Bioequivalence Study of 10 mg Ramipril Tablets in Healthy Thai Volunteers

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Objective: *To determine the bioequivalence of 10 mg dose of ramipril tablets between the test product (Ramtace® 10 mg, Unison Laboratories, Thailand) and the reference product (Tritace® 10 mg, Aventis Pharma SPA, Italy).*
Material and Method: *The present study was carried out with a single dose, 2-treatment, 2-period, 2-sequence randomized crossover design under fasting condition with a minimum of 14 days washout period in 24 healthy Thai male and female volunteers. Plasma samples for determination of ramipril and ramiprilat were obtained pre-dose and at frequent intervals for up to 72 h post dose. Ramipril and ramiprilat plasma concentrations were quantified by a validated method employing high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS). All of the pharmacokinetic parameters were investigated using non-compartmental analysis.*
Results: *The result demonstrated the 90% confidence interval (90%CI) of the geometric mean ratio (test/reference) of C_{max}, AUC_{0-72} and $AUC_{0-\infty}$ of ramipril were 97.26% (84.50%-111.93%), 100.70% (89.47%-113.34%) and 100.29% (88.90%-113.15%), respectively. For ramiprilat, the 90% CI for C_{max}, AUC_{0-72} and $AUC_{0-\infty}$ were 108.87% (103.00%-115.07%), 104.93% (100.50%-109.55%) and 103.30% (98.03%-108.85%), respectively.*
Conclusion: *the 90% confidence intervals for log-transformed geometric mean test/reference formulation ratios of primary parameters were entirely within 80.00%-125.00%. Thus, it can be concluded that the test formulation was bioequivalent to the reference formulation.*

Keywords: *Ramipril, Ramiprilat, Bioequivalent, LC-MS/MS*

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Ramipril is a potent and long-acting angiotensin-converting enzyme (ACE) inhibitor that is used for treatment of essential hypertension and congestive heart failure. Results from the HOPE study, indicate that ramipril reduced the relative risk of the composite outcome of MI, stroke and cardiovascular death[1,2]. Furthermore, in the Study to Evaluate Carotid Ultrasound Changes in patients treated with Ramipril and vitamin E (SECURE), ramipril (10mg/day) has also been found to reduce the progression of carotid artery wall thickening to a significant degree[3].

Ramipril is a prodrug that is rapidly absorbed from the gastrointestinal tract and converted to its active metabolite ramiprilat, a dicarboxylic acid, by cleavage of an ester group. These properties account for its potency and long duration of action. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat is 56%. Ramipril and its metabolites are mainly eliminated renally, with approximately 60% being excreted in the urine and approximately 40% excreted in the feces. As ramipril is an anti-hypertensive, the most common adverse reactions are effects secondary to its blood-pressure-lowing action[4-6].

The only original formulation of ramipril available in Thailand is innovator ramipril 10 mg tablets, Tritace® 10 mg, Aventis Pharma SPA, Italy, which is costly for patients. The availability of its generic formulation in the market will bring down the price of the original one and increase the choices for drug prescriptions for the treatment of hypertension. However, since 1994, the bioequivalence study has been mandated for certain generic formulations to be

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registered for marketing in Thailand[7]. The present study is designed to evaluate the quality of the generic formulation of 10 mg ramipril (Ramtace® 10 mg, Unison Laboratories, Thailand) and the reference product in comparison with the original formulation. The generic formulation can be prescribed interchangeably to the original if the present study shows the bioequivalence of the two formulations.

Material and Method

Study drugs

Ramtace® provided by Unison Laboratories Co., Ltd., Thailand (Lot No. 8BI001, Mfg. date 30 October 2008) and Tritace® manufactured by Aventis Pharma, S.P.A., Italy (Lot No. B478, Mfg. date February 2007), were used as test and reference formulations, respectively. Both formulations were prepared as tablets containing 10 mg ramipril.

Subjects

24 healthy Thai volunteers both male and female aged between 18-45 years with a body mass index between 18-24 kg/m^2, assessed to be in good physical condition by completion of medical and laboratory examination were eligible for study participation. They were informed of the details and purposes of the present study and provided written informed consent before participation. Clinical screening included a medical history, physical examination and the following laboratory tests: complete blood count, BUN, serum creatinine, serum potassium, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, fasting blood sugar, urinalysis and hepatitis B surface antigen. Eligible subjects did not smoke for at least 30 days before study participation. Pregnant women or lactating women or positive pregnancy test women were ineligible for enrollment. Urine pregnancy test was performed in female volunteers at the screening visit and prior to each dosing period. Exclusion criteria included allergy to either ramipril or related drugs or its constituents. Volunteers who either used any drugs affecting hepatic microsomal enzymes or other interaction drugs within 14 days before study participation, or had participated in other clinical studies within last 30 days also were excluded.

Study design

An open label, single dose, randomized, two-treatment, two-period, two-sequence crossover design with at least 14 days washout period were used in the present study. The volunteers were randomized and divided equally into two groups by the sequence of product taking that is Test-Reference (TR) and Reference-Test (RT) group. In each period, eligible subjects were confined to the research ward for 24 hours of dosing. A single dose of 10 mg ramipril, either the reference or test formulation was administered with 220 ml water under fasting conditions for at least 10 hours. In each period, 18 blood samples were obtained in EDTA tube. Sampling time points are 0 h (pre-dose sample) and 15, 30, 45, 60, 90 min and 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours after dosing. The clinical part was conducted at Siriraj Clinical Research Center and the bioanalytical part was done at Siriraj Bioequivalent Center, Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University. The present study protocol was approved by the Siriraj Institutional Review Board. The present study was performed in accordance with the Declaration of Helsinki for biomedical research involving human subjects and the Guideline for Good Clinical Practice.

Determination of plasma ramipril and ramiprilat analysis

Analysis of ramipril and ramiprilat were performed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Sample preparation was performed by using liquid-liquid extraction. Enalaprilat was using as an internal standard. Chromatographic separation was carried out on LC-MS/MS with C18 column. A mobile phase consisting of methanol and 1% formic acid (75:25% v/v) was delivered with a flow rate of 0.2 mL/min[8-10]. The mass spectrometer was operated in the multiple reaction monitoring (MRM) modes. The mass transition ion-pair for ramipril was selected as m/z 417.236 > 234.237 for primary daughter ion, for ramiprilat was selected as m/z 389.225 > 206.276 for primary daughter ion whereas for enalaprilat was selected as m/z 349.216 > 206.276 for primary daughter ion. The data acquisition was ascertained by Masslynx 4.1 software. Validation of this method for specificity, selectivity, linearity, precision, accuracy, recovery, and stability was performed in accordance with the USFDA guidelines[11].

Pharmacokinetic and statistical analysis

The individual plasma drug concentration-time curve was plotted and the pharmacokinetic parameters were calculated by non-compartmental methods using WinNonlin® software version 3.1

(Scientific Consulting Inc., Apex, North Carolina). Bioequivalence between the two treatments were compared with respect to $AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, T_{max}, $t_{1/2}$ and λ_z. For the purpose of bioequivalence analysis $AUC_{0-tlast}$, $AUC_{0-\infty(obs)}$ and C_{max} were considered as the primary variables. Two-way analysis of variance (ANOVA) for crossover design was performed for log-transformed data. The 90% confidence interval (CI) for the ratios of geometric mean Test/Reference (T/R) for $AUC_{0-tlast}$, $AUC_{0-\infty(obs)}$ and C_{max} was calculated based on least squares means from the ANOVA of log-transformed data. A non-parametric statistical analysis, Friedman's test using Kinetics 2000 software was performed on T_{max} and considered significant difference between test and reference formulations when $p < 0.05$. The formulations were considered bioequivalent, with regard to regulatory requirements, if the 90% geometric confidence intervals of the ratio (T/R) of least-squares means from the ANOVA of the log-transformed $AUC_{0-tlast}$, $AUC_{0-\infty(obs)}$ and C_{max} should be within 80.00% to 125.00%.

Tolerability

With concern for the safety of the volunteers, vital signs were measured and assessed as baseline prior to each study drug administration and repeated at hour 24, 48, and 72 hours of blood sampling. All adverse events occurred were recorded and evaluated for their seriousness, severity, and relationship to the given dose.

Results

Demographic data

Twenty-four subjects were enrolled and randomly divided into two groups, TR and RT groups. The mean age of subjects in group TR (7 male and 5 female) was 26 years and the mean body mass index (BMI) was 20.7 kg/m^2. For RT group (5 male and 7 female), the mean ages of volunteers was 29.3 years, and the mean body mass was 21.8 kg/m^2 at the time of screening. One volunteer did not attend the present study due to personal reasons.

Bioavailability and pharmacokinetic parameters

Ramipril pharmacokinetics

The geometric mean C_{max} was 44.4 ng/mL for the reference formulation and 43.5 ng/mL for the test formulation. The geometric mean $AUC_{0-tlast}$ for the reference and test formulations was 43.5 ng.h/mL and 42.6 ng.h/mL while the geometric mean $AUC_{0-\infty(obs)}$ for the reference and test formulations were 44.0 ng.h/mL and 42.9 ng.h/mL, respectively. The median (range) of the time taken to achieve the maximum concentration (T_{max}) was 0.50 (0.25-1.00) h for the reference formulation and 0.50 (0.25-1.00) h for the test formulation. The geometric mean value for $T_{1/2}$ obtained from the reference formulation was 2.58 h, whereas $T_{1/2}$ obtained from the test formulation was 2.66 h. The geometric mean terminal elimination rate constant (λ_z) for the reference and test formulation was 0.269 h^{-1} and 0.260 h^{-1}, respectively.

Ramiprilat pharmacokinetics

For ramiprilat, the geometric mean C_{max} was 31.1 ng/mL for the reference formulation and 32.7 ng/mL for the test formulation. The geometric mean $AUC_{0-tlast}$ for the reference and test formulations was 301 ng.h/mL and 310 ng.h/mL while the geometric mean $AUC_{0-\infty(obs)}$ for the reference and test formulations were 354 ng.h/mL and 361 ng.h/mL, respectively. The median (range) of the time taken to achieve the maximum concentration (T_{max}) was 2.50 (1.00-5.00) h for the reference formulation and 2.50 (1.00-5.00) h for the test formulation. The geometric mean value for $T_{1/2}$ obtained from the reference formulation was 28.2 h, whereas $T_{1/2}$ obtained from the test formulation was 27.3 h. The geometric mean terminal elimination rate constant (λ_z) for the reference and test formulation was 0.0246 h^{-1} and 0.0254 h^{-1}, respectively. Summary of pharmacokinetic parameters is shown in Table 1.

Bioequivalence analysis

Bioequivalence statistics 90% confidence interval of geometric mean ratio of bioavailability parameters between the test and reference formulation for ramipril and ramiprilat are presented in Table 2 and 3. The geometric mean of plasma concentration-time

Table 1. Summary of the pharmacokinetics parameters

Parameters	Ramipril		Ramiprilat	
	Reference	Test	Reference	Test
C_{max} (ng/mL)	53.6	47.7	36.4	40.0
$AUC_{0-tlast}$ (ng.h/mL)	54.7	47.7	320	335
$AUC_{0-\infty(obs)}$ (ng.h/mL)	55.2	48.0	381	395
T_{max} (h)	0.458	0.559	2.56	2.50
λz (h^{-1})	0.294	0.307	0.031	0.028
$T_{1/2}$ (h)	2.86	3.14	32.9	30.6

R = reference product: Tritace; T = test product: Ramtace

Table 2. Statistical summary of the comparative bioavailability data of ramipril (n = 23)

Dependent	Geometric mean ratio (T/R)	90% CI lower	90% CI upper	Power	Intra-subject coefficient of variation (CV%)
Ln (C_{max})	97.26	84.50	111.93	0.8385	28.20
Ln ($AUC_{0\text{-}tlast}$)	100.70	89.47	113.34	0.9291	23.60
$AUC_{0\text{-}\infty(obs)}$)	100.29	88.90	113.15	0.9210	24.10

T = test product; R = reference product

Table 3. Statistical summary of the comparative bioavailability data of ramiprilat (n = 23)

Dependent	Geometric mean ratio (T/R)	90% CI lower	90% CI upper	Power	Intra-subject coefficient of variation (CV%)
Ln (C_{max})	108.87	103.00	115.07	1.0000	10.94
Ln ($AUC_{0\text{-}tlast}$)	104.93	100.50	109.55	1.0000	8.50
$AUC_{0\text{-}\infty(obs)}$)	103.30	98.03	108.85	1.0000	10.33

T = test product; R = reference product

profile of ramipril and ramiprilat are also presented in Fig. 1 and 2. The statistical analysis of ramipril obtained from the present study (n = 23) showed that the point estimate (90% confidence interval) of the geometric mean ratio (test/reference) of C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty(obs)}$ were within the equivalence criteria (80.00-125.00%) which was 97.26% (84.50%-111.93%) for C_{max}, 100.70% (89.47%-113.34%) for $AUC_{0\text{-}tlast}$ and 100.29% (88.90%-113.15%) for $AUC_{0\text{-}\infty(obs)}$. For ramiprilat, the 90% CI for C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty(obs)}$ were entirely within the equivalence criteria (80.00-125.00%) which was 108.87% (103.00%-115.07%), 104.93% (100.50%-109.55%) and 103.30% (98.03%-108.85%) for C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty(obs)}$, respectively. There was no statistical difference of median T_{max} between the test and reference formulations ($p > 0.05$).

Tolerability

Safety profiles were noted between the two formulations of ramipril. Treatments were generally well tolerated. Sixteen adverse events were reported in seven volunteers (8 events after taking the reference product and 8 events after taking the test product). The most adverse events were pain and dizziness (3), the other adverse events including fever (2), diarrhea (2), sore throat (2), headache (1), nausea (1), malaise (1), palpitation (1), sweating (1), thirsty (1), and upper respiratory tract infection symptoms such as cough and running nose (1). All of the reported adverse events were mild in intensity. No serious adverse effects were observed throughout the present study. All of the occurred adverse events were reported to the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University. Adverse events that occurred in the present study are presented in Table 4.

Discussion

The ramipril and ramiprilat plasma concentration-time profiles of the generic and branded formulations were comparable. The pharmacokinetic parameters in these healthy Thai volunteers were in agreement with the previously reported values. These values are similar to previously reported values in other ethnic groups, like volunteers from Chinese, Italian and Brazilian population[12-14].The statistical analysis was carried out for both untransformed and log transformed data. The data is showing statistical equivalence for the important pharmacokinetic parameters *i.e.* C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty(obs)}$. The 90% confidence intervals are well within the limits and can be acceptable by any regulatory agency. The power of all parameters was above 80% indicating that a sample size of 23 volunteers was adequate.

The analytical method (LC-MS/MS) of thepresent study was precise and accurate (CVs% of ramipril and ramiprilat < 15%). The current method has shown acceptable precision and adequate sensitivity for the quantification of ramipril and ramiprilat in human plasma samples obtained for pharmacokinetic, bioavailability or bioequivalence studies.

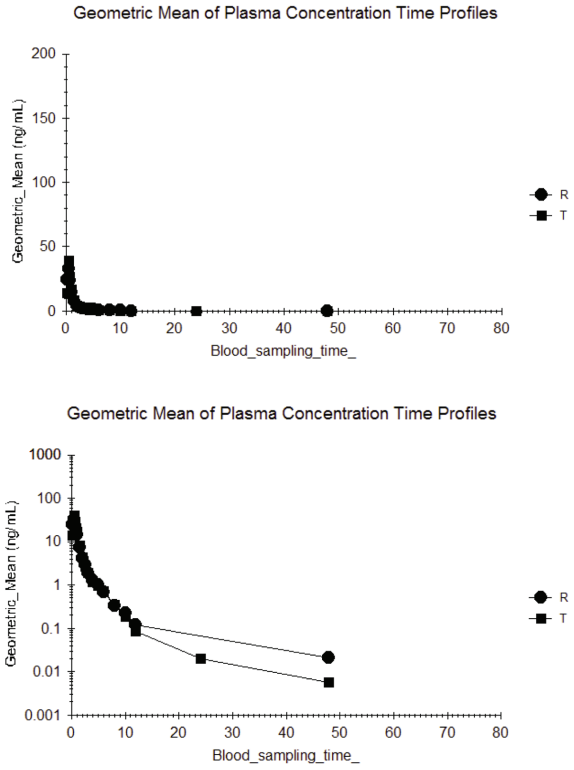

Fig. 1 Geometric mean of plasma concentration-time profile of ramipril (n = 24 for reference, n = 23 for test); normal plot (above) and semilog plot (below)

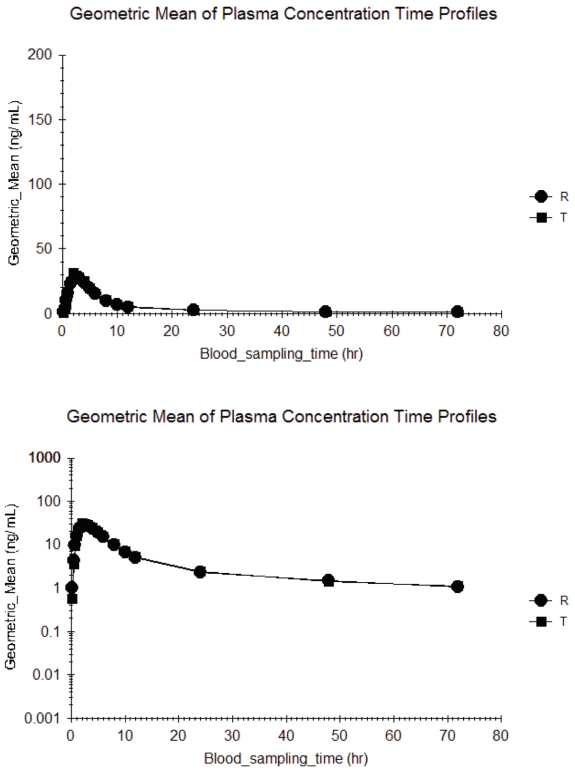

Fig. 2 Geometric mean of plasma concentration-time profile of ramiprilat (n = 24); normal plot (above) and semilog plot (below)

Table 4. Summary of adverse events

Adverse events	Reorted incidience by treatment groups		Total
	Tritace®	Ramtace®	
Dizziness	2	1	3
Sore throat	2	-	2
Fever	1	1	2
Diarrhea	1	1	2
Headache	1	-	1
Malaise	1	-	1
Nausea	-	1	1
Palpitation	-	1	1
Sweating	-	1	1
Thirsty	-	1	1
Upper respiratory tract infection symptom	-	1	1
Total	8	8	16

None of the reported AEs was considered serious. In the present study, the most common adverse event was dizziness. The subjects tolerated to well the present study medication.

Conclusion

The bioequivalence study of 10 mg ramipril tablet formulations was conducted in 24 healthy Thai male and female volunteers between a generic product

(Ramtace®) and the reference product (Tritace®). The results showed that both formulations were well tolerated. The 90% confidence intervals for log-transformed geometric mean test/reference formulation ratios of primary parameters including Cmax, $AUC_{0\text{-tlast}}$ and AUC0-∞ were entirely within 80.00%-125.00% [15]. There was no statistically significant difference of tmax between the reference and the test groups ($p > 0.05$). Thus, both reference and test products were bioequivalent as rate and amounts of drug absorption.

Acknowledgement

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Potential conflicts of interest

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การศึกษาชีวสมมูลของยาเม็ดรามิพริล ขนาด 10 มิลลิกรัม ในอาสาสมัครไทยที่มีสุขภาพแข็งแรง

สมฤดี ฉัตรสิริเจริญกุล, วีรวรรณ ตั้งบุญจิตร, ปิยาภัทร พงศ์นรินทร์, ขนิษฐา คนหาญ, กอบธัม สถิรกุล, สุพรชัย กองพัฒนากูล

วัตถุประสงค์: *เพื่อศึกษาชีวสมมูลของยาเม็ดรามิพริลขนาด 10 มิลลิกรัม ระหว่างผลิตภัณฑ์ยาสามัญ Ramtace® ของบริษัท ยูเนียน แลบบอราทอรีย์ ประเทศไทย กับผลิตภัณฑ์ยาต้นแบบ Tritace® ของบริษัท อเวนติส ฟาร์มา*

วัสดุและวิธีการ: *การศึกษานี้เป็นแบบ a single dose, 2-treatment, 2-period, 2-sequence randomized crossover design ในขณะท้องว่าง มีระยะเวลา washout period อย่างน้อย 14 วัน ทำการศึกษาในอาสาสมัครไทย สุขภาพดี ทั้งเพศหญิงและชาย จำนวน 24 ราย ทำการวัดระดับ ramipril และ ramiprilat ในตัวอย่างเลือดของอาสาสมัคร ตั้งแต่ก่อนรับประทานยาและตรวจวัดเป็นระยะจนถึง 72 ชั่วโมง การวัดระดับยานี้ใช้เทคนิค high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) จากนั้นนำค่าที่วัดได้มาหาค่าทางเภสัชจลนศาสตร์โดยใช้ non-compartment model*

ผลการศึกษา: *ค่าความเชื่อมั่นที่ 90% เมื่อเปรียบเทียบสัดส่วนของค่าเฉลี่ยระหว่างผลิตภัณฑ์ยาสามัญกับผลิตภัณฑ์ยาต้นแบบของ ramipril จะได้ค่าของ C_{max}, AUC_{0-72} และ $AUC_{0-\infty}$ เท่ากับ 97.26% (84.50%-111.93%), 100.70% (89.47%-113.34%) และ 100.29% (88.90%-113.15%) ตามลำดับ ในส่วนของ ramiprilat จะได้ค่าของ C_{max}, AUC_{0-72} และ $AUC_{0-\infty}$ เท่ากับ 108.87% (103.00%-115.07%), 104.93% (100.50%-109.55%) และ 103.30% (98.03%-108.85%) ตามลำดับ*

สรุป: *ค่าความเชื่อมั่นที่ 90% เมื่อเปรียบเทียบสัดส่วนของค่าเฉลี่ยระหว่างผลิตภัณฑ์ยาสามัญกับผลิตภัณฑ์ยาต้นแบบของค่าสำคัญทางเภสัชจลนศาสตร์อยู่ในช่วงที่ได้รับการยอมรับคือ 80.00%-125.00% ดังนั้นจึงสรุปได้ว่า ผลิตภัณฑ์ยาสามัญมีชีวสมมูลกับผลิตภัณฑ์ยาต้นแบบ*