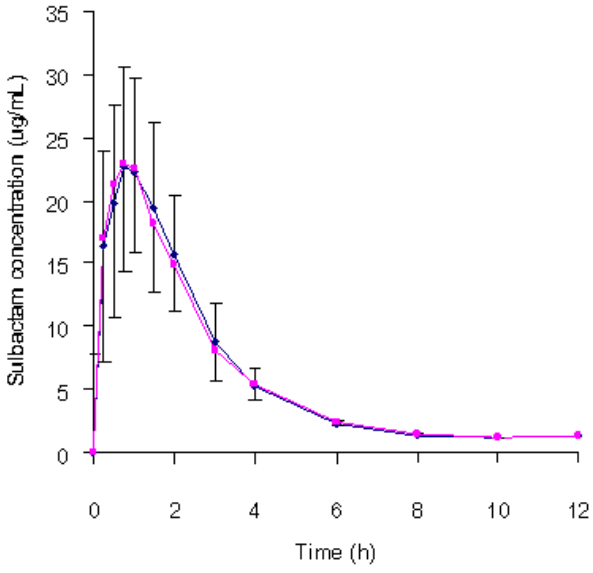

Figure 2 Average (and SD) sulbactam plasma concentrations at various sampling times of all volunteers after cefoperazone/sulbactam (1.0/0.5 g) IM injection. (◆) generic product (■) innovator's product (n = 20)

Table 1. Pharmacokinetic parameters of cefoperazone and sulbactam from the generic and the innovator's product. (n = 20)

Active ingredient	Pharmacokinetic parameter	Generic product	Innovator'sproduct	p-value*
Cefoperazone	C_{max} (µg/mL)	61.9 ± 20.3	59.4 ± 17.7	0.459
	T_{max} (h)	1.9 ± 0.8	1.8 ± 0.9	0.543
	AUC_{0-t} (µg.h/mL)	247.4 ± 63.7	245.0 ± 66.5	0.671
	$AUC_{0-\infty}$ (µg.h/mL)	264.8 ± 64.7	258.81 ± 67.4	0.419
	k_e (h^{-1})	0.3 ± 0.1	0.3 ± 0.1	ND
	$t_{1/2}$ (h)	2.6 ± 1.4	2.1 ± 0.6	ND
	MRT (h)	4.2 ± 1.2	4.2 ± 1.4	ND
Sulbactam	C_{max} (µg/mL)	25.5 ± 10.4	25.5 ± 8.0	0.623
	T_{max} (h)	0.8 ± 0.3	0.8 ± 0.4	0.727
	AUC_{0-t} (µg.h/mL)	64.2 ± 21.3	65.4 ± 22.4	0.431
	$AUC_{0-\infty}$ (µg.h/mL)	69.2 ± 24.1	70.6 ± 24.8	0.334
	k_e (h^{-1})	0.5 ± 0.2	0.5 ± 0.2	ND
	$t_{1/2}$ (h)	1.8 ± 1.7	2.1 ± 2.0	ND
	MRT (h)	2.6 ± 0.9	2.9 ± 1.2	ND

*Wilcoxon Signed Rank test

ND = not determined

nificantly different ($p > 0.05$).

Bioequivalence analysis

For cefoperazone, the 90% CI of the ratio of AUC_{0-12h}, $AUC_{0-\infty}$ and Cmax between the generic and the innovator's product were 0.94-1.10, 0.96-1.11 and 0.94-1.17, respectively. For sulbactam, the 90% CI of the ratio of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} between the generic and the innovator's product were 0.94-1.03, 0.94-1.02 and 0.86-1.09, respectively as shown in Table 2. Analysis of variance for the two way cross-over test of these parameters didn't show any significant difference between the generic and the innovator's product. Assessment of sequence, period and treatment factors didn't show any significant effects on the pharmacokinetic parameters as shown in Table 3 and 4. The result supported the bioequivalence between these two products.

Adverse drug reactions

No serious side effects were noticed except for mild diarrhea on the next day after drug adminis tration in 2 volunteers with the innovator's product and 1 volunteer with the generic product. All of them recovered

Table 2. Pharmacokinetic parameters of cefoperazone and sulbactam from the generic and the innovator's product and 90% confidence interval. (n = 20)

Pharmacokinetic parameters		Difference (Ln Unit)			Ratio (Regular Unit)		
		Mean	90% confidence interval		Mean	90% confidence interval	
			Lower	Upper		Lower	Upper
Cefoperazone	C_{max}	0.048	-0.062	0.158	1.0492	0.9399	1.1712
	AUC_{0-t}	0.019	-0.058	0.097	1.0192	0.9436	1.1019
	$AUC_{0-\infty}$	0.035	-0.038	0.108	1.0356	0.9627	1.1140
Sulbactam	C_{max}	-0.034	-0.153	0.085	0.9666	0.8581	1.0887
	AUC_{0-t}	-0.021	-0.067	0.025	0.9792	0.9352	1.0253
	$AUC_{0-\infty}$	-0.024	-0.065	0.018	0.9763	0.9371	1.0182

Table 3. Analysis of variance for two-way crossover of log-transformed pharmacokinetic parameters of cefoperazone after given test products by intramuscular injection (n = 20, α = 0.05)

Tests of Between-Subjects Effects

Dependent Variable: LNC_{max}

Source		Type III Sum of Square	df	Mean Square	F	Sig.
Intercept	Hypothesis	638.339	1	638.339	3633.186	<0.001
	Error	3.163	18	0.176[a]		
PERIOD	Hypothesis	0.057	1	0.057	1.496	0.237
	Error	0.691	18	0.038[b]		
SEQUENCE	Hypothesis	0.043	1	0.043	0.243	0.628
	Error	3.163	18	0.176[a]		
DRUG	Hypothesis	0.022	1	0.022	0.574	0.459
	Error	0.691	18	0.038[b]		
SUBJECT(SEQUENCE)	Hypothesis	3.163	18	0.176	4.579	0.001
	Error	0.691	18	0.038[b]		

Dependent Variable: $LNAUC_{0-t}$

Source		Type III Sum of Square	df	Mean Square	F	Sig.
Intercept	Hypothesis	1160.418	1	1160.418	8440.466	<0.001
	Error	2.475	18	0.137[a]		
PERIOD	Hypothesis	0.007	1	0.007	0.373	0.549
	Error	0.346	18	0.019[b]		
SEQUENCE	Hypothesis	0.045	1	0.045	0.326	0.575
	Error	2.475	18	0.137[a]		
DRUG	Hypothesis	0.004	1	0.004	0.186	0.671
	Error	0.346	18	0.019[b]		
SUBJECT(SEQUENCE)	Hypothesis	2.475	18	0.137	7.143	<0.001
	Error	0.346	18	0.019[b]		

Dependent Variable: $LNAUC_{0-\infty}$

Source		Type III Sum of Square	df	Mean Square	F	Sig.
Intercept	Hypothesis	1188.595	1	1188.595	9758.846	<0.001
	Error	2.192	18	0.122[a]		
PERIOD	Hypothesis	0.016	1	0.016	0.970	0.338
	Error	0.305	18	0.017[b]		
SEQUENCE	Hypothesis	0.063	1	0.063	0.519	0.480
	Error	2.192	18	0.122[a]		
DRUG	Hypothesis	0.012	1	0.012	0.685	0.419
	Error	0.305	18	0.017[b]		
SUBJECT(SEQUENCE)	Hypothesis	2.192	18	0.122	7.183	<0.001
	Error	0.305	18	0.017[b]		

[a]test against MS(SUBJECT(SEQUENCE))

[b]test against MS(Error)

Table 4. Analysis of variance for two-way crossover of log-transformed pharmacokinetic parameters of sulbactam after given test products by intramuscular injection (n = 20, α = 0.05)

Tests of Between-Subjects Effects

Dependent Variable: LNC_{max}

Source		Type III Sum of Square	df	Mean Square	F	Sig.
Intercept	Hypothesis	390.506	1	390.506	1604.962	<0.001
	Error	4.380	18	0.243[a]		
PERIOD	Hypothesis	0.005	1	0.005	0.110	0.743
	Error	0.812	18	0.045[b]		
SEQUENCE	Hypothesis	0.012	1	0.012	0.048	0.829
	Error	4.380	18	0.243[a]		
DRUG	Hypothesis	0.011	1	0.011	0.250	0.623
	Error	0.812	18	0.045[b]		
SUBJECT(SEQUENCE)	Hypothesis	4.380	18	0.243	5.392	<0.001
	Error	0.812	18	0.045[b]		

Dependent Variable: $LNAUC_{0-t}$

Source		Type III Sum of Square	df	Mean Square	F	Sig.
Intercept	Hypothesis	655.161	1	655.161	2463.108	<0.001
	Error	4.788	18	0.266[a]		
PERIOD	Hypothesis	0.036	1	0.036	5.400	0.032
	Error	0.122	18	0.007[b]		
SEQUENCE	Hypothesis	0.012	1	0.012	0.047	0.831
	Error	4.788	18	0.266[a]		
DRUG	Hypothesis	0.004	1	0.004	0.650	0.431
	Error	0.122	18	0.007[b]		
SUBJECT(SEQUENCE)	Hypothesis	4.788	18	0.266	39.380	<0.001
	Error	0.122	18	0.007[b]		

Dependent Variable: $LNAUC_{t-\infty}$

Source		Type III Sum of Square	df	Mean Square	F	Sig.
Intercept	Hypothesis	677.501	1	677.501	2348.288	<0.001
	Error	5.193	18	0.289[a]		
PERIOD	Hypothesis	0.024	1	0.024	4.353	0.051
	Error	0.097	18	0.005[b]		
SEQUENCE	Hypothesis	0.001	1	0.001	0.003	0.960
	Error	5.193	18	0.289[a]		
DRUG	Hypothesis	0.005	1	0.005	0.985	0.340
	Error	0.097	18	0.005[b]		
SUBJECT(SEQUENCE)	Hypothesis	5.193	18	0.289	53.385	<0.001
	Error	0.097	18	0.005[b]		

[a]test against MS(SUBJECT(SEQUENCE))
[b]test against MS(Error)

without any medication.

Discussion

The pharmacokinetic parameters of cefoperazone and sulbactam from the generic and the innovator's product in 20 healthy Thai volunteers were not significantly different. The results demonstrated that Tmax of cefoperazone and sulbactam in volunteers who were injected with both generic and innovator's product were not significantly different ($p > 0.05$). In addition, the 90% confidence interval of the ratio of AUC_{0-t}, $AUC_{0-\infty}$, and Cmax for both cefoperazone and sulbactam of the generic and innovator's product were in the range of 0.80 to 1.25 as required by the United States Pharmacopeial 28 (USPC, 2005). and the Thai FDA (DCD, 2007). Therefore, bioequivalence was indicated between the generic and the innovator's product in terms of the rate and extent of drug entry into the systemic circulation.

As the protocol of this study was approved by the Drug Control Division, Thai Food and Drug Administration, Ministry of Public Health, this generic product could be a candidate for a new registration product of cefoperazone/sulbactam (1/0.5 g). The physician could use this generic product as an alternative to the innovator's product for cheaper cost of treatment. However, it should be noted that this finding was limited only to the drug lot used and healthy volunteers who participated in the present study. In addition, the therapeutic effect of long term use with multiple doses in patients should be considered for further evaluation.

Conclusion

We can conclude that bioequivalence of cefoperazone and sulbactam has been shown between the test generic and innovator's product.

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