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A Bioequivalence Comparison of Two Captopril Formulations (25 mg Tablets): An Open-Label, Randomized, Two-Treatment, Two-Way Crossover Study in Healthy Volunteers

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Abstract

This was an open-label, randomized, 2-treatment, 2-way crossover study with 1 week washout period between the 2 study arms. Healthy volunteers received a 25 mg tablet of the test formulation or 25 mg tablet of the reference formulation. Plasma concentrations of captopril were analyzed using a validated LC-MS/MS method. The mean values for C_{max}, T_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ with the test formulation of captopril were 235.21 ng/mL, 0.82 hours, 329.25 ng/mL•h, and 337.43 ng/mL•h, respectively; for the reference formulation, the values were 228.28 ng/mL, 0.72 h, 315.87 ng/mL•h, and 323.90 ng/mL•h. For captopril, the 90% CIs for the test formulation/reference formulation ratio for both log C_{max} and $AUC_{0-\infty}$ were within the bioequivalence limit of 80% to 125% (81.08–122.78% and 85.19–117.68%). Both formulations appeared well tolerated in the population studied.

Keywords: Captopril; Bioequivalence; Pharmacokinetics; Hypertension; LC-MS/MS

Introduction

Captopril is a specific competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I to angiotensin II. Captopril is indicated for the treatment of hypertension, heart failure, left ventricular dysfunction after myocardial infarction and diabetic nephropathy. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. It contains a sulphydryl group and binds readily to albumin and other plasma proteins. It also forms disulphides and endogenous thiol-containing compounds (cysteine, glutathione), as well as disulphide dimer of parent compound [1]. The measurement of free or unchanged captopril concentration needs to be preceded by addition of a chemical stabilizer and molecule derivatization of biological samples in order to prevent captopril disulphide formation [2].

Published HPLC methods for captopril in plasma have utilized either UV detection following derivatization with *p*-bromophenacylbromide [1,3] or fluorescence detection after treatment with N-(1-pyrenyl)-maleimide [4,5]. As these reagents are not water soluble, an aliquot of the plasma sample must be mixed volumetrically with a solution of the appropriate reagent in a water-miscible organic solvent which is impractical when numerous samples must be collected over a short period of time, as typically occurs in clinical pharmacokinetic studies. Therefore, the more water soluble N-ethylmaleimide (NEM) is used as the stabilizing agent, which has the advantage of allowing non-volumetric addition of blood samples to tubes containing an excess of powdered or crystalline reagent. In order to prevent oxidative degradation of captopril, its sulphydryl group was immediately protected by treatment with NEM. The resulting NEM adduct was then converted into the bis-pentafluorobenzyl derivative, allowing the formation of a single chromatogram peak [6].

In Malaysia, bioequivalence study is essential for the registration of generic products. The Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies [7] was published by the Ministry of Health to provide guidance to local researchers in conducting bioequivalence studies in accordance with established international standards, such as those published by the US Food and Drug Administration (FDA) [8] and the European Medicines Agency (EMA) [9]. The objective of the present study was to compare, under fasting conditions in healthy volunteers, the rate and extent of absorption of a generic captopril tablet in oral dosage form versus the proprietary equivalent formulation for the purpose of registration approval of the test formulation.

Subjects and Methods

Study design

This was an open-label, randomized, 2-way crossover study (2 treatments, 2 periods and 2 sequences) with 1 week washout period between the 2 study arms. Bioequivalence study needs to be conducted in a clinical study ward due to the need to properly control and monitor the subjects. Ethical approval was obtained from the Medical Ethics Committee of the University Malaya Medical Centre (Kuala Lumpur, Malaysia). The study was conducted in compliance with the principles of the Declaration of Helsinki [10], the Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies [7], and the Malaysian Guidelines for Good Clinical Practice [11]. Written informed consent was obtained from all volunteers after presentation of verbal and written explanations of the study and before initiation of any screening procedures.

Volunteers were randomized to receive 1 of the 2 study formulations

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according to a computer-generated randomization scheme. Each volunteer was assigned a subject number; the treatment sequence was randomized, and all subjects received the test and reference formulations. The test formulation* comprised 1 tablet containing 25 mg of captopril (batch no. 90701; manufacturing date July 2009; expiration date, July 2013). The reference formulation† comprised a commercially available tablet containing 25 mg of captopril (batch no. JX7756; expiration date, August 2015).

*Caporil (manufactured by Scanlab Sdn. Bhd., Batu Caves, Selangor, Malaysia).

†Trademark: Apo Capto (manufactured by Apotex Inc., Toronto, Canada).

Subjects and procedures

Healthy volunteers were recruited through response to an advertisement and assessed for inclusion in the study. A medical history was taken, including the recording of any illnesses; allergies; consumption of tobacco, alcohol, and drugs of abuse; and current use of other medically active substances. After a physical examination which was carried out to exclude any abnormality of the cardiovascular, respiratory, abdominal and central nervous system, blood pressure and pulse rate were measured and general examination of the subject was conducted to exclude any illness or abnormality (e.g., anemia, cyanosis, clubbing, jaundice and lymphadenopathy). Resting blood pressure was recorded using a sphygmomanometer while the subject was in a sitting position. Blood samples (10 mL) were collected for full blood count, urea and electrolytes, liver function tests, renal function tests, and random blood glucose. Serologic tests were conducted for the presence of hepatitis B surface antigen and HIV antibodies. Blood analysis for these parameters was performed by a clinical diagnostic laboratory with ISO 15189/9001 certification. Urine samples were also collected for urine-formed elements with microscopic examination analysis, and urinary pregnancy tests were conducted in all female subjects. Subjects were admitted to the study after review of pathology reports, medical history, and checked to see that they have met all the study inclusion and exclusion criteria. Blood samples were drawn from each subject at the end of the study for assessment of all laboratory parameters as mentioned here, except for the HIV antibodies and hepatitis B surface antigen, which were not tested again.

Inclusion and exclusion criteria

Eligible subjects were healthy volunteers between the ages of 18 and 55 years, who had passed all the screening parameters and had a body mass index (BMI) between 18 and 30 kg/m^2. They had to be able to communicate effectively with the study personnel, be literate and be able to give consent. Female volunteers of child-bearing potential had to be practicing an acceptable method of birth control (eg, condoms, foams, jellies, diaphragm, intrauterine device, abstinence), as judged by the investigator, for the duration of the study. Women who were breastfeeding were ineligible.

Subjects were excluded if they had a history of allergic responses to captopril or other related drugs; a history of drug dependence or a recent (i.e., within 1 month) history of alcoholism or of moderate (ie, ≤2 drinks/day) alcohol use; significant diseases or clinically significant abnormal findings during screening, medical history, physical examination, laboratory evaluations, ECG, and radiographic assessments; any disease or condition that might compromise the hematopoietic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous, or other body system; diabetes mellitus or psychosis; a history or presence of asthma (including aspirin-induced asthma) or nasal polyp; a positive screening for hepatitis; a positive test result for HIV antibody or syphilis (rapid plasma reagin/venereal disease research laboratory tests); or a history of difficulty with donating blood (based on subjects' experience in any blood taking procedures) or difficulty with accessibility of veins. Smokers who smoked ≥ 10 cigarettes per day or those who could not refrain from smoking during the study period were excluded. Also excluded were the following: anyone who was receiving an investigational product or who had participated in a drug research study within 90 days before the first dose of study medication administration (elimination $t_{1/2}$ of the study drug should be considered for inclusion of subject in the trial, if blood loss was ≤ 200 mL); subjects who had donated a minimum of 350 mL of blood within 90 days before receiving the first dose of study medication (if blood loss was ≤ 200 mL, subject could be enrolled in the trial if 60 days had passed since blood donation); or anyone adhering to an unusual diet, for whatever reason (e.g., low sodium), for whatever reason, for 4 weeks before receiving the study medication and throughout the subject's participation in the study.

Admission and procedures

The subjects were admitted to the Clinical Examination Ward of the University of Malaya Medical Centre between 7:30 and 8:30 PM the day before drug administration day. No other medications or outside foods were permitted. The nature and the risks of the study were again explained by study personnel, and subjects then signed informed-consent forms for participation in study. Blood pressure and pulse rate were measured after subjects had rested for 10 minutes; this was followed by a physical examination conducted by a medical physician. Subjects ate a standardized meal between 8:30 and 10:00 PM. A standardized meal consisted of typical Malaysian food (boiled rice [± 400 kcal] with a meat dish [± 300 kcal] and a vegetable dish [± 40 kcal]. No foods were allowed after 10:00 PM.

Starting from 7:00 AM of the dosing day (day 1), a 20-gauge cannula was placed in a forearm vein of the subjects, and 5 mL of blood were drawn into EDTA tubes for baseline sampling. The tubes were then centrifuged at 5000 rpm for 10 minutes. The plasma was carefully pipetted into duplicate cryo vials containing 0.5% NEM and stored at -80°C. Resting blood pressure, radial pulse, and oral temperature were measured for tolerability assessments. Starting from 8:00 AM, subjects (in a seated position) received the study drug according to their randomization schedule, taken with 240 mL of water at ambient temperature. Drug administration was followed by a mouth check to assess compliance with dosing. After drug administration, subjects were allowed to engage in non-strenuous activities such as watching television or reading but had to maintain an upright position for ≥2 hours. Subsequent blood samples were collected at 20, 40 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h post-dose. This sampling protocol was determined based on T_{max} after oral administration of captopril, which ranges from 0.75 to 1.5 h [8], and a $t_{1/2}$ of <3 h [12]. Blood pressure and radial pulse were checked 1, 2, and 4 h ± 40 min post-dose. Standardized meals (lunch, tea break, and dinner) were served 4 hours after dosing.

A medical physician who was blinded to the study treatment was present at all times throughout the study to monitor the subjects and looked out for possible adverse effects of the medication. Subjects were asked questions at the time of blood pressure examination regarding their overall well-being and any feelings of discomfort. All events reported by the subjects (serious or mild) were recorded on adverse-event forms. Blood samples were again drawn and analyzed (full blood

count and clinical chemistry) at the end of the study to monitor any changes.

Analysis of plasma samples

All the plasma samples obtained from this study were analyzed and stored at UBAT laboratory (Kuala Lumpur, Malaysia). The plasma samples were stored at -80°C until further analysis. Concentrations of captopril were measured in plasma using an LC-MS/MS method previously validated to demonstrate adequate sensitivity, specificity, linearity, accuracy, and precision [13]. All the validation parameters tested had to fulfill the criteria as outlined in the FDA's guidelines for bioanalytical method validation.

Experimental

LC-MS/MS

The samples were analyzed using a LC-MS/MS instrument with a Shimadzu HPLC (Shimadzu, Japan) system equipped with an AB Sciex QTRAP 5500 mass spectrometer (AB Sciex, USA). Chromatographic separation was performed on Phenomenex Gemini-NX C_{18} 110A column (internal diameter, 200 × 2.0 mm; particle size, 5 µm) from Phenomenex, USA, with the column oven compartment set at 40°C. The system was controlled by Analyst (ver. 1.5.2) software supplied by Applied Biosystems. For qualitative confirmation of captopril and ranitidine (internal standard) analysis, transition ions were monitored in the multiple reaction monitoring modes (MRM) given at m/z 341.04 → m/z 216.00 for captopril and m/z 315.01→m/z 176.10 for ranitidine respectively. The mobile phase used was 100% acetonitrile and 0.1% formic acid.

Sample preparation

Plasma extraction was achieved using protein precipitation method. In Eppendorf tube 0.1 mL plasma, 50 µL ranitidine (1000 ng/mL) was added and vortex-mixed for 20 s. The tube was shaken again for 30 s with 0.75 mL acetonitrile, and then centrifuged at 14800 rpm for 5 min. The supernatant was transferred in an autosampler vial and 15 µL were injected into the LC-MS/MS system.

Validation

Method validation was conducted in accordance with the currently accepted FDA's guidelines for industry [13]. Specificity was verified using six different plasma blanks obtained from University of Malaya Medical Centre (Kuala Lumpur, Malaysia). No interference was found in the chromatograms of six randomly selected human plasma samples at the retention times of captopril (1.39 min) or internal standard (0.58 min) due to the specificity of selected signals. The concentration of the analytes was determined automatically by the instrument data system using the internal standard method. Peak area ratios (captopril/internal standard) were plotted versus nominal plasma concentrations, and fitted by weighted (*1/x*, *x*=concentration of captopril in ng/mL) least squares linear regression. Calibration curves in spiked plasma were linear (R^2>0.990) from 0.5-200 ng/mL. The calibration model was accepted, if the residuals were within ± 20% at the lower limit of quantification (LLOQ) and within ± 15% at all other calibration levels and at least 2/3 of the standards met this criterion, including highest and lowest calibration levels.

The within- and between-run precision (%CV) and accuracy of the assay procedure were determined by analysis on the same day of five different samples at each of the lower (1.5 ng/mL), medium (100 ng/mL), and higher (180 ng/mL) levels of the considered concentration range and one different sample of each on five different occasions, respectively, Intraday %CVs for quality-control concentrations of captopril were 5.54%, 6.13%, 2.85%, and 2.71%, respectively, and interday values were 9.32%, 8.86%, 4.55% and 3.15% for LOQ and low, medium, and high concentrations. The mean percent inaccuracy values of captopril for LOQ and low, medium and high concentrations were 7.33%, 6.18%, 5.97%, and 5.46% for intraday values and 1.11%, 1.00%, 5.97%, and 5.46% for interday values. The inaccuracy and imprecision for the LOQ level were <20%.

The relative recoveries at each previously three levels of concentration and limit of quantification were measured by comparing the response of the treated plasma standards with the response of standards in solution with the same concentration of analytes as the prepared plasma sample. Mean recovery percentages of captopril and ranitidine were 105.28% and 66.99%, respectively. Recovery of the analyte need not be 100%, but the extent of recovery of an analyte and of the internal standard should be consistent, precise, and reproducible [13]. During the samples assay, the low, medium and high QC samples were injected along with the sample run. In each batch run, three QC samples were analyzed. All the QC results were lower than 15% inaccuracy from the nominal concentrations.

The stability of the analytes in human plasma was investigated in four ways, in order to characterize each operation during the process of bioequivalence studies: room temperature or bench-top stability, autosampler stability, freeze-thaw stability and long-term stability below -70°C. For all stability studies, captopril was found to be stable for at least 6 h in the autosampler. The sample was stable for 3 freeze-thaw cycles. For long-term stability, the frozen sample (below -70°C) was stable for at least 1 month. Bench-top stability was conducted for up to 6 hours and the %CVs for captopril at low and high concentrations were 6.10% and 5.24%, respectively,

Pharmacokinetic analysis

All pharmacokinetic parameters were determined using non-compartmental analysis [14,15]. Pharmacokinetic analysis was performed for the concentration of captopril in plasma before and up to 10 h after dosing. All the parameters were determined from the actual plasma concentration of captopril. C_{max} and T_{max} were obtained directly from the individual plasma concentration–time data. AUC_{0-t} was determined using the linear trapezoidal rule. $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-t} and $AUC_{t-\infty}$, and $AUC_{t-\infty}$ values were obtained by extrapolating the last measurable plasma concentration to the time axis using the following equation [16,17]:

$$AUC_{t-\infty} = \frac{C_t}{K_e}$$

Where k_e is the elimination rate constant that was obtained as the slope of linear regression of ln-transformed plasma concentration–time curve in the elimination phase. The elimination $t_{1/2}$ was calculated using the following equation [16,17]:

$$t_{1/2} = \frac{\ln 2}{K_e}$$

Statistical analysis

The sample size for this study was estimated using a power calculation conducted on the basis of data obtained from earlier bioequivalence studies [12,18]. The significance of the bioavailability parameters C_{max} and $AUC_{0-\infty}$ obtained after administration of the test

and reference formulations was analyzed, with and without logarithmic (log_{10}) transformation, using ANOVA for crossover studies that accounted for variations due to subjects, formulations and periods. Analyses were conducted using WinNonlin version 5.3 (Pharsight Corporation, Mountain View, California).

Bioequivalence testing was based on the 90% CIs for the ratio of the population means (test formulation/reference formulation) for C_{max} and AUC. The formulations were considered bioequivalent if the 90% CIs for AUC and C_{max} were within the predetermined equivalence range of 80% to 125% [7-9,19]. The European Commission and the EMEA (EC-EMEA) and the National Pharmaceutical Control Bureau of Malaysia also set bioequivalence limits (75–133%) for C_{max} [7,9]. Using CIs rather than hypothesis testing is in accordance with internationally accepted guidelines for the assessment of bioequivalence [20]. This method is considered equivalent to the corresponding Schuirmann's two 1-sided *t* tests, with the null hypothesis of bioinequivalence set at the 5 % significance level [21].

The difference in T_{max} values between test and reference formulations have been performed using nonparametric Wilcoxon Signed Rank Test. Statistical analysis was conducted using SAS version 5.1 (SAS Institute Inc., Cary, North Carolina).

Results

Demographic charateristics

24 healthy subjects (20 males, 4 females), with a mean age of 21.3 years (range, 19-25 years) and a mean BMI of 22.15 kg/m^2 (range, 18.29-29.07 kg/m^2), were enrolled in this study (Table 1). All 24 subjects completed the trial as outlined in the protocol.

Pharmacokinetic analysis

Captopril was measurable in plasma at the first sampling time (20 min) in all 24 subjects after administration of the test and reference formulations. The mean plasma captopril concentrations versus time for the 2 formulations are depicted in Figure 1. Table 2 displays the pharmacokinetic parameters obtained for the reference and test formulations for captopril, respectively. The mean values for C_{max}, T_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ with the test formulation of captopril were 235.21 ng/mL, 0.82 h, 328.25 ng/mL·h, and 337.43 ng/mL·h, respectively; for the reference formulation, the values were 228.28 ng/mL, 0.72 h, 315.87 ng/mL·h and 323.90 ng/mL·h.

Table 3 shows the 90% CIs and the mean ratios of the test-to-reference formulations for log C_{max}, log AUC_{0-t}, and log $AUC_{0-\infty}$. For captopril, the 90% CIs for the test formulation/reference formulation ratio for both log C_{max} and log $AUC_{0-\infty}$ was within the US Food and Drug Administration (FDA), The European Commission and the EMEA (EC-EMEA) and the National Pharmaceutical Control Bureau of Malaysia (NPCB) acceptable 90% CIs of 80% to 125% (81.08-122.78% and 85.19-117.68%, respectively). The differences in T_{max} values for the test and reference formulations did not reach the level of statistical significance. Therefore, applying the criteria used in the guidelines as noted here, the test and reference formulations met the regulatory definitions to assume bioequivalence for captopril.

Based on analysis using the Wilcoxon signed ranks test, there was

Subject Number	Gender	Height, cm	Weight, kg	Body Mass Index (BMI), kg/m^2	Age, y
1	Female	149.0	53.0	23.90	25.0
2	Female	159.0	55.0	21.76	25.0
3	Male	175.0	63.0	20.57	19.0
4	Male	167.0	77.0	27.61	20.0
5	Male	169.0	70.0	24.50	20.0
6	Male	164.0	56.0	20.82	20.0
7	Male	169.0	70.0	24.51	21.0
8	Male	172.0	65.0	21.97	20.0
9	Male	156.0	65.0	26.70	20.0
10	Male	173.0	56.0	18.71	21.0
11	Male	160.0	58.0	22.66	21.0
12	Male	160.0	60.0	23.44	22.0
13	Male	167.0	51.0	18.29	21.0
14	Male	172.0	86.0	29.07	21.0
15	Male	161.0	48.0	18.50	21.0
16	Male	159.0	50.0	19.78	21.0
17	Male	173.0	65.0	21.72	21.0
18	Male	171.0	62.0	21.20	21.0
19	Male	167.0	64.0	22.95	22.0
20	Male	165.0	51.0	18.73	21.0
21	Male	169.0	58.0	20.30	19.0
22	Male	186.0	75.0	21.68	21.0
23	Female	153.0	45.0	19.22	24.0
24	Female	150.0	52.0	23.11	24.0
Mean		165.3	60.6	22.15	21.3
SD		8.6	10.0	2.88	1.7
Minimum		149.0	45.0	18.29	19.0
Maximum		186.0	86.0	29.07	25.0

Table 1: Subject demographic characteristics.

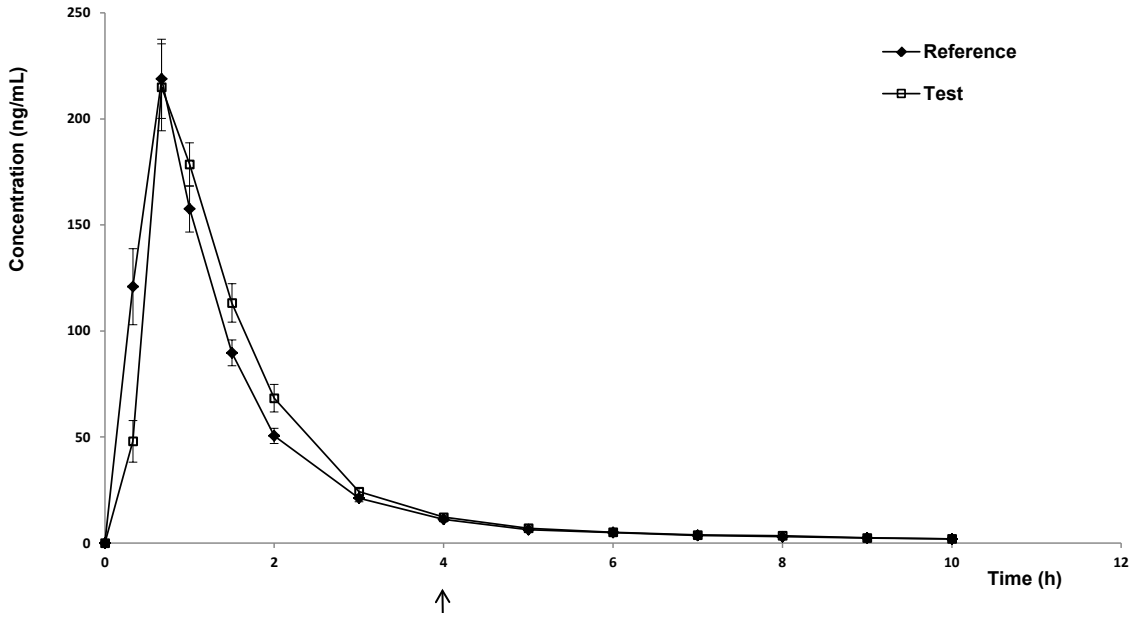

Figure 1: Mean (SD) plasma captopril concentrations versus time after a single oral dose of 25-mg captopril. Arrow indicates the meals given at 4 h post dose. Test = 1 Caporil tablet (25 mg) manufactured by Scanlab Sdn. Bhd., Batu Caves, Selangor, Malaysia; Reference = 1 Apo Capto tablet (25 mg) manufactured by Apotex Inc., Toronto, Canada.

	Present study		Rastkari et al. [18]	
Parameter	**25 mg Test* Formulation**	**25 mg Reference† Formulation**	**50-mg Test Formulation**	**50-mg Reference Formulation**
C_{max}, ng/mL	235.21 ± 275.79 (89.40)	228.28 ± 198.72 (86.25)	668 (324)	674 (296)
T_{max}, h	0.82 ± 0.68 (0.25)	0.72 ± 0.39 (0.16)	0.84 (0.27)	0.75 (0.23)
AUC_{0-t}, ng/mL·h	329.25 ± 188.43 (81.55)	315.87 ± 228.21 (85.98)	1017.7 (583.4)	1032.4 (544.3)
$AUC_{0-\infty}$, ng/mL·h	337.43 ± 192.13 (82.64)	323.90 ± 225.90 (86.16)	1023.6 (590.6)	1057.4 (551.3)
$t_{1/2}$, h	2.83 ± 1.14 (0.49)	2.86 ± 1.20 (0.42)	3.37 (0.95)	3.24 (0.87)

*Caporil (manufactured by Scanlab Sdn. Bhd., Batu Caves, Selangor, Malaysia).
†Trademark: Apo Capto (manufactured by Apotex Inc., Toronto, Canada).

Table 2: Mean (SD) pharmacokinetic parameters for captopril after administration of the 2 formulations to 24 subjects in the present study and data from an earlier study.

no statistical significant differences in T_{max} values ($p>0.21$) for the reference and test formulations.

Tolerability

There was no adverse event reported or observed during the entire period of the study. All results of laboratory blood tests for all subjects, as assessed at the end of the study, were within clinically acceptable ranges. In addition, the vital signs recorded during the study for all volunteers were within the normal range for healthy subjects (mean systolic/diastolic: 109/65 mmHg).

Discussion

All 24 volunteers who enrolled for the study, completed it; the number of subjects had sufficient statistical power for ANOVA for both log C_{max} and log $AUC_{0-\infty}$. In this bioequivalence study, the single 25 mg tablet of captopril was assessed to compare its bioavailability with the 25 mg tablet of the reference formulation. All the pharmacokinetic parameters (T_{max} and $t_{1/2}$) obtained from this study are in agreement with the results obtained by Rastkari et al. [18], which are summarized in Table 2. Rastkari et al. conducted bioequivalence study of captopril in a group of 12 healthy male volunteers at a single oral dose of a 50 mg tablet. According to their findings, both formulations appeared to be bioequivalent. The C_{max} and AUC values were higher for captopril in the study by Rastkari et al. compared with our study because the dose given in that study was slightly higher. Both formulations appeared to be well tolerated in these healthy, fasting volunteers, as no adverse events were recorded.

In our present study, we have utilized the protein precipitation method which was fast and straightforward compared to the liquid-liquid extraction (LLE) as performed by the Rastkari et al. and solid phase extraction (SPE). The main advantage is the sample preparation by protein precipitation and besides its simplicity, that sample treatment allows obtaining a good recovery of the analyte. The developed method also showed good linearity, specificity and precision over calibration range and demonstrated some advantages over previous method [22]. The simple sample preparation by protein precipitation, while using less organic solvent with small amounts of sample plasma volume; the relatively short run time and the selected signals for monitoring allowed a specific and efficient analysis of plasma sample, making the method more productive and thus more cost effective. The method

	Captopril	
Parameter	Test/Reference Ratio, %	90% CI
Log_{10} C_{max}	106.53	81.08–122.78
Log_{10} AUC_{0-t}	105.85	84.33–118.71
Log_{10} $AUC_{0-\infty}$	105.50	85.19–117.68

Table 3: 90% CIs for the mean ratio of the test* to reference† formulations for log $AUC_{0-\infty}$, log AUC_{0-t}, and log C_{max} for captopril.

met all FDA criteria for a validated bioanalytical method and was successfully applied to accurately measure captopril concentration on a large number of human plasma samples from a bioequivalence study.

Conclusions

This bioequivalence study found that the 25 mg test tablet and the 25 mg reference tablet of captopril met the regulatory criteria for assuming bioequivalence in healthy volunteers. Both formulations were well tolerated in the population studied.

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