Bioequivalence Study of Ondansetron Tablet in Healthy Thai Male Volunteers

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Abstract

Objectives : To assess the average bioequivalence of two formulations of 8-mg ondansetron tablets - test product (Unison Laboratories, Thailand) and reference product (Glaxo Wellcome, USA) - in 14 healthy Thai male volunteers.

Material and Method : In a randomized, single dose, fasting, two-period, crossover study design with a 1-week washout period, each subject received an 8-mg ondansetron tablet. Serum samples were collected over a 24-hour period after administration. Subsequently serum concentrations of ondansetron were analyzed by using a validated HPLC-UV method. Pharmacokinetic parameters were determined by using non-compartmental analysis.

Results : No significant difference was observed in any of the pharmacokinetic parameters analyzed. The time to reach the maximal concentration (T_{max}, hour), the peak concentration (C_{max}, ng/ml) and the area under the concentration-time curve ($AUC_{0-\infty}$, ng.h/ml) of ondansetron for reference and test preparations were 2.6 ± 1.8 *vs* 2.2 ± 0.6, 49.5 ± 18.9 *vs* 48.5 ± 13.7 and 352.2 ± 184.7 *vs* 323.8 ± 154.5, respectively. The 90 per cent confidence intervals for Test/Reference ratio of C_{max} and $AUC_{0-\infty}$ were found within the bioequivalence range of 80-125 per cent (90.3-110.0% and 88.4-99.6%, respectively).

Conclusion : The bioequivalence of these two ondansetron preparations was demonstrated.

Key word : Bioequivalence, Ondansetron

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Ondansetron is a selective 5-HT_3 receptor antagonist widely used for chemotherapy-induced nausea and vomiting and post-operative nausea and vomiting (PONV). Ondansetron is well absorbed from the gastrointestinal tract with biovailability of 56 per cent. Following oral administration of 8 mg ondansetron, the peak serum concentration (C_{max}) and time to peak serum concentration (T_{max}) are 40 ng/ml and 1.7 hours, respectively. When administered with food, ondansetron bioavailability increases approximately 17 per cent. After being absorbed, 70-76 per cent of ondansetron is bound to plasma protein. It is widely distributed throughout the body including red blood cells. Ondansetron is extensively metabolized *via* CYP1A2, CYP2D6 and CYP3A4. Its elimination half-life is 3.5-5.5 hours[1-4].

The recommended dose for prevention of moderate-to-severe nausea and vomiting associated with emetogenic cancer chemotherapy is 8-24 mg, 30 minutes before beginning cancer chemotherapy and a repeated dose of 8 mg at 8 hours after the first dose. The recommended dose for prevention of nausea from radiation is 8 mg at 1-2 hours before starting cancer chemotherapy and three times daily thereafter. For the prevention of post-operative nausea and vomiting, the recommended dose is 16 mg at 1 hour prior to anesthetic induction[3].

The objective of this study was to assess the average bioequivalence of two formulations of 8-mg ondansetron tablets : Test product from Unison Laboratories, Thailand and Reference product from Glaxo Wellcome, USA, in healthy Thai male volunteers. The clinical protocol was reviewed and approved by the Ethics Committee of the Ministry of Public Health, Thailand.

MATERIAL AND METHOD

Ondansetron preparations

Reference preparations: 100 tablets (Glaxo Wellcome, USA) containing 8 mg ondansetron per tablet (Lot no. 1B004837-2, Mfg. 10.08.99).

Test preparations: 100 tablets (Unison Laboratories, Thailand) containing 8 mg ondansetron per tablet (Lot no. T02/2, Mfg. 28.06.99).

Study design and clinical protocol

In a randomized, single dose, fasting, two-period, two-sequence, crossover study with a 1-week washout period, fourteen healthy Thai male volunteers aged between 18-45 years (20.8 ± 2.4 years) and body mass index between 18-24 (20.5 ± 1.9) participated in the study. After explaining the details and purpose of the study, all healthy volunteers provided written informed consent before enrollment. The volunteers were non-smoking, non-alcoholic and free from significant cardiac, hepatic, renal, gastrointestinal, and hematological diseases, as assessed by physical examination and the following laboratory tests: complete blood count, total bilirubin, serum creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase and hepatitis B surface antigen.

During each period, the volunteers were admitted to the Bioequivalence Test Center, Naresuan University at 6.00 p.m. and had an evening meal before 9.00 p.m. After an overnight fast, they received an 8-mg ondansetron tablet at 7.00 a.m. along with 240 ml of water. They were then in the seated position for at least 30 minutes and fasted for 2 hours, thereafter a standard lunch was consumed. An evening meal was provided at 9 hours after dosing. No other food was permitted during the study period. Liquid consumption was permitted ad libitum after lunch but xanthine containing and any acidic beverages were prohibited. After each period of the study, the volunteers were re-examined by a physician.

Drug analysis

Ten milliliters of each blood sample was collected into a tube by catheterized venupuncture at forearms before dosing (t = 0) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours after the administration of each ondansetron formulation. The blood samples were centrifuged (2,000 g, 10 minutes) and the serum samples were separated within 10 minutes after collecting blood. All samples were kept at -80°C until analysis. Serum ondansetron was measured by a validated high pressure liquid chromatographic method modified from the methods of Colthup et al and VanDenBerg et al[5,6]. The lower limit of quantitation was 2 ng/ml, using ramosetron as an internal standard. In brief, the serum samples were extracted by Alltech CN solid phase extraction column, which was preconditioned by sequential additions of 2 ml of methanol and 2 ml of water. Subsequently, 1 ml of serum sample with internal standard was applied with addition of 50 µl of 1M HCl, waiting for 10 minutes before allowing the samples to pass through the columns and dried with full vacuum for 10 minutes. Columns were then washed with 2.4 ml of water and dried with full vacuum for 20 minutes. The analyte was eluted with 3 ml of 1 per cent ammonia in isopropanol solution. Eluates were evaporated until

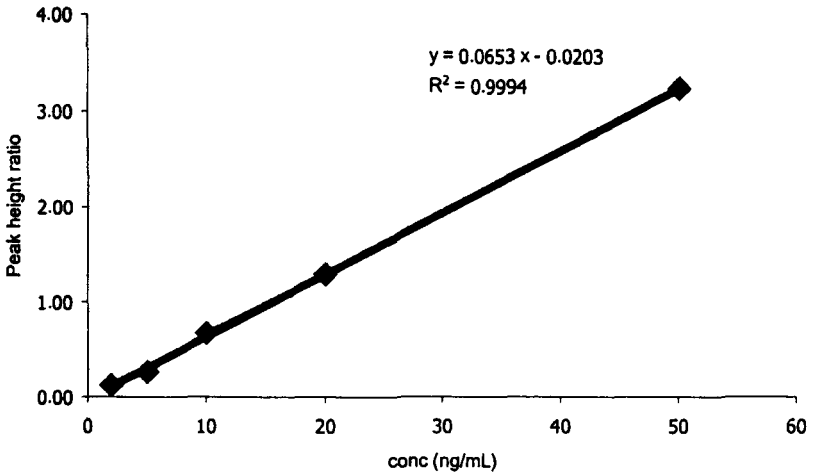

Fig. 1. Calibration curve of ondansetron in serum.

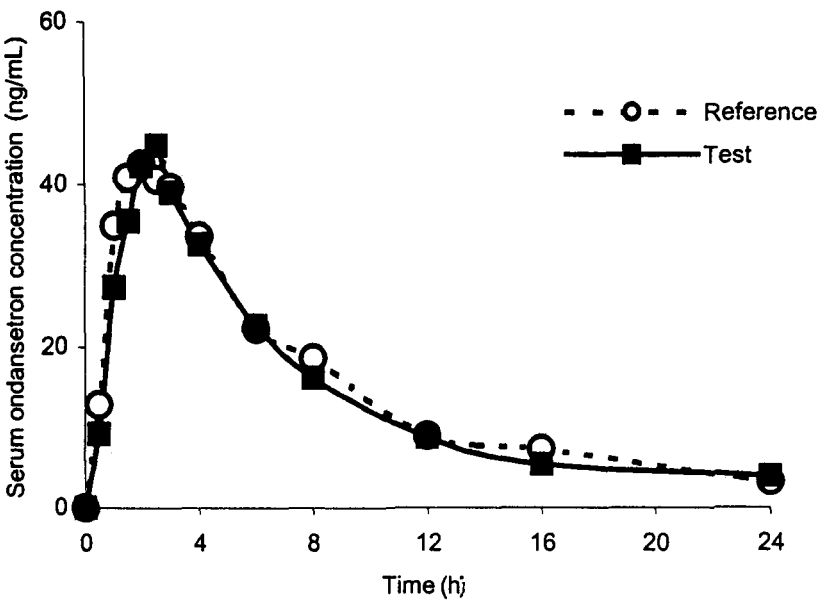

Fig. 2. Mean serum concentration-time curve of ondansetron after 8-mg single dose administrations of reference and test products in 14 healthy Thai male volunteers.

dry and dissolved with 200 µl of the eluent. The eluates (approximately 150 µl) were injected into a Waters Spherisorb 5SW 5x100 mm column with a silica guard column. The mobile phase consisting of acetonitrile:acetate buffer (41:59 v/v), pH 4.7 was pumped into the system at a flow rate of 0.8 ml/min by an ConstaMetric 3500 isocratic HPLC pump (Thermo Separation Product, Freemont, USA). The column effluent was monitored by a SpectroMonitor 3200 UV detector (Thermo Separation Product, Freemont, USA) at 305 nm. The peaks were recorded and integrated by PeakSimple for Windows. The calibration curve of ondansetron in serum ranged from 2-50 ng/ml (Fig. 1).

Table 1. Pharmacokinetic parameters of ondansetron after 8-mg single dose administrations of reference and test preparations in healthy Thai male volunteers (n = 14, mean ± SD).

Formulation	T_{max} (h)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)	$t_{1/2}$ (h)
Reference	2.6 ± 1.8	49.5 ± 18.9	352.2 ± 184.7	4.3 ± 1.3
Test	2.2 ± 0.6	48.5 ± 13.7	323.8 ± 154.5	4.1 ± 1.1

Table 2. ANOVA tables of C_{max} and $AUC_{0-\infty}$ (log transformed) of ondansetron following 8-mg single dose administrations of reference and test preparations in 14 healthy Thai male volunteers.

	Source of Variation	DF	SS	MS	F	P
A. C_{max}	Total	27	2.057			
	Sequence	1	0.017	0.017	0.114	0.741
	Subject (sequence)	12	1.775	0.148	6.941	0.001
	Formulation	1	0.000	0.000	0.003	0.955
	Period	1	0.010	0.010	0.453	0.514
	Error	12	0.256	0.021		
B. $AUC_{0-\infty}$	Total	27	4.265			
	Sequence	1	0.142	0.142	0.440	0.520
	Subject (sequence)	12	3.887	0.324	21.351	0.000
	Formulation	1	0.053	0.053	3.478	0.087
	Period	1	0.001	0.001	0.042	0.841
	Error	12	0.182	0.015		

Table 3. The mean and 90 per cent confidence intervals of C_{max} and $AUC_{0-\infty}$ (log transformed) of ondansetron after 8-mg single dose administrations of reference and test preparations in 14 healthy Thai male volunteers.

	Mean ± SD		SEM[a]	90% CI[b] (Test/Reference)	Acccptable range
	Test	Reference			
C_{max}	3.85 ± 0.26	3.85 ± 0.30	0.055	90.3-110.0	80-125
$AUC_{0-\infty}$	5.69 ± 0.42	5.78 ± 0.39	0.047	88.4-99.6	80-125

[a] $SEM = \sqrt{EMS*(1/N_A+1/N_B)}$; [b] 90% $CI = (X_B - X_A) \pm (t_{12,0.1}*SEM)$

Pharmacokinetic and statistical analysis

A non-compartmental pharmacokinetic method was used to determine the pharmacokinetic parameters of ondansetron. The time to peak plasma concentration (T_{max}) and the peak concentration (C_{max}) were obtained directly from the data. The area under the concentration-time curve ($AUC_{0-\infty}$) and half-life ($t_{1/2}$) were determined by using WinNonlin Standard (version 3.0).

An analysis of variance (ANOVA) was performed on C_{max} and $AUC_{0-\infty}$, using general linear models (GLM) procedure, in which sources of variation were sequence, subjects within sequence, period, and preparation. Bioequivalence between two formulations could be concluded when the 90 per cent confidence intervals for Test/Reference ratio of C_{max} and $AUC_{0-\infty}$ lay within 80-125 per cent.

RESULTS AND DISCUSSION

Ondansetron was well tolerated. No volunteer was withdrawn and no serious adverse event

was found during the study. The average serum concentrations of ondansetron over a 24-hour period are demonstrated in Fig. 2 and the pharmacokinetic parameters are summarized in Table 1. No significant difference was observed in any of the pharmacokinetic parameters analyzed. Maximum ondansetron levels were observed after 2.2 hours (Test) and 2.6 hours (Reference). The average peak concentrations (C_{max}), areas under the concentration-time curve ($AUC_{0-\infty}$), and half-lives for test and reference products were 48.5 *vs* 49.5 ng/ml, 323.8 *vs* 352.2 ng.h/ml and 4.1 *vs* 4.3 hours, respectively. The relative bioavailability of Test/Reference was 0.93. The 90 per cent confidence intervals for Test/Reference of C_{max} and $AUC_{0-\infty}$ were 90.3-110.0 per cent and 88.4-99.6 per cent, respectively (Tables 2 and 3).

SUMMARY

With regard to both C_{max} and $AUC_{0-\infty}$ of ondansetron, bioequivalence of both formulations of 8-mg ondansetron tablets was concluded. These two formulations, therefore, can be used interchangeably.

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การศึกษาชีวสมมูลของยาเม็ดออนแดนซีตรอนในอาสาสมัครชายไทยสุขภาพดี

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จากการศึกษาชีวสมมูลของยาเม็ดออนแดนซีตรอนขนาด 8 มิลลิกรัม ระหว่างยาสามัญ (ผลิตโดยบริษัท ยูนีซัน แล็บบอราตอรี่ ประเทศไทย) และยาต้นแบบ (ผลิตโดยบริษัท Glaxo Wellcome ประเทศสหรัฐอเมริกา) ในอาสาสมัครชายไทยสุขภาพดีจำนวน 14 คน ซึ่งศึกษาแบบสุ่มข้ามสลับ 2 ระยะ ห่างกัน 1 สัปดาห์ แต่ละระยะ อาสาสมัครได้รับยาเม็ดออนแดน-ซีตรอนขนาด 8 มิลลิกรัม จำนวน 1 เม็ดครั้งเดียว และเก็บตัวอย่างซีรัมภายใน 24 ชั่วโมงหลังจากได้รับยา เพื่อนำไปวิเคราะห์หาระดับยาออนแดนซีตรอน โดยใช้เครื่องมือ HPLC-UV และหาตัวชี้วัดทางเภสัชจลนศาสตร์ โดยใช้ non-compartmental analysis ผลการศึกษาพบว่า เวลาที่ยาขึ้นสูงสุดในซีรัม (T_{max}) ระดับยาสูงสุดในซีรัม (C_{max}) และพื้นที่ใต้โค้งระหว่างความเข้มข้นของยาในซีรัมกับเวลา ($AUC_{0-\infty}$) ของยาต้นแบบและยาสามัญเท่ากับ 2.6 กับ 2.2 ชั่วโมง, 49.5 กับ 48.5 นาโนกรัม/มิลลิลิตร และ 352.2 กับ 323.8 นาโนกรัม.ชั่วโมง/มิลลิลิตร ตามลำดับ ร้อยละ 90 ของระดับความเชื่อมั่นของระดับยาสูงสุดในซีรัม และพื้นที่ใต้โค้งระหว่างความเข้มข้นกับเวลาของยาออนแดนซีตรอน ของยาทั้งสองตำรับเท่ากับร้อยละ 90.3-110.0 และร้อยละ 88.4-99.6 ตามลำดับ ซึ่งอยู่ในช่วงร้อยละ 80-125 ดังนั้น ยาเม็ดออนแดนซีตรอนทั้งสองตำรับจึงมีชีวสมมูลซึ่งกันและกัน

คำสำคัญ : ออนแดนซีตรอน, ชีวสมมูล

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