

Bioequivalence Study of Two Formulations of 35mg Trimetazidine Modified Release Tablets in Healthy Thai Volunteers Under Fasting and Fed Conditions

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Abstract

Background: The generic product of trimetazidine, an anti-anginal agent, is currently available in Thailand. Bioequivalence study is used to compare rate and extent of absorption between generic and innovator's products.

Objective: To determine the bioavailability of two modified release tablets of 35mg trimetazidine dihydrochloride (Matenol[®] MR; generic product and Vastarel[®] MR; innovator's product)

Materials and methods: The study was conducted according to a single-dose, two-treatment, two-period, two-sequence randomized crossover design under fasting and fed conditions with a minimum of 7 days washout period. Twenty-four healthy Thai male and female volunteers were enrolled; however, only twenty-two subjects in the fasting group and twenty-three subjects in the fed group were completed the studies. For both conditions, each volunteer received a 35mg trimetazidine modified release tablet of both formulations. Every volunteers were obtained blood samples 16 times over a period of 24 hours after each oral administration. The trimetazidine plasma concentrations were quantified using a validated method employing liquid chromatography with tandem mass spectrometry with the lower limit of quantification of 0.25 ng/mL. All of the pharmacokinetic parameters were investigated using non-compartmental analysis model.

Results: The 90% confidence interval of the geometric mean ratio of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were within the equivalence criteria (80.00-125.00%) which were 105.53% (95.71%-116.36%), 104.28% (96.24%-112.98%), and 105.26% (96.61%-114.67%) under fasting condition and 110.21% (102.72%-118.25%), 101.95% (94.33%-119.19%), and 99.7% (91.18%-109.02%) under fed condition, respectively. No statistical differences of median T_{max} ($p > 0.05$) between two formulations in both conditions were observed. Furthermore, both preparations were well tolerated and had a few non-serious adverse events including nausea, dizziness, drowsiness and headache.

Conclusion: These two trimetazidine products have comparable bioavailability.

Keywords: Trimetazidine; Bioequivalence; Pharmacokinetics

Introduction

Trimetazidine dihydrochloride is a clinically effective, well-tolerated anti-anginal agent which has been used in the prophylaxis and treatment of angina pectoris [1]. It also has been reported to be an effective agent for treating heart failure [2]. The chemical structure of trimetazidine was shown in Figure 1. This drug acts via metabolic pathway by inhibition of the enzyme 3-ketoacyl coenzyme A thiolase, results in a shift of cardiac metabolism from free fatty acid metabolism to glucose oxidation [3,4]. The cardiac utilization of glucose as a substrate for energy production is an effective approach to treat ischemic myocardium because it requires less oxygen consumption to produce the same amount of adenosine triphosphate [4,5]. Two formulations of trimetazidine are available in the clinical practice, the immediate-release and the modified-release tablet. The latter dosage form was developed to reduce frequency of dosing while maintaining a sustained 24 hour coverage [6]. It has been shown to improve patient compliance thus more effective than a conventional tablet [7]. The pharmacokinetic profiles of two dosage forms of trimetazidine are different. After oral administration, both trimetazidine tablets are rapidly absorbed. The immediate-release tablet reached peak plasma concentration within 2 hours compared with 5 hours for the modified-release tablet [8]. Trimetazidine is widely distributed throughout the body and mainly excreted in urine with approximately 60% eliminated unchanged. Eight metabolites of the drug have been detected in urine,

but their properties were not known [1]. The elimination half life of conventional tablet and modified-release tablet are approximately 6 and 7 hours, respectively [8].

Trimetazidine modified-release tablet has been manufactured and marketed by several pharmaceutical companies. The bioavailability of different brands are doubted. Bioequivalence is a surrogate for therapeutic equivalence used to demonstrate whether two different drug products with the same active substance, strength and dosage form are comparable in terms of rate and extent of absorption. The present study aimed to compare bioavailability of two trimetazidine modified-release products in healthy Thai volunteers. The first one is a local or test product, Matenol[®] MR manufactured by Unison

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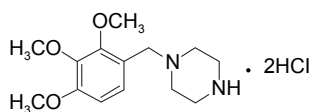


Figure 1: Trimetazidine dihydrochloride.

Laboratories Co., Ltd, Thailand and another one is an innovator or reference product, Vastarel[®] MR manufactured by Les Laboratoires Servier Industries, France.

Methods

Subjects

Twenty four healthy Thai volunteers of both sex who have the age range from 18 to 45 years old with a body mass index between 18-24 kg/m² were enrolled into the study. After passing a clinical screening procedure which included a medical history, physical examination and laboratory tests (hematology, blood biochemistry, hepatitis B surface antigen, urine analysis and urine pregnancy test in only female volunteers). The volunteers were given a detailed explanation of the aims, restrictions and possible adverse effects which could be experienced as a result from administration of a study drug. Written informed consent was obtained. Eligible volunteers were instructed to abstain from alcohol, smoking and medication including over-the-counter products during the study.

The study protocol and related materials were reviewed and approved by Siriraj Institutional Review Board (SIRB) of Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The study was conducted according to the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines [9] at the Siriraj Clinical Research Center (SICRC), Siriraj Hospital, Bangkok, Thailand.

Study drugs

Test preparation: Matenol[®] MR (Unison Laboratories Co., Ltd, Thailand) containing 35 mg trimetazidine per tablet (Lot no. T06/8-247, Mfg. date 8 April 2008, Exp. date 29 July 2010).

Reference product: Vastarel[®] MR (Les Laboratoires Servier Industries, France) containing 35 mg trimetazidine per tablet (Lot no. 762598, Mfg. date May 2006, Exp. date May 2009).

Study procedures

This was a single-dose, randomized, open-label, two-sequence crossover design consisting of separated fasting and fed parts. In each part, the volunteers were randomly allocated into two groups by sequence of product taken (test-reference (TR) and reference-test (RT) group) using a pre-printed randomization table. A single dose of 35 mg trimetazidine modified-release tablet of either the test or reference formulation were administered with 220 ml drinking water. Subjects were confined to the research ward and observed by physicians and nurses until 24 hours after administration of a study drug. The study was repeated with the alternative formulation after a minimum of 7 days washout period.

In both the fasting and fed studies, all volunteers had an overnight fasting of at least 10 hours. Only water was allowed to be taken before and after an hour of dosing. In the fed group, a standard meal was

served 30 minutes prior to drug administration. Administration of a study drug was under supervision of registered nurses to ensure that a drug was all ingested. After drug administration, volunteers were not allowed to recline for the first 2 hours. In both studies, standard meals were served at 4, 8 and 12 hours after drug administration. A total of 16 blood samples (6 ml each sample) were collected from each volunteer in each part of the study using lithium heparinized tube. Sampling time points are at 0 hour (pre-dose sample) and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12 and 24 hours after dosing. The samples were centrifuged to separate from the plasma and stored at -70°C until analysis.

Safety assessment

Safety monitoring was done throughout the study period. Physical examination and vital signs measurement was assessed as baseline prior to each study drug administration, repeated at 24 hour of blood sampling and reassessed whenever subjects reported or experienced any adverse events. All reported adverse events were evaluated and recorded by the study physicians.

Sample analysis

The plasma concentration of trimetazidine was analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method [10]. Trimetazidine was extracted from samples by liquid-liquid extraction with n-hexane and methyl t-butyl ether. Lidocaine was used as an internal standard and was added to plasma sample or trimetazidine standard sample. After well mixed, all samples were centrifuged at 12418 g for 10 minutes. The organic layer was transferred into a new conical microtube and was dried by evaporating under a nitrogen stream. The residue was reconstituted with reconstituting solvent and was injected into the LC-MS/MS system.

Chromatographic separation was carried out on LC-MS/MS with C18 column (50×3.0 mm, 2.5 μm material). A mobile phase consisting of acetonitrile and 10 mM ammonium acetate (60:40, v/v) was delivered with a flow rate of 0.2 mL/min. Mass spectra were obtained using a Quattro Micro mass spectrometer (Micromass, UK) equipped with electrospray ionisation (ESI) source. The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode. The data acquisition and analysis were calculated using Masslynx 4.0 software. The mass transition ion-pair for trimetazidine was selected as *m/z* from 267.13 to 181.18 and 267.13 to 166.13, for lidocaine from 235.14 to 86.28.

The bioanalytical method was validated for specificity, selectivity, linearity, precision, accuracy, recovery of extraction and stability according to the USFDA guidance [11]. This method has a lower limit of quantification (LLOQ) of 0.25 ng/mL. A linearity calibration curve for trimetazidine was established in the range of 0.25 to 1000 ng/mL with the coefficient of determination (*r*²) of 0.997967. Precision, accuracy and stability were within the acceptable range.

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters of trimetazidine were analyzed by non-compartmental methods using WinNonlin[®] software version 3.1. To evaluate the bioequivalence between the test and the reference, *C*_{max}, *AUC*_{0-t} and *AUC*_{0-∞} were considered as the primary pharmacokinetic parameters. An analysis of variance (ANOVA) was used to assess the effects of formulation, period, sequence and subject within sequence on *C*_{max}, *AUC*_{0-t} and *AUC*_{0-∞}. Since there were dropouts, ANOVA type III was used for unbalanced data analysis. Pharmacokinetic equivalence

was concluded if the 90% geometric confidence intervals of the ratio (test/reference) of least-squares means from the ANOVA of the log-transform C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were within 80-125%.

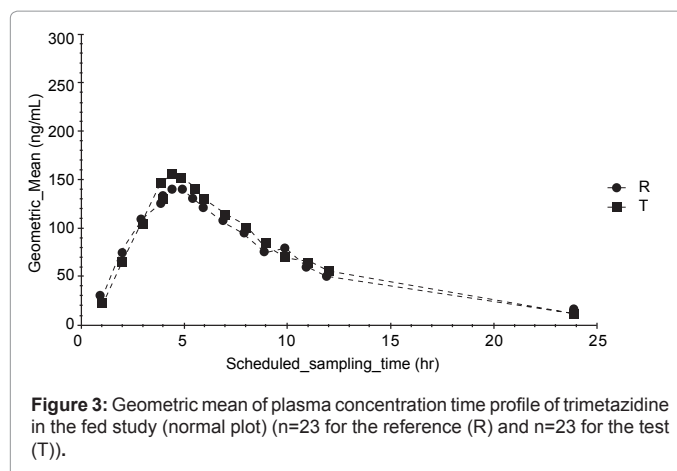
Results

Demographic data

Of the 24 healthy Thai volunteers originally enrolled, 3 withdrew from the studies due to personal reason. As a consequence, there were only 22 subjects from the fasting study and 23 subjects from the fed study included in the statistical analysis of pharmacokinetics parameters. The number of remaining subjects, however, was sufficient for analysis. For demographic data, mean \pm SD of age, weight, height and BMI were 26.2 ± 4.6 years, 59.6 ± 7.9 kg, 167.3 ± 8.1 cm and 21.2 ± 1.7 kg/m², respectively. The laboratory data of all subjects were within an acceptable range.

Pharmacokinetic parameters and bioequivalence analysis

The geometric mean plasma concentration-time profile after oral administration of Matenol[®] MR (T) and Vastarel[®] MR (R) under fasting and fed state were shown in Figure 2 and 3, respectively. In the fasting condition, the geometric mean C_{max} of the test formulation was 142 ng/mL with median T_{max} at 5 h (range 2-7 h) while these of the reference product were 135 ng/mL and 4.5 h (range 3-6 h), respectively. In the fed state, the presence of food was slightly increase the geometric mean C_{max} of both formulations, which were 183 ng/mL for the test and 169 ng/mL for the reference formulation. Nonetheless, food did not affect the median T_{max} of both formulations, as their values were slightly changed compare to those in the fasting state, which were 4.5 h (range 3-6 h) for the test and 5 h (range 3-8 h) for the reference product. The pharmacokinetic parameters and bioequivalence analysis of two products of trimetazidine under fasting and fed state were summarized in Table 1. In the fasting condition, the 90% confidence intervals of geometric mean ratio (test/reference) of the log-transform for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were entirely within equivalence criteria (80.00-125.00%) which were 105.53% (95.71%-116.36%) for C_{max} ratio, 104.28% (96.24%-112.98%) for AUC_{0-t} ratio and 105.26% (96.61%-114.67%) for $AUC_{0-\infty}$ ratio. In the fed condition, all values were also within the acceptable bioequivalence range which were 110.21% (102.72%-118.25%) for C_{max} ratio, 101.95% (94.33%-119.19%) for AUC_{0-t} ratio and 99.7% (91.18%-109.02%) for $AUC_{0-\infty}$ ratio. In addition, a non-parametric statistical analysis (Friedman's test) using Kinetics 2000 software found no significant differences of



the T_{max} between the two studied formulations ($p > 0.05$). Therefore, it was concluded that the two modified release tablet formulations of 35 mg trimetazidine dihydrochloride were bioequivalent in terms of rate and extent of absorption.

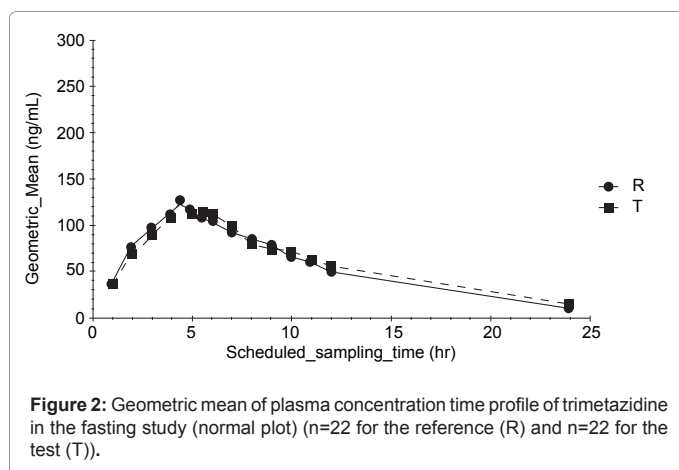
Adverse events (AEs)

The two trimetazidine formulations were well tolerated under both fasting and fed conditions. No serious adverse events occurred. Nonetheless, a total number of 13 AEs from 8 volunteers were reported. In the fasting condition, 5 AEs were reported included 3 dizziness from the test product and 2 nausea (one event from the reference product and another event from the test product). In the fed study, 8 AEs were reported which were 2 dizziness (one event from the reference product and another event from the test product), 3 drowsiness (1 AE from the reference product and 2 AEs from the test product), an AE of nausea and headache from the reference product, and an AE of common cold from the test product. All of AEs were graded mild degree in intensity and required no additional medical treatment. The causality was assessed by the study physician for all AEs, except common cold, as possibly or probably related to study drug.

Discussion

The aim of this present study was to compare the bioavailability of a single orally administered of the generic 35 mg trimetazidine modified-release tablet with the innovator's product. This study was performed according to the USFDA guidance [12,13] which recommended that bioequivalence studies of orally administered modified-release products be performed under both fasting and fed conditions. The acceptance bioequivalence criteria were similar among regulatory agencies which suggested that the 90% confidence intervals of the geometric mean ratios (test/reference) of log transformed values of AUC and C_{max} were within the range of 80.00-125.00% [12,14,15]. The results of our study showed that these values of AUC and C_{max} were all within the acceptable range in both fasting and fed state. The median of T_{max} of the test and the reference drugs were not significantly different. In fact, their values were consistent with other previous report [16]. The power of the test was also calculated for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. The power of all parameters were above 0.80 which indicated that this study has adequate sample size.

Both trimetazidine modified-release products were well tolerated in the study population as there were only mild adverse events reported.



Pk Parameters	Conditions					
	Fasted			Fed		
	Product (Geometric Mean \pm CV%)		90% CI of the mean ratios (T/R) of log transformed values	Product (Geometric Mean \pm CV%)		90% CI of the mean ratios (T/R) of log transformed values
	Matenol [®] (Test) (n=22)	Vastarel [®] (Reference) (n=22)		Matenol [®] (Test) (n=23)	Vastarel [®] (Reference) (n=23)	
C _{max} (ng/mL)	142 \pm 37.3	135 \pm 41.9	95.71 - 116.36	183 \pm 42.4	169 \pm 38.9	102.72 - 118.25
AUC _{0-t} (ng-hr/mL)	1320 \pm 42.5	1270 \pm 44.7	96.24 - 112.98	1440 \pm 46.7	1450 \pm 46.9	94.33 - 119.19
AUC _{0-∞} (ng-hr/mL)	1430 \pm 41.8	1360 \pm 45.2	96.61 - 114.67	1530 \pm 47.6	1580 \pm 53.8	91.18 - 109.02
T _{max} (hr)*	5 (2-7)	4.5 (3-6)	-	4.5 (3-6)	5 (3-8)	-
T _{1/2} (hr)	5.62 \pm 17.5	5.32 \pm 13.8	-	4.97 \pm 26.6	5.29 \pm 33.3	-

C_{max} = maximum plasma concentration
AUC_{0-t} = area under the curve over 24 hours
AUC_{0-∞} = area under the curve to infinite time
T_{max} = time of maximum plasma concentration * data expressed as median (range)
T_{1/2} = elimination half-life
90% CI = 90% confidence intervals

Table 1: Pharmacokinetic parameters of Matenol[®] (test) and Vastarel[®] (reference) with 90% confidence interval of the geometric mean ratios (Test/Reference).

The limitation of this study is its generalization. Since this study was included only healthy Thai volunteers, its results may not be applied to other populations.

Conclusion

The bioequivalence study of two modified-release tablets of 35mg trimetazidine in healthy Thai volunteers were completed and revealed pharmacokinetic equivalence in terms of both rate and extent of absorption.

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