Food Effect on Bioavailability of Modified-Release Trimetazidine Tablets

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This study aimed to investigate a food effect on the bioavailability of modified-release (MR) trimetazidine tablets in 36 healthy volunteers. Trimetazidine, an anti-ischemic drug, protects the myocardial cell from the harmful effects of ischemia. The authors investigated the effect of being under a fasting or fed state at the time of drug intake on the bioavailability of trimetazidine 35-mg MR tablets in a randomized, open-label, crossover, 2-arm, 4-period, 2-sequence bioequivalence study design with a 14-day washout period. Plasma concentration of trimetazidine was assayed in timed samples with a validated high-performance liquid chromatography/mass selective detector that had a lower limit of quantification of 2.5 ng/mL. Test and reference formulations gave a mean trimetazidine Cmax of 63.26 ng/mL and 69.18 ng/mL for the fasting state and 64.19 ng/mL and 63.11 ng/mL for the fed state, respectively. The AUC0-tlast mean of trimetazidine was 726.31 ng·h/mL and 733.01 ng·h/mL for the fasting state and 706.40 ng·h/mL and 691.40 ng·h/mL for the fed state for test/reference formulations. There were no significant differences in pharmacokinetic parameters between the 2 formulations and the fasting/fed states. The authors showed that there is no food effect and no need for a 4-period study to evaluate the bioequivalence of trimetazidine MR tablets.

Keywords: trimetazidine; bioavailability; food effect; pharmacokinetics; bioequivalence

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Trimetazidine (1-(2,3,4-trimethoxybenzyl)piperazine)(Biopharmaceutics Classification System, class II [BCS II]; Figure 1) is an anti-ischemic drug that protects the myocardial cell from the harmful effects of ischemia.1 The major drug-related component observed in plasma and urine is unchanged trimetazidine.2 In addition to the parent drug, 10 metabolites have been detected in urine. However, none of them is active. Seven routes of metabolism have been identified in humans, including 2 phase I oxidation reactions and 5 phase II conjugation reactions. Trimetazidine and its metabolites are predominantly eliminated in urine.2 A small proportion of trimetazidine (6%) is also excreted in the feces.2

The feeding state at the time of oral drug administration may change the bioavailability (BA) of a drug and influence the bioequivalence (BE) of test and reference products. Food may alter BA and have clinically significant consequences by various means.3 For modified-release (MR) drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance.

Trimetazidine 35-mg MR tablets were developed to maintain effective plasma concentrations. Time of peak plasma concentration (tmax) is longer for MR tablets, and trimetazidine MR produces sustained plasma levels compared to immediate-release (IR) tablets, with a resulting enhancement of pharmacokinetic effects.2 However, as mentioned above, the formulation, dose, and fed/fasting state are important pharmacokinetic parameters.

Therefore, we investigated the effect of being under the fasting or fed state at the time of drug intake on the bioavailability of trimetazidine MR tablets in this crossover clinical trial. The analytical methods used in the determination of trimetazidine have been reported in studies that are suitable for analyzing trimetazidine from plasma and applicable to bioequivalence studies.4,5 In this study, we report the food effect on the pharmacokinetics of trimetazidine in healthy...
volunteers. We also determined the bioequivalence of 2 different formulations of trimetazidine.

PARTICIPANTS AND METHODS

Test and Reference Medications

Trimetazidine tablets were obtained from the following pharmaceutical companies: Mentis Ilac Sanayi ve Ticaret A.S., Turkey (batch number 2008010773) for test products and Les laboratories Servier, France (816883) for reference products.

Participants

A total of 36 healthy male volunteers were enrolled in the trial. All of them fulfilled the following inclusion criteria: male, white, aged between 18 and 55 years, physically and mentally healthy as judged by standard physical and laboratory examinations, negative drug screening tests, and body mass index (BMI) between 17 and 29 kg/m². A total of 36 volunteers (mean [SD] age, 33.6 [9.5] years; height, 168.9 [7.4] cm; weight, 72.7 [9.5] kg) completed the trial according to the protocol. Exclusion criteria were as described by the European Medicines Agency (EMEA) Guideline on the Investigation of Bioequivalence.7 The study was performed in accordance with the relevant articles of the Declaration of Helsinki (1964) and its latest revision in Seoul (2008); the note on Guidance on Good Clinical Practice (CPMP/ICH/135/95), with the Committee for Proprietary Medicinal Products (CPMP) note on Guidance for Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98); and Turkish law and regulations. Before being enrolled in the clinical study, each volunteer signed a written informed consent after being informed about the nature, scope, possible consequences, and design of the study. Before the start of the study, all documents were approved by the ethics committee of Yeditepe University School of Medicine in Istanbul and the Central Ethics Committee of the Turkish Ministry of Health in Ankara, Turkey.

Study Design and Procedures

This was a randomized, open-label, crossover, 2-arm, 4-period, 2-sequence bioavailability and bioequivalence study. In periods I and II, participants received a single dose of either reference (arm A) or test (arm B) drug containing trimetazidine 35 mg as MR tablets after an overnight fast (at least 10 hours), and in periods III to IV, they received a single dose of the same tablets within 30 minutes of consuming a standard breakfast (650 kcal) with a 14-day washout (t½ = 6-12 hours) between each period (Figure 2). Venous blood samples were taken before and at regular intervals after drug administration as described below. Plasma concentrations of trimetazidine were measured from each blood sample. Standard pharmacokinetic parameters were calculated.

Blood Sample Collection

Blood samples (6 mL) were drawn just before the drug administration (predose) and at 0.5, 1, 1.33, 1.66, 2.0, 2.33, 2.66, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 72 hours postdose. The blood samples were centrifuged no later than 20 minutes after sampling to separate the plasma. Plasma samples were frozen and kept below −70°C until analysis.

Bioanalytical Method

The method developed and validated before the study to determine trimetazidine used a high-performance liquid chromatography (HPLC)/mass selective detector (MSD). The internal standard was lidokain. Separation was achieved by using a Zorbax Eclipse C18 column (4.6 × 150 mm, 5 µm; Agilent Technologies, Santa Clara, California) with methanol-aqueous 0.1% trifluoroacetic acid (40:60, v/v) at a flow rate of 0.6 mL/min after liquid-liquid extraction in the range of 2.5 to 2000 ng/mL. Trimetazidine was obtained from Cipla (Mumbai, India) as the standard, lidokain and HPLC-grade methanol were from Sigma-Aldrich (St Louis, Missouri), isooamyalcohol was from Merck (Darmstadt, Germany), and ethylacetate and sodium hydroxide were from
Riedel-de-Haen (Berlin, Germany). All other chemicals were also analytical grade, and solvents of HPLC-grade and Millipore (Billerica, Massachusetts) HPLC-grade water were used throughout the study. Drug-free plasma samples were obtained from the Turkish Blood Centre, Istanbul, Turkey.

Pharmacokinetic and Statistical Analysis

To evaluate the treatment and study design effects, we used an analysis of variance (ANOVA) statistical model. The pharmacokinetic evaluation included the model-independent determination of the individual $C_{\text{max}}$, $t_{\text{max}}$, and $AUC_{0-\infty}$ using WinNonlin version 5.0.1 software (Pharsight Corporation, Mountain View, California).

The food effect on the bioavailability of both the test and reference formulations and the bioequivalence between them both under the fed and fasting state were determined by calculating the 90% confidence intervals (CIs) for $AUC_{0-\infty}$ and $C_{\text{max}}$ values using log-transformed data.

In studies to determine bioequivalence after a single dose, the parameters to be analyzed are $AUC_{0-\infty}$ and $C_{\text{max}}$. For these parameters, the 90% CI for the ratio of the test and reference products should be contained within the acceptance interval of 80% to 125%.

RESULTS

No changes of the protocol were carried out after the start of the study, and no major deviations from the protocol were observed.

Figures 3 and 4 show that both formulations were absorbed from the gastrointestinal tract when they were taken under a fasting or fed state. None of the basic pharmacokinetic parameters was influenced by the feeding state for both the test and the reference formulations (Table I, Figures 3 and 4).

When the 2 products were compared, no statistically significant difference in $AUC_{0-\text{tlast}}$ and $AUC_{0-\infty}$ values was found (Table I). Under the fasting state, the test/reference ratio (90% CI) was 1.00 (95.96%-102.81%) for $C_{\text{max}}$, 0.97 (91.69%-101.95%) for $AUC_{0-\infty}$, and 0.99 (94.30%-103.27%) for $AUC_{0-\text{tlast}}$. On the other hand, the test/reference ratios (90% CI) under the fed condition were as follows: 1.02 (99.55%-106.34%) for $C_{\text{max}}$, 1.02 (97.68%-109.66%) for $AUC_{0-\infty}$, and 1.02 (97.98%-110.62%) for $AUC_{0-\text{tlast}}$. These results indicate that the bioequivalence criteria were highly fulfilled in all aspects (Figure 5) and that the 90% CIs for both $AUC_{0-\text{tlast}}$ and $AUC_{0-\infty}$ were narrow and symmetrical around 1.0 and within the acceptance ranges for bioequivalence trials in both fed and fasting states. The results presented here showed a minimal intraindividual variance of 22.63% and 24.81% for trimetazidine under the fed and fasting state, respectively. Median $t_{\text{max}}$ value was 5 hours for both fasting (90% CI, 84.89%-102.59%) and fed (110.11%-131.97%) states. The test and reference formulations were well tolerated in both fasting and fed states, and no adverse effects were seen during the study.
Table I  Median $t_{\text{max}}$, Mean $C_{\text{max}}$, and Mean AUC Values for the Test and the Reference Formulations (n = 36)

<table>
<thead>
<tr>
<th></th>
<th>$t_{\text{max}}$, h (Range)</th>
<th>$C_{\text{max}}$, ng/mL, Mean ± SD</th>
<th>$P$ Value</th>
<th>$\text{AUC}<em>{0-t</em>{\text{last}}}$, ng·h/mL, Mean ± SD</th>
<th>$P$ Value</th>
<th>$\text{AUC}_{0-\infty}$, ng·h/mL, Mean ± SD</th>
<th>$P$ Value</th>
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<tbody>
<tr>
<td>Test</td>
<td></td>
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<tr>
<td>Fasting</td>
<td>5 (2.0-8.0)</td>
<td>63.3 ± 15.7</td>
<td>.796</td>
<td>726.3 ± 196.3</td>
<td>.647</td>
<td>831.3 ± 265.7</td>
<td>.704</td>
</tr>
<tr>
<td>Fed</td>
<td>5 (2.6-8.0)</td>
<td>64.2 ± 14.5</td>
<td></td>
<td>706.4 ± 170.5</td>
<td></td>
<td>806.0 ± 226.5</td>
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<tr>
<td>Reference</td>
<td></td>
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<tr>
<td>Fasting</td>
<td>5 (2.3-8.0)</td>
<td>63.2 ± 13.3</td>
<td>.986</td>
<td>733.0 ± 180.5</td>
<td>.354</td>
<td>853.4 ± 243.4</td>
<td>.305</td>
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<tr>
<td>Fed</td>
<td>5 (1.6-5.0)</td>
<td>63.1 ± 17.1</td>
<td></td>
<td>691.4 ± 197.2</td>
<td></td>
<td>793.4 ± 249.0</td>
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</table>

DISCUSSION

It is particularly important to characterize the effects of food on the performance of MR formulations to ensure that the formulation performs in a predictable manner in the absence and presence of food-formulation interactions; the release of controlling excipients depends on environmental conditions of the gastrointestinal tract.3

Both the Food and Drug Administration (FDA) and the EMEA require that bioequivalence studies of orally administered MR products be performed under both fasting and fed conditions.7

In this study, there were no statistically significant differences between $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ values in fasting and fed states when they were compared by logarithmic transformation and no difference in $t_{\text{max}}$ when compared without transformation. A statistically insignificant sequence effect shows that there is no carryover effect. The point estimates of the 90% confidence interval for test/reference ratios indicate that bioequivalence criteria were highly fulfilled in all aspects. The results demonstrate that the 90% confidence intervals for both $\text{AUC}_{0-\text{last}}$ and $\text{AUC}_{0-\infty}$ were narrow around 1.000 and within the acceptance ranges for the bioequivalence trial. The median $t_{\text{max}}$ of trimetazidine MR tablets was similar after administration of formulations with or without food.

In conclusion, because these values of the 2 products are within the 0.80 to 1.25 range and also within the 90% CI, they are considered bioequivalent. The results of the meal interaction study showed that the performance of the formulation was not influenced...
by the meal, and the rate and the extent of absorption were not significantly different between fed and fasted conditions. Therefore, trimetazidine MR tablets may be taken without regard to meals as far as pharmacokinetic factors are concerned.

Crossover study designs are optimal for food effect BA and fed BE studies.\(^3,7\) There is no food effect on the pharmacokinetic parameters of trimetazidine, which can be taken under a fed or fasted state. The results of this study also showed that there is no need for a 4-period study under the fed or fasting state to evaluate the bioequivalence of trimetazidine MR tablets.

The authors thank all volunteers for participating in our study.

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REFERENCES

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