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Bioequivalence study of clindamycin phosphate for intramuscular administration in healthy Thai volunteers

Duangchit Panomvana Na Ayudhaya*
Somkit Ounsaenathum** Tatta Sriboonruang*

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Problem / Background : *Since there are many commercial brands of clindamycin phosphate injection available in Thai market. Bioequivalence study is necessary in order to assure quality and efficacy of the products.*

Objective : *To determine the bioequivalence of two formulations of clindamycin phosphate injection in human.*

Design : *A randomized, single dose, two- way crossover study with a 2-weeks washout period.*

Setting : - *Department of (Clinical) Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University.*
- *Department of Medicine, Rajavithi Hospital.*

Materials and Methods : *Twenty four healthy Thai volunteers were intramuscular administered with 150 mg/ml, 2 ml clindamycin phosphate of two brands, serial blood samples were collected over a period of 24 hours. Serum clindamycin concentrations were determined by HPLC-UV detector and the pharmacokinetic parameters were evaluated by WIN NONLIN program.*

* Department of (Clinical) Pharmacy , Faculty of Pharmaceutical Sciences, Chulalongkorn University
** Department of Medicine, Rajavithi Hospital, Department of Medical Services, Ministry of Public Health

Results : *Ninety percent confidence interval of the mean log-transformed ratio (test/reference) of C_{max}, $AUC_{(0 - t\ last)}$ and $AUC_{(0-\infty)}$ were 102.83-120.14 %, 104.88 -119.08 % and 105.82–120.51 %, respectively.*

Conclusion : *The study indicates that clindamycin phosphate injection 150 mg/ml of both preparations are bioequivalent.*

Keywords : *Clindamycin phosphate, Bioequivalence, Intramuscular Injection.*

Reprint request : Panomvana Na Ayudhaya D. Department of (Clinical) Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand.

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เหตุผลของการทำวิจัย : *ยาฉีดคลินดามัยซินฟอสเฟต ที่มีจำหน่ายในท้องตลาดของประเทศไทยมีหลายชื่อการค้า การศึกษาชีวสมมูลจึงจำเป็นเพื่อทำให้เกิดความมั่นใจในคุณภาพและประสิทธิภาพของผลิตภัณฑ์*

วัตถุประสงค์ : *เพื่อศึกษาชีวสมมูลในมนุษย์ เปรียบเทียบระหว่างผลิตภัณฑ์ยาฉีดคลินดามัยซิน-ฟอสเฟต 2 ชื่อการค้า*

รูปแบบการวิจัย : *การศึกษาเชิงข้ามสลับ แบบสุ่ม โดยให้ยาครั้งเดียว และเว้นระยะบริหารยาห่างจากครั้งแรก 2 สัปดาห์*

สถานที่ดำเนินการศึกษา : *- ภาควิชาเภสัชกรรม (คลินิก) คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*
- ภาควิชาอายุรศาสตร์ โรงพยาบาลราชวิถี

ตัวอย่างและวิธีการศึกษา : *ศึกษาในอาสาสมัครชาวไทยสุขภาพดี จำนวน 24 คน โดยฉีดยาคลินดามัยซิน ขนาด 150 มก./มล. ปริมาตร 2 มล.ของ 2 ชื่อการค้าเข้ากล้ามเนื้อ เก็บตัวอย่างเลือดตามระยะเวลาต่าง ๆ ภายใน 24 ชั่วโมง วัดระดับยาคลินดามัยซินในเลือด โดยใช้เครื่อง HPLC และ UV detector คำนวณและแปลผลค่าทางเภสัชจลนศาสตร์ โดยใช้โปรแกรมวินนอนลิน*

ผลการศึกษา : *ช่วงความมั่นใจ 90 % ของอัตราส่วนค่าพารามิเตอร์ที่เปลี่ยนแปลงเป็น log แล้วของ C_{max}, $AUC_{(0 - t\ last)}$ และ $AUC_{(0 - \infty)}$ ระหว่างผลิตภัณฑ์ทั้งสองมีค่าในช่วง 102.83 – 120.14 %, 104.88 – 119.08 % และ105.82–120.51 % ตามลำดับ*

สรุป : *การศึกษานี้ชี้ให้เห็นว่ายาฉีดคลินดามัยซินฟอสเฟต ขนาด 2 มล, 150 มก./มล.ปริมาตร 2 มล. ทั้ง 2 ชื่อการค้ามีชีวสมมูลกัน*

คำสำคัญ : *คลินดามัยซินฟอสเฟต, ชีวสมมูล, ยาฉีดเข้ากล้ามเนื้อ*

Clindamycin, a lincosamide antibiotic, is generally used for the treatment of serious infection caused by susceptible gram-positive bacteria and anaerobic bacteria. Clindamycin appears to inhibit protein synthesis by binding to 50S ribosomal subunits of susceptible organism and shows both bacteriostatic and bactericidal actions, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. [1] For injection, clindamycin phosphate is presented and can be administered by intramuscular injection or by intermittent or continuous intravenous infusion. [1-3] After administering 300 mg of clindamycin by intramuscular injection, area under the curve (AUC_{0-24}), maximum plasma clindamycin concentration (C_{max}), and time to reach C_{max} (T_{max}) were reported to be 34.61-50.75 μg.hr/ml, 2.97-5.15 μg/ml and showed up within 2 hours, respectively. [4] Clindamycin was 40-90 % binding to plasma protein and the half life ($T_{½}$) was approximately 4.5-5.3 hours. Most of clindamycin (>90 %) is metabolized via liver and its active metabolites are excreted into urine and feces 10 % and 3.6 %, respectively. Dosage adjustment may be required in patients who have impaired renal or hepatic functions. The common adverse drug reactions (ADRs) of clindamycin are nausea, vomiting, diarrhea, abdominal pain, pain at site of injection. The importance ADRs which rarely occur are pseudomembraneous colitis and reversible elevated of hepatic enzyme. [5-10] There are many commercial brands available in Thai market, bioequivalence studies are necessary in order to assure quality and efficacy.

Materials and Methods

Test and reference medications

The test medication was clindamycin phosphate injection: Rosil® 150 mg/ml Lot No.936262 manufactured by Siam Bheasach while Dalacin C® injection Lot KH1223 manufactured by Pharmacia was used as reference medication.

Subjects

Twenty four healthy male volunteers, aged between 18-42 years, and average BMI equaled to 22.6 were enrolled in the study. The sample size, 24 subjects, was sufficient to ensure a power of 80 % for correctly concluding bioequivalence under the following assumptions: $\alpha = 0.05$, $H_o: \mu_T / \mu_R = 1$ with confidence interval of log-transformed data lie between 0.8 and 1.25 ($\pm$ 20 %). All subjects were healthy according to their medical history, physical examination, blood pressure, and standard laboratory test results.

This study has been approved by the Ethics Committee, Rajavithi Hospital and it was conducted in accordance under the requirement of Good Clinical Practice (GCP).

Study design

The randomized, single dose, two-way crossover with a wash out period of 2 weeks was described. Each volunteer received a single dose of 300 mg of either the test (T) or reference (R) medication by injecting into the gluteus maximus during each treatment. A number was assigned to each volunteer, the researcher closed the eyes and point a finger on the page of number table to randomly choose the starting product for each volunteer.

Approximately 5-10 ml blood sample were collected into heparinized tubes through the cannula before (0) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after intramuscular administration. Blood samples were immediately centrifuged at 4°C, the

plasma was separated and kept frozen at -20°C until the HPLC analysis.

Analysis of plasma samples

Analysis of plasma samples from healthy volunteers was performed by a Contract Research Organization (Bioequivalence Study Center, Bureau of Drug and Narcotic, Nonthaburi 11000) using a validated high-pressure liquid chromatographic method with UV detection at 204 nm, Clindamycin and internal standard, phenacetin, were extracted from plasma using solid-phase extraction technique. The limit of quantitation for clindamycin was 250 ng/ml. All validation parameters complied with the USFDA Guidance: Bioanalytical Method Validation 2001.

Pharmacokinetics analysis [11]

The maximum plasma concentration (C_{max}) and the corresponding time of peak plasma concentration (T_{max}) were determined from individual plasma concentration-time profile. Non-compartmental pharmacokinetic characteristics ($AUC_{(0 - t\ last)}$ and $AUC_{(0-\infty)}$) including the half-life were calculated using WIN NONLIN program.

Statistical evaluation [12-13]

Statistical analysis of C_{max}, $AUC_{(0 - t\ last)}$ and $AUC_{(0-\infty)}$, after log-transformation, were performed by analysis of variance (ANOVA) using 2-way crossover design for sequence, subject, period and formulation effects. Ninety percent confidence interval (90 %CI) of the ratio (test/reference) of log-transformed values of C_{max}, $AUC_{(0 - t\ last)}$ and $AUC_{(0-\infty)}$ were used for bioequivalence assessment. Bioequivalence of the two products would be accepted if 90 % CI of the ratio of all parameters were within the range of 80 -125.

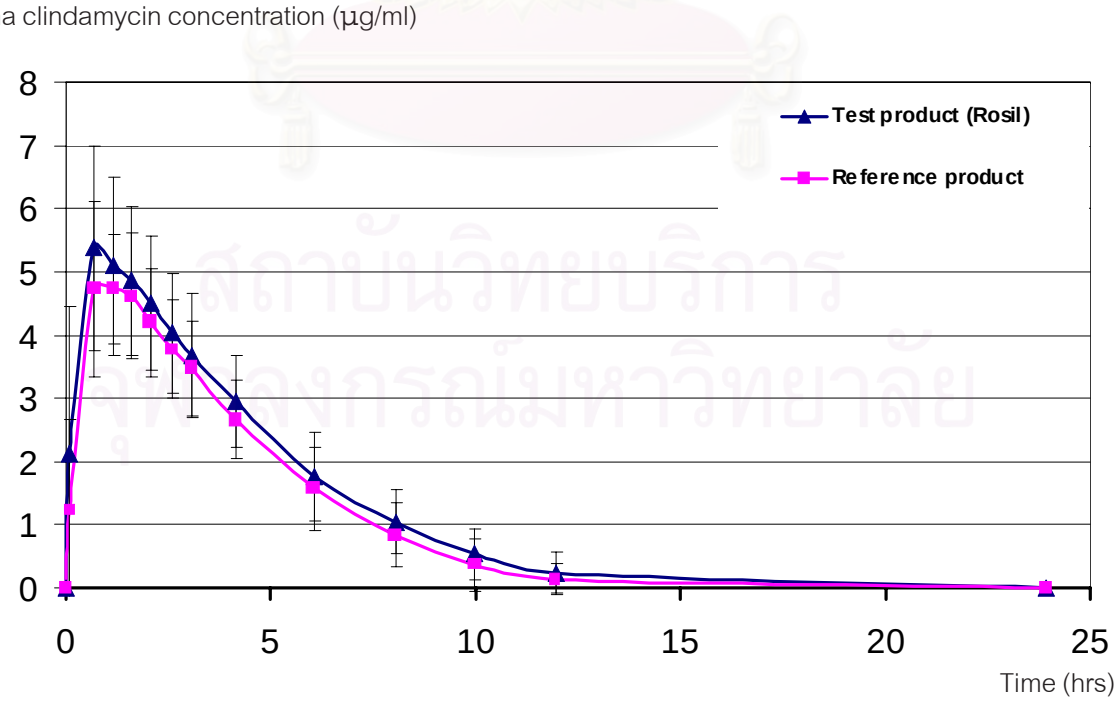

Figure 1. Average clindamycin plasma concentration-time curve of 24 volunteers after administration of 150 mg, 2 ml clindamycin test and reference intramuscular injections.

Results and Discussion

All subjects did not show any significant clinical relevant adverse effect after consumed either medication except for dizziness and pain at injection site in few patients. The plasma concentration-time curves of clindamycin phosphate after administering the reference and test medications were shown in figure 1 and the pharmacokinetic parameters including AUC, C_{max}, T_{max}, $T_{½}$ were summarized in table 1. Compare with those previously reported, a little higher mean C_{max} in this study might due to weight of Thai people which is normally lower than the western people[4], the $AUC_{(0 - t\ last)}$ was lower which might be the result of a shorter half life (faster metabolized).[11]

Statistical analysis of pharmacokinetic parameters used to evaluate bioequivalence of the test and the reference products are presented in table 2. 90 % CI of the mean ratios of ln $AUC_{(0 - t\ last)}$ ln $AUC_{(0-\infty)}$ and ln C_{max} between test and reference products were all within the range of 80-125. Analysis of variance (ANOVA) showed no significant differences in period, sequence and subject effects in any of the pharmacokinetic parameters, power of the tests for all parameters were higher than 0.998.

Table 1. Pharmacokinetic parameters of clindamycin after intramuscular clindamycin phosphate administrations (150 mg, 2 ml) of test and reference products.

Parameters	Test Medication (n=24)				
	$AUC_{(0 - t\ last)}$ (μg.hr/ml)	$AUC_{(0-\infty)}$ (μg.hr/ml)	C_{max} (μg /ml)	T_{max} (hr)	$T_{½}$ (hr)
Min	15.84	16.11	2.69	0.33	1.01
Max	41.09	43.88	8.53	2.63	5.13
Ar mean	26.20	27.87	5.70	1.05	2.34
% CV	27.50	29.84	25.47	57.41	36.7

Parameters	Reference Medication (n=24)				
	$AUC_{(0 - t\ last)}$ (μg.hr/ml)	$AUC_{(0-\infty)}$ (μg.hr/ml)	C_{max} (μg /ml)	T_{max} (hr)	$T_{½}$ (hr)
Min	14.89	26.92	3.15	0.57	1.41
Max	38.00	42.37	7.62	1.68	3.49
Ar mean	23.28	24.47	5.09	1.14	2.16
% CV	26.33	28.74	22.44	32.9	23.56

Table 2. Statistical comparisons of clindamycin between test and reference medications, after intramuscular clindamycin phosphate administrations (150 mg/ml, 2 ml).

Pharmacokinetic parameters	Medication (Mean ± SD)		90 % Confidence interval of the mean log- transformed ratio
	Test	Reference	
C_{max} ; µg/ml	5.70 ± 1.45	5.09 ± 1.14	102.83-120.14
$AUC_{(0\text{-t last})}$; µg.hr/ml	26.20 ± 7.20	23.28 ± 6.13	104.88-119.08
$AUC_{(0-\infty)}$; µg.hr/ml	27.87 ± 8.31	24.47 ± 7.03	105.82-120.51

Conclusions

This study indicates that clindamycin phosphate injection 150 mg/ml of both preparations are bioequivalent.

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