นิพนธ์ต้นฉบับ • Original Article

การศึกษาชีวสมมูลของยา ceftazidime เมื่อให้โดยการฉีดเข้ากล้ามเนื้อในอาสาสมัครชาวไทยที่มีสุขภาพดี

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Bioequivalence Study of Ceftazidime by Intramuscular Administration in Healthy Thai Volunteers

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Background: Ceftazidime is a third generation cephalosporin that has been commercially available through several manufacturers and distributors in Thailand because of its widely clinical use. However, there is no bioequivalent study of this drug in Thais. The present study was conducted to compare the *in vivo* bioequivalent of ceftazidime obtained from an original (reference), and a local (tested) manufacturer in healthy Thai volunteers.

Objective: To determine if two ceftazidime preparations (Fortum® and Forzid®) of different manufacturers are bioequivalent when administered intramuscularly.

Design: Double-blind single-dose, two-period, randomized crossover study.

Subjects: Fourteen Healthy Thai Volunteers.

Methods and Interventions: Ceftazidime 1 g was administered intramuscularly to subjects. Blood samples were collected at predetermined intervals and assayed for ceftazidime concentration with HPLC. Pharmacokinetic parameters were calculated from the observed plasma-concentration time profiles. Maximum plasma concentration (C_{max}), time to peak concentration (T_{max}), areas under the concentration-time curve from 0 to 12 h

หลักการและเหตุผล: Ceftazidime เป็นยากลุ่ม cephalosporins รุ่นที่ 3 ซึ่งปัจจุบันถูกนำมาใช้อย่างกว้างขวางทางคลินิก ในประเทศไทยมีผู้ผลิตจำหน่ายหลายราย แต่การศึกษาด้านชีวสมมูลของยาในชาวไทยยังไม่มี งานวิจัยชิ้นนี้จึงต้องการเปรียบเทียบชีวสมมูลของยา ceftazidime ระหว่างตำรับยาเตรียมจากบริษัทต้นแบบ (ตำรับอ้างอิง) กับตำรับยาเตรียมที่ผลิตขึ้นในประเทศ (ตำรับทดสอบ) ในอาสาสมัครชาวไทยที่มีสุขภาพดี

วัตถุประสงค์การวิจัย: เพื่อศึกษาว่ายาเตรียม ceftazidime 2 ตำรับ คือ Fortum® และ Forzid® ซึ่งผลิตจากบริษัทต่างกันมีความเท่าเทียมกันทางชีวสมมูลหรือไม่ เมื่อให้กับอาสาสมัครโดยการฉีดเข้ากล้ามเนื้อ

รูปแบบการวิจัย: ให้ยาครั้งเดียว แบบ double blind ชนิดสุ่มไขว้สลับ 2 ระยะ

ประชากรที่ศึกษา: อาสาสมัครชาวไทยสุขภาพดีจำนวน 14 ราย

วิธีการวิจัย: อาสาสมัครทุกคนได้รับยาในขนาด 1 กรัม โดยการฉีดเข้ากล้ามเนื้อครั้งเดียว จากนั้นจึงถูกเก็บตัวอย่างเลือดที่ช่วงเวลาระยะต่างๆ ที่กำหนดไว้ล่วงหน้า เพื่อนำไปวิเคราะห์หาปริมาณยา cetazidime โดยวิธี HPLC ค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาคำนวณจากระดับยาในเลือดในช่วงเวลาต่างๆ ส่วนพารามิเตอร์ปฐมภูมิที่ใช้ในการตัดสินความเท่าเทียมกันทางชีวสมมูลได้แก่ค่าระดับยาสูงสุดในเลือด (C_{max}) เวลาที่พบระดับยาสูงสุดในเลือด (T_{max}) พื้นที่ใต้เส้นโค้งความสัมพันธ์ระหว่างระดับยาในเลือดกับเวลาที่เวลา 0 ถึง 12 ชม. (AUC_{0-12}) และที่เวลา 0 ถึงอนันต์ ($AUC_{0-\infty}$)

(AUC_{0-12}) and 0 to infinity ($AUC_{0-\infty}$) were the primary parameters considered in the determination of bioequivalence.

Results: The two ceftazidime preparations were generally well tolerated by all volunteers. Administration of both preparations resulted in similar mean values for every pharmacokinetic parameters. Statistical analysis revealed no significant difference between the two preparations in any parameter, indicating that the two preparations are statistically bioequivalent ($p<0.05$). The 90% confident interval (CI) for the ratio of the means for the C_{max} (0.9281-1.1272) and $AUC_{0-\infty}$ (0.9311-1.0184), are within the Food and Drug Administration Guideline range of bioequivalence (0.80 to 1.25).

Conclusions: These results demonstrated that the tested ceftazidime preparation (Forzid®) is bioequivalent to the reference ceftazidime preparation (Fortum®) when administered intramuscularly.

ผลการวิจัย: อาสาสมัครทุกคนสามารถทนต่อการได้รับเตรียม ceftazidime ทั้ง 2 ตำรับได้ดี โดยมีค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ทุกพารามิเตอร์ใกล้เคียงกัน ผลการวิเคราะห์ข้อมูลทางสถิติไม่พบว่าค่าพารามิเตอร์เหล่านี้มีความแตกต่างกันอย่างมีนัยสำคัญ ซึ่งแสดงถึงความเท่าเทียมกันทางชีวสมมูลของยาเตรียมทั้ง 2 ตำรับ ($p < 0.05$) ที่ระดับความเชื่อมั่น 90% ค่าสัดส่วนของค่าเฉลี่ยของ C_{max} อยู่ในช่วง 0.9821-1.1272 และค่าสัดส่วนของค่าเฉลี่ยของ $AUC_{0-\infty}$ อยู่ในช่วง 0.9311-1.0184 ซึ่งอยู่ในเกณฑ์มาตรฐานที่ถือว่ามีความเท่าเทียมกันทางชีวสมมูลตามที่สำนักงานคณะกรรมการอาหารและยากำหนดไว้ (0.80-1.25)

สรุปผลการวิจัย: ผลการวิจัยครั้งนี้แสดงว่ายาเตรียม ceftazidime ตำรับทดสอบ (Forzid®) มีความเท่าเทียมทางชีวสมมูลกับตำรับอ้างอิง (Fortum®) เมื่อให้ยาโดยวิธีฉีดเข้ากล้ามเนื้อ

ศรีนครินทร์เวชสาร 2545; 17(4), 254-260 • Srinagarind Med J 2002; 17(4), 254-260

Introduction

Ceftazidime is a third generation cephalosporin that has been commercially available for years. Ceftazidime possesses the basic β-propiolactam ring, which is essential for its antibacterial activity. It binds with high affinity to penicillin-binding proteins (PBPs) in the bacterial cell wall, thus interfering with peptidoglycan synthesis. Peptidoglycan is a heteropolymeric structure that provides the cell wall with mechanical stability. The final stage of the synthesis of peptidoglycan is catalyzed by the transpeptidase enzyme which can be inhibited by ceftazidime. At low concentration ceftazidime binds with high specificity to PBP3 in both *E. coli* and *P. aeruginosa* and binds to other PBPs only when concentration exceed the minimum inhibitory concentration (MIC). It has a broad spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria[1]. The broad spectrum appears to be credited to efficient penetration of the bacterial cell wall, a high affinity for the target PBPs and less efficient inducer of the β-lactamase[2].

Ceftazidime is bactericidal against a wide range of pathogenic bacteria responsible for infection in hospitals[3]. It is active against *H. influenza, E. coli, K. pneumoniae, Proteus spp., and Neiseria spp.* with MIC_{50} of 0.05 mg/l or less. It is also active against *P. aeruginosa* with an MIC_{50} of 1.6 mg/l. It is active against a range of gram-positve organisms but excludes enterococci. Synergistic inhibition of the drug with an aminoglycoside has been demonstrated for selected pathogens. Ceftazidime is highly stable to many β-lactamase produced by various gram-positive and gram-negative bacteria. Ceftazidime can be used in both single and multiple doses. The adult dose ranges from 1 to 6 g daily, although doses up to 12 g have been reported for certain serious infections.

Ceftazidime is not absorbed from the gastrointestinal tract, thus required administration via parenteral routes. The bioavailability of intramuscular (IM) injection is appoximately 91% of the intravenous (IV) administration[4]. Plasma half-life is about 1.8 h in normal volunteers but rises to about 2.2 h in older patients albeit they have normal renal function[5]. The volume of distribution (V_d) after a 0.5-2 g dose given by IV or IM route is 0.21 to 0.29 l/kg[6]. The V_d is significantly larger in those with hepatic dysfunction (0.6 l/kg) than normal volunteers. Peak plasma

concentration (C_{max}) of 139 and 43 mg/l at 0.7-1.0 h post-injection have been reported after IV and IM administration of 1 g respectively[7]. Plasma clearance is 110-120 ml/min. The drug is not metabolized and almost (80-90%) recovered in the urine within 24 h. Elimination occurs almost entirely by glomerular filtration with renal clearance lies between 90-115 ml/min[8] and biliary excretion accounts for less than 1%[9]. There is no evidence for enterohepatic circulation of the drug. Approximately 10% (range 5-17%) of the drug is protein bound. The elimination half-life of ceftazidime is 1.6-2.0 h and is prolonged in patients with hepatic dysfunction (5.4 h), preterm infants (6.9 h) and the elderly (4.5h).

Ceftazidime is currently available through several manufacturers and distributors in Thailand because of its widely clinical use. However, to our knowledge there was no comparative pharmacokinetic study of ceftazidime in Thais. The present study was conducted to compare the *in vivo* bioequivalent of ceftazidime obtained from an original (reference), and a local (tested) manufacturer when given 1 g intramuscularly to healthy Thai volunteers.

Materials and Methods

Materails

Standard ceftazidime were bought from USP-reference providers. Other chemicals used were of analytical grade and purchased from local distributors. Fortum® (Lot No. FTML0020A, manufacturing date 20/03/2000, expiration date 20/03/2003), and tested product, Forzid® (Lot No. 00077, manufacturing date 8/06/2000, expiration date 4/02/2002), were used in the present study.

Subjects

Fourteen male Thai volunteers enrolled in the study ranging in age from 21 to 40 years (mean ± SD, 30 ± 6 years). Their body mass index was in the range of 19.1-23.8. Each subject was healthy as indicated by medical history, physical examination and standard clinical laboratory tests. Exclusion criteria included those whom had medical history of asthma, atopic disorders, hepatitis, drug abuse, alcoholism, AIDS or HIV sero-positive. Volunteers with drug allergy record, especially to penicillin and cephalosporin groups were not recruited. The protocol was approved by the Ethic Committee of Khon Kaen University, and all volunteers gave written informed consent to all procedures.

Study Design

The study was conducted using a double blind, randomized, two-way crossover design with a washout period of two weeks between regimens. The use of other drugs and the consumption of alcohol and caffeine were prohibited for 2 weeks before dosing and throughout the study. The volunteers were overnight fasted and confined to the study site for at least one hour before the start of each study interval. The volunteers received either of the ceftazidime product in a random, cross-over fashion i.e. a single of 1-g dose of reference product, Fortum® or tested product, Forzid® administered by intramuscular injection (buttock muscle) after dissolving in 3 ml of sterile water. Both medications were administered by a third party-nurse to maintain the blind. During each study interval, an approximate 8-ml blood sample was obtained before dosing, and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10 and 12 h after each dose. All blood samples were drawn through an indwelling catheter placed in the arm or by venipuncture into collecting tubes containing an anticoagulant, EDTA. The plasma was separated, transferred to labeled tubes, and stored at or below -70 °C until assay.

Volunteers were encouraged to report any adverse event or unpleasant feeling while in the study interval. A standard breakfast was served after 1-hour blood sample had been collected. A standard lunch was served 4 hours after dosing and dinner was served 10 hours after dosing. Water was permitted *ad libitum* throughout the study interval. After each dose, volunteers remained in the study unit until the 12-hour blood sample had been collected.

Ceftazidime assay

Plasma concentrations of ceftazidime was assayed by modified method of Ayrton[10] using reverse-phase HPLC with ultraviolet detection following protein precipitation of sample plasma. The sample was prepared by adding a 50 µl of internal standard (theophylline 20 µg/ml) and 150 µl of 0.8 M perchloric acid to a 200 µl aliquot of plasma. The sample was then thoroughly mixed by vortexing and centrifuge at 10,000g for 5 min. A 25 µl aliquot of the supernatant was then analyzed by injected on to a YMC-Pack Pro C18 column (150 x 4.6 mm i.d., 5 µm, YMC Co., Ltd., Kyoto, Japan) with ultraviolet absorbance detection at 257 nm using 5% acetonitrile in 0.01M sodium acetate, pH 4.0 as mobile phase. Twenty-five-microlitre aliquots of the ceftazidime standards and quality assurance samples were assayed under the same condition. The ceftazidime standard concentrations were ranging from 0.5 to 50 mg/l; the ceftazidime concentrations for the quality assurance samples was 15.0 mg/l. Ceftazidime concentrations in quality control and study samples were quantified by comparison of the peak height ratios between ceftazidime peak and internal standard peak with those of the standard curve. The within-day precision

of ceftazidime assay under the conditions employed were determined in 5 replicated samples. Within-day coefficients of variation were 7.0 and 4.3% at ceftazidime concentrations of 15.5 and 50 mg/l respectively. The between-day precision of ceftazidime assay was determined over a period of 2 weeks. Between-day coefficients of variation for ceftazidime were 6.5 and 2.6% at 10 and 50 mg/l respectively. Stability study of plasma ceftazidime under -70° C was determined and the result showed that the drug was stable up to 1 month of storage. The assay in the present study were carried out within 3 weeks after sample collection.

Pharmacokinetic and statistical analysis

The plasma concentration-time curve of ceftazidime were analyzed by non-compartmental model. The maximum concentration (C_{max}) and time of maximum plasma concentration (T_{max}) was determined by visual inspection of the data. The area under the plasma drug concentration-time curve from time 0 to 12 h (AUC_{0-12}) was calculated with use of trapezoidal rule up to the last measured concentration (C_{12}). AUC was extrapolated to infinity using the formula $AUC_{0-\infty} = AUC_{0-12} + C_{12}/\lambda z$.

The C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$ were the primary parameters considered in the determination of bioequivalence. The analysis of variance for cross over designs was used to provide estimate of adjusted means and error variability and to test for significant first-order carryover effects. The primary parameters were transformed to a logarithmic scale and analyzed for bioequivalence using a two one-sided tests procedure. Under the criteria of the US-FDA and Thai-FDA, bioequivalence was established if the ratio of parameter means (i.e. C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$) fell within the 90% CI of 0.80 to 1.25. An alpha level of 0.05 was used to alpha test equivalence at both upper and lower confidence limits.

Results

Fourteen volunteers completed this study without any serious adverse drug events. Demographic data of all volunteers was shown in Table 1. Mean and SD of plasma concentrations of both preparations were compared in Figure 1.

Following an intramuscular administration of 1 g of the test drug (Forzid®), the absorption rate was rapid with the mean T_{max} of 1.18 ± 0.5 h and the mean C_{max} of 31.96 ± 8.12 mg/l. These two kinetic parameters were very closed to those observed in the reference drug (Fortum®) (T_{max} of 1.14 ± 0.49 h and C_{max} of 31.15 ± 7.69 mg/l). The

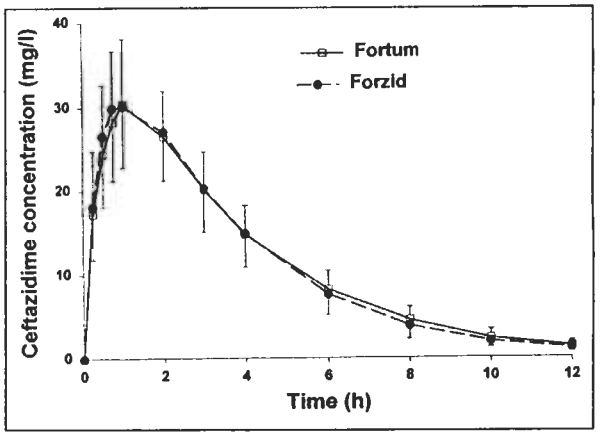

Figure 1 Comparative plasma concentration-time of ceftazidime in 14 volunteers after receiving 1g IM of either Fortum® or Forzid®. Data represent mean and SD.

mean AUC_{0-12} and $AUC_{0-\infty}$ for the test drug were 133.48 ± 30.12 and 138.06 ± 30.50 mg*h/l whereas those calculated for the reference drug were 135.86 ± 26.10 and 141.11 ± 27.74 mg*h/l .

The comparative ratios of C_{max} and $AUC_{0-\infty}$ (log transformed) of ceftazidime between Forzid® (T) and Fortum® (R) were shown on Table 2. The statistical analysis (ANOVA) of C_{max} and $AUC_{0-\infty}$ for all possible effects i.e. sequence, subject, period, formulation and experiment error were shown on Table 3 and Table 4.

Discussion

Two ceftazidime products, Fortum® and Forzid®, investigated in this study have been approved for clinical used by the Food and Drug Administration, Ministry of Public Health of Thailand. Both preparations were generally well tolerated and had similarity in plasma drug concentration-time profile when followed at least up to 12 h post-intramuscular administration. The drugs were rapidly absorbed from the site of injection and reached peak plasma concentration with mean T_{max} of 1.14 ± 0.49 h (Fortum®) and 1.18 ± 0.56 h (Forzid®). The percent differences of T_{max} between the test and reference drug were less than 4 %. The mean C_{max} of Fortum® and Forzid® were 31.15 ± 7.96 and 31.96 ± 8.12 mg/l respectively. Plasma T1/2 of ceftazidime found in the present study were 2.35 ± 0.38 and 2.46 ± 0.86 h for Fortum® and Forzid® respectively. It is noteworthy that C_{max} and plasma $T_{1/2}$ of ceftazidime found in the present study were comparable with the values reported in other studies (C_{max} 43 mg/l, and $T_{1/2}$ 1.8-2.2 h)[5, 11].

The means of the ratios of C_{max} between Forzid® and

Table 1 Demographic data of the subjects enrolled in the study.

Subject No.	Age (yr)	Height (cm)	Weight (kg)	Body mass index
1	24	175	72	23.51
2	40	172	70	23.66
3	32	164	64	23.80
4	21	160	49	19.14
5	28	166	63	22.86
6	31	165	60	22.04
7	29	169	64	22.41
8	29	177	71	22.66
9	40	160	53	20.70
10	32	174	67	22.13
11	38	163	60	22.58
12	34	181	76	23.20
13	25	165	55	20.20
14	23	173	67	22.39
Mean	**30**	**169**	**64**	**22**
SD	**6**	**7**	**8**	**1**

Table 2 Comparative ratio of C_{max} and $AUC_{0-\infty}$ (log transformed) of ceftazidime between Forzid® (T) and Fortum® (R).

Subject no.	Ln (C_{max})			Ln ($AUC_{0-\infty}$)		
	T	R	F rel (T/R)	T	R	F rel (T/R)
1	3.2371	3.3247	0.9737	4.9870	4.9899	0.9994
2	3.2347	3.1157	1.0382	4.8131	4.9618	0.9700
3	3.4187	3.1489	1.0857	4.9465	4.8640	1.0170
4	3.4569	3.7554	0.9205	4.8147	4.9384	0.9749
5	3.2193	3.0787	1.0457	4.8782	4.7826	1.0200
6	3.0662	3.2906	0.9318	4.7382	4.8754	0.9719
7	3.5619	3.5305	0.9321	4.8754	4.8686	1.0014
8	3.6738	3.4667	1.0597	4.8736	4.8069	1.0139
9	3.8214	3.7707	1.0135	5.3833	5.4058	0.9959
10	3.6504	3.4372	1.0620	4.8276	4.9300	0.9792
11	3.4039	3.7150	0.9162	4.7915	4.9666	0.9647
12	2.9275	3.0426	0.9622	4.5320	4.6046	0.9842
13	3.6849	3.5401	1.0409	5.1835	5.0744	1.0215
14	3.7023	3.5246	1.0504	5.0590	5.0063	1.0105

Table 3 Statistical analysis (ANOVA) and 90% confidence interval of C_{max} (log transformed) between Forzid® (T) and Fortum® (R).

Source	Degree of freedom	Sum of squares	Mean of squares	Computed F	P-values
Total	27	1.7368			
Sequence	1	0.0440	0.0440	2.11	0.1715
Subject	12	1.4406	0.1201	5.77	0.0024
Period	1	0.0036	0.0036	0.17	0.6860
Formulation	1	0.0009	0.0005	0.04	0.8393
Error	12	0.2495	0.0208		
		Mean		90% Confidence interval	
Forzid® (T)		3.4327		3.2874-3.5395	
Fortum® (R).		3.4101		3.2918-3.5284	
Ratio (F rel T/R)		1.0078		0.9809-1.10347	

Table 4 Statistical analysis (ANOVA) and confidence interval of $AUC_{0-\infty}$ (log transformed between Forzid® (T) and Fortum® (R).

Source	Degree of freedom	Sum of squares	Mean of squares	Computed F	P-values
Total	27	0.9611			
Sequence	1	0.1753	0.1753	39.65	0.0001
Subject	12	0.7167	0.0597	13.50	0.0001
Period	1	0.0049	0.0049	1.12	0.3117
Formulation	1	0.0111	0.0056	2.52	0.1383
Error	12	0.0531	0.0044		
		Mean		90% Confidence interval	
Forzid® (T)		4.9074		4.8106-5.0042	
Fortum® (R).		4.9339		4.8496-5.0183	
Ratio (Frel T/R)		0.9946		0.9311-1.0184	

Fortum® was 1.0078 with 90% confidence interval of 0.9809-1.0347 and the ratios of $AUC_{0-\infty}$ between Forzid® and Fortum® was 0.9946 with 90% confidence interval of 0.9311-1.0184. These values were well within the bioequivalent ratio range of 0.8-1.25 as required by the regulatory standard of US-FDA. The means of T_{max} differences between the two product were less than 20%, an US-FDA acceptable value. Thus, the two ceftazidime preparations when administered intramuscularly to healthy Thai male volunteers were bioequivalent regarding rate and extent of absorption.

Conclusions

The bioequivalence study of 1 g of ceftazidime (Fortum® and Forzid®) were conducted in 14 healthy Thai male volunteers. The results showed that these two formulations were well tolerated. The pharmacokinetic parameters of ceftazidime obtained from the present study were comparable to those values reported in the Cuacasian subjects. We also demonstrated bioequivalence of these two products regarding the rate and extent of absorption. The parametric 90% CI of the ratios of the key pharmacokinetic parameters were within the acceptable range

based on the standard bioequivalence guidelines. Therefore, the two products, Forzid® and Fortum®, can be used interchangeably when the cost-effectiveness is concerned.

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