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Pharmacokinetics and bioequivalence of two different 20 mg olmesartan tablets: A randomized, single-dose, two-period crossover study in healthy Korean male volunteers

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ORIGINAL ARTICLE

Olmesartan is an angiotensin receptor blocker (ARB) and is widely used in clinical practice to treat hypertension. To compare the pharmacokinetic (PK) parameters and tolerability of two oral formulations of olmesartan (test drug: OMETAN® 20 mg tablet, reference drug: OLMETEC® 20 mg tablet) and assess their bioequivalence, a randomized, single dose, two-treatment crossover clinical study was conducted. At each period, 40 subjects received the test drug or the reference drug. Blood samples were collected at pre-dose and up to 48 h after study drug administration of each period. Plasma concentrations of olmesartan were measured using liquid chromatography-tandem mass spectrometry. To evaluate PK profiles, maximum plasma concentration (C_{max}) and area under the concentration-time curve from zero to last measurable time (AUC_{last}) were estimated using a non-compartmental method. Tolerability was evaluated based on the incidence of adverse events, vital signs, electrocardiograms, and laboratory tests. A total of 39 subjects completed the study. The geometric mean ratio and 90% confidence intervals (CI) of test drug to reference drug were 1.027 (0.969–1.088) for C_{max} and 1.014 (0.957–1.074) for AUC_{last}, respectively. There were no serious adverse events and both formulations of olmesartan were well tolerated. The OMETAN 20 mg tablet was judged to be bioequivalent to the OLMETEC 20 mg tablet.

Introduction

Without early detection and appropriate treatment, hypertension remains the most significant risk factor for myocardial infarction, stroke, and death.[1] To lower the risk of cardiovascular events or kidney failure, the blood pressure of hypertensive patients should be strictly controlled. There are many classes of antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists (ARBs), beta-blockers, thiazide diuretics, and calcium channel blockers.[2,3]

Olmesartan is an ARB drug, which blocks the angiotensin II type 1 receptor in vascular muscle.[4] It is administered as the prodrug olmesartan medoxomil, which is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. When administered orally, olmesartan is rapidly absorbed and reaches peak plasma concentrations 1–3 h after administration with a terminal half-life reported to be 10–15 h.[5] Approximately 40% of the olmesartan dose is excreted by the kidneys, and the remainder is excreted in feces; the active metabolite is excreted without further metabolism. A number of randomized clinical trials have confirmed the antihypertensive efficacy and tolerability of olmesartan in healthy volunteers and hypertensive patients.[5,6]

The primary objective of the present study was to compare the pharmacokinetics and bioavailability of OMETAN 20 mg film-

coated tablets (Jin Yang Pharm Co. Ltd, Seoul, South Korea) with OLMETEC 20 mg film-coated tablets (Daewoong Pharmaceutical Co. Ltd, Seoul, South Korea) and to evaluate the bioequivalence of the two formulations in 40 healthy Korean male volunteers under fasting conditions.

Methods

The study was conducted at the Clinical Trials Center, Kyung Hee University Hospital, Seoul, South Korea in compliance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice Guidelines of the International Conference on Harmonization, and local laws and regulations.[7] The protocol was approved by the institutional review board at Kyung Hee University Hospital. The study was conducted in accordance with the bioequivalence study guidelines published by Ministry of Food and Drug Safety, South Korea.

Study Population

Eligible subjects were Korean male volunteers aged between 19 and 55 years. Volunteers were judged to be in good health based on previous medical history, physical examination, and laboratory tests. Subjects were excluded if evidence indicated a history of clinically significant diseases. Subjects were also excluded if they could not abstain from drinking alcohol, smoking, or drug use throughout the study, or the use of any prescribed medication during the screening period.

Study design

This study was performed using a randomized-sequence, single-dose, two-period, two-treatment crossover design in under fasting conditions. The doses of olmesartan used in this study were determined based on the therapeutic dose for hypertension.[4] Eligible subjects were randomized into two sequence groups. The subjects in one sequence group were administered a single tablet of test formulation with 240 mL tap water in the first period and, after a 7-day washout period, they received a single tablet of reference formulation in the second period. The subjects in the other sequence group were administered a reference tablet in the first period, and a test tablet in the second period. All the subjects were admitted to the Clinical Trials Center of Kyung Hee University Hospital and on the day before the administration of study drug in each period (day 1, 8). After overnight fasting (for more than 10 hours), they received a dose of either the test or the reference formulation. They were discharged the day after dosing, and they revisited study center for pharmacokinetic evaluation on day 3. Any beverages containing caffeine or alcohol were not allowed during hospitalization.

Sample collection for pharmacokinetic analyses

Blood samples (7 mL each) for pharmacokinetic assessment were collected from a forearm vein catheter or immediate venipuncture at the following time points: 0 (predose), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 h after study drug administration. Before each blood sampling, 1 mL of blood was discarded to completely eliminate flushing solution. Collected blood samples were immediately transferred into heparinized tubes and temporarily stored on ice. The tubes were then centrifuged for 10 min at 1,800×g below 4°C. Plasma was aliquoted and stored below -70°C until analysis.

Quantification of olmesartan plasma concentration

The plasma concentration of olmesartan was determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS; Agilent 1200 system; Agilent Technologies, Santa Clara, CA, USA) method.[8] Chromatographic separation was conducted using a Luna hydrophilic interaction liquid chromatography (HILIC; Phenomenex Inc., Torrance, CA, USA). The calibration curve ranged from zero to 1,000 ng/mL for olmesartan. The lower limit of quantitation was 5 ng/mL. Intra-day and inter-day accuracies were 94.97–99.43% and 98.75–100.01%, respectively. Intra-day and inter-day precisions were ≤4.54% and ≤3.52%, respectively (Supplementary Table 1).

Pharmacokinetic analyses

Pharmacokinetic (PK) parameters were derived using a non-compartmental analysis using Phoenix® WinNonlin® (Version 6.3; Pharsight, Mountain View, CA, USA). The maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were obtained directly from the observed values. Area under the plasma concentration from zero to infinity (AUC_{inf}) was calculated by adding C_{last}/λ_z to AUC_{last}, where C_{last} is the last measurable concentration. The apparent clearance (CL/F) was also calculated by dividing the dosage amount by AUC.

Statistical analysis

Arithmetic means, standard deviations (SDs), median, maximum and minimum values were calculated for continuous data. For categorical data, absolute and relative frequencies were calculated. AUC_{last} and C_{max} were used as primary variables for evaluation of bioequivalence.

The number of study subjects was calculated to demonstrate the bioequivalence between both formulations. The intra-subject coefficient of variance (CV) for primary PK parameters were assumed as 30% A total 40 of subjects were needed to

Table 1. Demographic characteristics of the study subjects

Characteristics	Mean	Median [min–max]	SD	CV (%)
Age (years)	24.9	25.0 [19.0–37.0]	3.5	14.0
Height (cm)	176.2	177.0 [166.0–186.0]	4.8	2.7
Weight (kg)	70.6	70.0 [56.2–95.0]	8.0	11.3

demonstrate the bioequivalence between both formulations with a power of 80% at a 5% significance level.[9]

The generalized linear mixed model was applied for the analysis of log-transformed data of AUC_{last} and C_{max}, using the SAS system (version 9.3; SAS Institute Inc., Cary, NC, USA). The model considered "period," "sequence," and "formulation" as fixed effects and "subjects within each sequence group" as a random effect. For all analyses, effects were considered statistically significant if *P* values were less than 0.05. Based on the mixed model result, 90% confidence intervals (CI) for the ratio of geometric means for test/reference formulations of C_{max} and AUC_{last} were calculated. The formulations were considered bioequivalent if the 90% CIs for those parameters were within the predetermined range 0.8–1.25.

Safety and tolerability assessment

Safety and tolerability were assessed in every subject who received one or more doses of a study drug. Adverse events were assessed for severity, duration, and relationship to the study drug throughout the study. Physical examinations, vital signs, laboratory tests, and 12-lead electrocardiogram (ECG) were also conducted as per protocol.

Results

Subjects

In all, 40 healthy Korean male volunteers were enrolled in this study and one subject dropped out due to consent withdrawal (after administration of reference drug in period 1). Demographics were evaluated for every subject who enrolled the study (Table 1). Mean ± standard deviation (SD) of age was 24.9 ± 3.5 years. Mean weight and height were 70.6 ± 8.0 kg and 176.2 ± 4.8 cm, respectively. There were no significant differences between the sequence groups in terms of subject height, age, or weight.

Pharmacokinetic results

Pharmacokinetics was evaluated for the 39 subjects who completed the study. After administration of a single dose, the mean concentration-time curves of both the test drug and the refer-

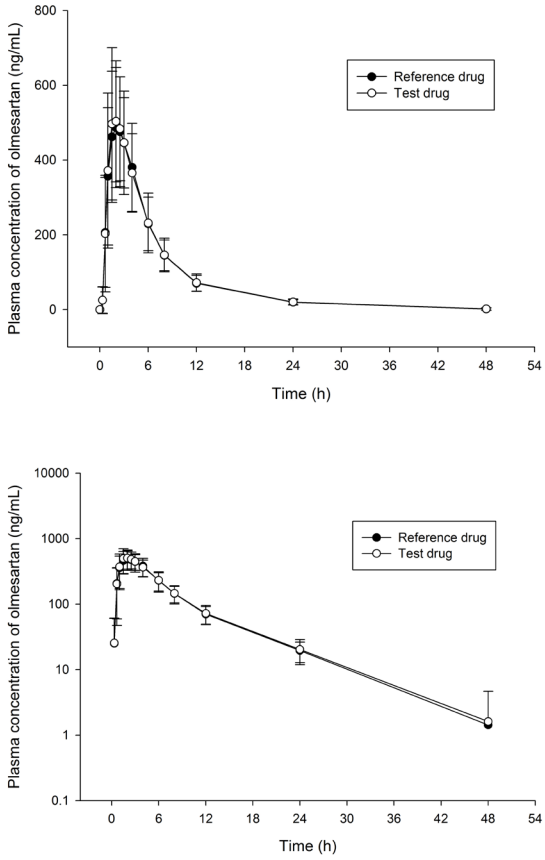

Figure 1. Mean plasma concentration versus time curves of olmesartan after oral administration of a single dose 20 mg olmesartan in healthy Korean subjects (n=39). The error bars represent the standard deviation of olmesartan plasma concentrations (Upper: linear scale, Lower: log scale).

Table 2. Pharmacokinetic parameters of olmesartan after a single administration of 20 mg test and reference drug in Korean healthy subjects (*n* = 39)

Parameters	Test drug (*n* = 39)			Reference drug (*n* = 39)			Intrasubject CV (%)	Intersubject CV %
	Mean	SD	CV (%)	Mean	SD	CV (%)		
T_{max}(h)$^{+}$	2.0 [1.5 – 6.0]			2.0 [1.0 – 4.0]			-	-
C_{max} (ng/mL)	561.56	155.19	27.64	541.31	138.00	25.49	15.24	21.33
AUC_{last} (ng·h/mL)	3560.70	938.58	26.36	3490.45	848.44	24.31	14.88	20.00
AUC_{inf} (ng·h/mL)	3670.40	930.79	25.36	3628.67	882.33	24.32	14.19	20.40
CL/F (L/h)	5.80	1.45	25.09	5.83	1.41	24.20	-	-

$^{+}$Data are presented as median [min - max]. AUC_{last}, area under the plasma concentration time curve from 0 h to the last measurable time; AUC_{inf}, area under the plasma concentration from 0 h to infinity; C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; CL/F, apparent clearance.

Table 3. Pharmacokinetic parameters of olmesartan for the bioequivalence study with geometric mean ratios (test/reference) and 90% confidence intervals after a single dose of reference or test formulation in healthy Korean subjects

Parameters	Geometric mean		Test/Reference ratio	90% confidence interval
	Test	Reference		
C_{max} (ng/mL)	540.368	526.147	1.027	0.969–1.088
AUC_{last} (ng·h/mL)	3440.653	3394.303	1.014	0.957–1.074
AUC_{inf} (ng·h/mL)	3558.072	3528.250	1.001	0.954–1.063

AUC_{last}, area under the plasma concentration time curve from 0 h to the last measurable time; C_{max}, maximum plasma concentration; AUC_{inf}, area under the plasma concentration from 0 h to infinity; C_{max}, maximum plasma concentration.

ence drug were similar, as shown in Figure 1. The calculated PK parameters of olmesartan are summarized in Table 2. The C_{max} and AUC_{last} of the test drug were comparable to those of the reference drug. Specifically, the mean ± SD of AUC_{last} for the test drug and the reference drug were 3560.70 ± 938.58 ng·h/mL, 3490.45 ± 848.44 ng·h/mL, respectively. The mean ± SD of C_{max} for the test and reference drugs were 561.56 ± 155.19 ng/mL and 541.31 ± 138.00 ng/mL, respectively. $AUC_{\%extrap}$ were under 5% for both test drug and reference drug (2.99% and 3.80%, respectively).

Assessment of bioequivalence

The bioequivalence statistics for the PK parameters of the two olmesartan formulations are presented in Table 3. Analysis of variance (ANOVA) of log-transformed data for C_{max}, AUC_{last} and AUC_{inf} did not suggest significant differences between the two formulations. No period, formulation, or sequence effects were detected. Analysis of variance (ANOVA) results for PK parameters were described in Supplementary Table 2. The test/reference geometric mean ratios of primary PK parameters were close to 1.0 (1.027, 1.014, and 1.001 for C_{max} AUC_{last} and AUC_{inf}, respectively). The 90% CIs for olmesartan C_{max}, AUC_{last} and AUC_{inf} were 0.969–1.088, 0.957–1.074, and 0.954–1.063, respectively; all the values of the parameters were within the predetermined range of 80–125% based on the FDAs definition of bioequivalence (Table 3). Intra-subject CV (%) was 15.24%, 14.88% and 14.19% for C_{max}, AUC_{last} and AUC_{inf}, respectively. On the other hand, inter-subject CV (%) was 21.33%, 20.00%, 20.40% for C_{max}, AUC_{last} and AUC_{inf}, respectively.

Safety Profiles and Tolerability

All subjects who took at least one dose of the study drug were included in the tolerability assessment. Both olmesartan formulations were well tolerated in every subject. No serious adverse events were reported. There were no significant clinical findings in the hematology tests, blood chemistry examinations, urine tests, or ECG of the study subjects during the study periods. Blood pressure, pulse rate, body temperature, and the physical examination results of the study subjects showed no clinically significant changes.

Discussion

This study was conducted to evaluate the pharmacokinetics and bioavailability of a single 20 mg dose of olmesartan. In our study, 20 mg tablets of OMETAN® and OLMETEC® were pharmacokinetically comparable; the 90% CIs for the geometric mean ratios of C_{max} and AUC_{last} satisfied the commonly accepted bioequivalence criteria.[10]

Our PK results are consistent with previous clinical studies even in different ethnic groups. Using the same 20 mg dose, a previous clinical study found the AUC_{inf} of olmesartan was 4051 ± 784 ng·h/mL in healthy Chinese subjects which was similar to the finding of this study (i.e. 3670.40 ± 930.79 ng·h/mL, Table 2).[5] Kazutaka Yoshihara et al. also reported that PK profile of olmesartan was not significantly different between Westerners and Japanese based on a population pharmacokinetic model described by a two-compartment linear model with first-order absorption.[11]

PK profiles of olmesartan are reportedly affected by both changes in renal function and age. Hypertension is the leading cause of renal disease, since high blood pressure can damage blood vessels in the kidneys.[12,13] The AUC of olmesartan is reported to increase by 39% and 82% in patients with mild and moderate renal insufficiency, respectively, compared to in healthy subjects.[1] Moreover, systemic exposure of olmesartan is reported to increase in elderly patients as compared to younger patients as a result of decreased renal clearance.[14]

In summary, this study found that the PK values for the test and reference products, which were both film coated tablets containing 20 mg olmesartan, were within the commonly accepted bioequivalence range of 80%–125%. Both formulations of olmesartan were well tolerated by healthy subjects.

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Conflict of interest

None of the authors have any conflicts of interest to disclose.

References

1. von Bergmann K, Laeis P, Puchler K, Sudhop T, Schwocho LR, Gonzalez L. Olmesartan medoxomil: influence of age, renal and hepatic function on the pharmacokinetics of olmesartan medoxomil. J Hypertens Suppl 2001; 19:S33-S40.
2. Nelson M. Drug treatment of elevated blood pressure. Aust Prescr 2010; 33:108-112.
3. Jaques H. NICE guideline on hypertension. Eur Heart J 2013;34:406-408.
4. Greathouse M. A review of olmesartan medoxomil monotherapy: antihypertensive efficacy similar to that of other angiotensin II receptor blocker/hydrochlorothiazide combinations? Congest Heart Fail 2002;8:313-320.
5. Jiang J, Liu D, Hu P. Pharmacokinetic and safety profile of olmesartan medoxomil in healthy Chinese subjects after single and multiple administrations. Pharmazie 2009;64:323-326.
6. Rozza F, Trimarco V, Izzo R, Santoro M, Manzi MV, Marino M, et al. Antihypertensive response to combination of olmesartan and amlodipine does not depend on method and time of drug administration. High Blood Press Cardiovasc Prev 2013;20:25-32.
7. Domjan A, Kakuk P, Sandor J. The Helsinki Declaration at 50 years: comments on the 2013 modifications. Lege Artis Med 2014;24:152-158.
8. Jemal M. High-throughput quantitative bioanalysis by LC/MS/MS. Biomed Chromatogr 2000;14:422-429.
9. Julious SA. Sample sizes for clinical trials with normal data. Stat Med 2004;23:1921-1986.
10. Houin G. Bioequivalence studies: a new EMA guideline. Arzneimittelforschung 2010;60:169-170.
11. Yoshihara K, Gao Y, Shiga H, Wada DR, Hisaoka M. Population pharmacokinetics of olmesartan following oral administration of its prodrug, olmesartan medoxomil: in healthy volunteers and hypertensive patients. Clin Pharmacokinet 2005;44:1329-1342.
12. Johns EJ. The neural regulation of the kidney in hypertension and renal failure. Exp Physiol 2014;99:289-294.
13. Monhart V. Hypertension and chronic renal insufficiency-chronic kidney failure. Vnitr Lek 2003;49:388-394.
14. Volpe M, Tocci G. Olmesartan in the treatment of hypertension in elderly patients: a review of the primary evidence. Drugs Aging 2013;30:987-998.