Evaluation of the Pharmacokinetic Interaction between Candesartan Cilexetil and Felodipine

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Abstract

The study was performed to evaluate the pharmacokinetic interaction of test formulation of candesartan 16 mg tablet and felodipine extended release 5 mg tablet together in a combination package, comparing with the fasting period intake of commercial formulations of both Atacand® 16 mg tablet and Splendil® extended release 5 mg tablet (Test formulation and reference formulation from AstraZeneca, Brazil) in 36 volunteers of both sexes. The study was conducted open with randomized three period crossover design and a one week wash out period. The candesartan and felodipine were analyzed by LC-MS-MS. The mean ratio of parameters Cmax and AUC0-t and 90% confidence intervals of correspondents were calculated to determine the pharmacokinetic interaction. Geometric mean of candesartan exposure together in a combination package felodipine individual percent ratio was 102.51% AUC0-t and 110.40% for Cmax. The 90% confidence intervals were 90.00 - 116.77% and 93.94 - 129.74%, respectively. Geometric mean of candesartan exposure together in a combination package candesartan individual percent ratio was 102.69% AUC0-t and 96.17% for Cmax. The 90% confidence intervals were 89.46 - 117.88% and 82.07 - 112.69%, respectively. The major variable in this respect, AUC, was not significantly affected by felodipine and candesartan with concomitant administration. The Cmax of candesartan was not significantly affected by co-administration of felodipine. Based on these data and in presence of isolated candesartana and felodipino formularizations used in combination in medical practice, it is concluded that there are no risk with concomitant administration between felodipine and candesartan.

Keywords: Candesartan; Felodipine; Biological availability; Pharmacokinetics; Chromatography; Bioequivalence

Introduction

Angiotensin II receptor antagonists have been thought to provide potential advantages over angiotensin converting enzyme inhibitors (ACEIs). One of the advantages is their high specificity in blocking the effects of circulating and tissue angiotensin II at the AT1 receptor level [20]. ACEIs prevent the enzymatic cleavage of angiotensin I and thus the formation of angiotensin II. They have been proven to be effective in the treatment of hypertension or heart failure. However, in addition to blocking renin-angiotensin system ACEIs increase the levels of other substrates of ACE, including bradykinin that produces dry cough [45]. Thus, AT1 receptor antagonists can be used to replace ACEIs in patients who do not tolerate them and suffer from cough or angioedema. The angiotensin-converting enzyme (ACE) converts the inactive decapeptide angiotensin I to angiotensin II. The discovery of specific angiotensin II receptor antagonists led to the identification of various subtypes of angiotensin II receptors [48]. Candesartan cilexetil has been developed at with the aim of identifying a non-peptide angiotensin II receptor antagonist with a longlasting and insurmountable effect [32]. It is administered orally as candesartan cilexetil, which is completely converted during enteric absorption to the active compound, candesartan [44]. Candesartan cilexetil, is rapidly and completely hydrolysed to the active compound candesartan during absorption from the gastrointestinal tract. Candesartan is a potent, long-acting, selective angiotensin II AT1 receptor blocker which is well-tolerated and effective with a once-daily dosing regimen in hypertensive patients [26].

The pharmacokinetics of candesartan cilexetil have not been investigated in patients < 18 years of age. The pharmacokinetics of candesartan have been studied in the elderly (≥ 65 years). The plasma concentration of candesartan was higher in the elderly (Cmax was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration. There is no difference in the pharmacokinetics of candesartan between male and female subjects. In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and Cmax were approximately doubled in patients with severe renal impairment ( creatinine clearance < 30 mL/ min/1.73m 2 ) compared to patients with normal kidney function. The pharmacokinetics of candesartan in hypertensive patients undergoing hemodialysis are similar to those in hypertensive patients with severe renal impairment. Candesartan cannot be removed by hemodialysis. No initial dosage adjustment is necessary in patients with renal insufficiency. Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours. In a study of patients with impaired renal function (mean creatinine clearance of 19 mL/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours. The pharmacokinetics of candesartan were compared in patients with mild...
The clinical part of the study was conducted at Scentryphar Clinical. Consent was obtained from participants prior to study commencement. The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline, and informed consent was obtained from participants prior to study commencement. The study protocol was approved by the University of Campinas/Unicamp with the ethical principles described in the Declaration of Helsinki, guidelines for International Conference on Harmonization-Good clinical practices (ICH-GCP).

All subjects provided written informed consent to participate after explaining the nature and purpose of the study. The study protocol was approved by the University of Campinas/Unicamp with the ethical principles described in the Declaration of Helsinki, guidelines for International Conference on Harmonization-Good clinical practices (ICH-GCP).

All volunteers were healthy as assessed by physical examination, ECG, and the following laboratory tests: blood glucose, urea, creatinine, AST, ALT, alkaline phosphatase, Gamma GT, total bilirubin, albumin and total protein, triglycerides, total cholesterol, hemoglobin, hematocrit, total and differential white cell counts and routine urine. All subjects were negative for HIV, HBV (except for serological scare) and HCV.

Drug products

The test formulation employed was Candesartan 16 mg tablet and Felodipine extended release 5 mg tablet (lot number 81234/81211) and the reference formulation was: Atacand® 16 mg tablet (lot number 81234) and Splendil® extended release 5 mg tablet (lot number 81211).

Study design

The study was performed to evaluate the pharmacokinetic interaction of candesartan 16 mg tablet and felodipine extended release 5 mg tablet together in a combination package, comparing with the fasting period intake of commercial formulations of both Atacand® 16 mg tablet and Splendil® extended release 5 mg tablet (Test formulation and reference formulation from AstraZeneca, Brazil).

The study was conducted in an open label trial, crossover assignment, single-arm pharmacokinetics study, in which healthy volunteers received 3 treatments in 6 sequences and in 3 periods (Williams’ Plan) with a 1 week wash out period between the doses. Candesartan was supplied in 16 mg simple tablets together with felodipine, in an extended release 5 mg tablet or one 16 mg simple tablet of Atacand® together with Splendil®, extended release 5 mg tablet, according to the aleatorization plan. Tablets were given to healthy volunteers with 200 mL of pure mineral non-sparkling water. All volunteers were then fasted 05 hours following the drug administration, after which a standard lunch was consumed and an evening meal was provided 10 hours after dosing. No other food was permitted during the “in-house” period. Liquid consumption was permitted ad libitum after lunch but xanthine-containing drinks including tea, coffee and cola were avoided. Systolic and Diastolic arterial pressure, heart rate and temperature were recorded just before and hourly after drug administration.

Blood samples (06 mL) from a suitable antecubital vein were collected into EDTA containing tubes before and hourly after drug administration.

Felodipine is used in the treatment of all forms of hypertension. There is a close relationship between the felodipine concentration in plasma and the lowering of blood pressure. More sustained plasma concentrations might thus produce a more even effect on blood pressure, minimize concentration dependent side effects and at the same time increase the duration of effect [2,3].

Plasma concentrations of felodipine, after a single dose and at steady state, increase with age. Mean clearance of felodipine in elderly hypertensives (mean age 74) was only 45% of that of young volunteers (mean age 26). At steady state mean AUC for young patients was 39% of that for the elderly. Data for intermediate age ranges suggest that the AUCs fall between the extremes of the young and the elderly. In patients with hepatic disease, the clearance of felodipine was reduced to about 60% of that seen in normal young volunteers. Renal impairment does not alter the plasma concentration profile of felodipine; although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive [6,12].

Few studies of the combination of candesartan and other types of antihypertensive drugs, such as calcium antagonists, have been reported [25]. The objective of this study was to evaluate the pharmacokinetic interaction of test formulation of candesartan 16 mg tablet and felodipine extended release 5 mg tablet together in a combination package, comparing with the fasting period intake of commercial formulations of both Atacand® 16 mg tablet and Splendil® extended release 5 mg tablet (Test formulation and reference formulation from AstraZeneca, Brazil).

Methods

Study protocol

The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline, and informed consent was obtained from participants prior to study commencement. The clinical part of the study was conducted at Scentryphar Clinical Research (Campinas City, São Paulo, Brazil) and the bioanalytical part at Core Clinical Research (Bragança Paulista, São Paulo, Brazil).

Subjects

Thirty six healthy volunteers of both sexes (18 males and 18 females) who were between the ages of 18 and 49 (mean ± SEM: 30.83 ± 9.26 years), who had heights between 148.0 cm and 182.0 cm (166.0 ± 10.0 cm), and who weighed between 47.60 kg and 83.50 kg (65.55 ± 9.94 kg) and within 15% of their ideal body weight were enrolled in the study. Subjects were judged eligible for enrolment in this study if they were in compliance with all the inclusion and exclusion criteria described in the protocol.

The subjects provided written informed consent to participate after explaining the nature and purpose of the study. The study protocol was approved by the University of Campinas/Unicamp with the ethical principles described in the Declaration of Helsinki, guidelines for International Conference on Harmonization-Good clinical practices (ICH-GCP).

All volunteers were healthy as assessed by physical examination, ECG, and the following laboratory tests: blood glucose, urea, creatinine, AST, ALT, alkaline phosphatase, Gamma GT, total bilirubin, albumin and total protein, triglycerides, total cholesterol, hemoglobin, hematocrit, total and differential white cell counts and routine urine. All subjects were negative for HIV, HBV (except for serological scare) and HCV.

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Blood samples (06 mL) from a suitable antecubital vein were collected into EDTA containing tubes before and hourly after drug administration.
36.00, 48.00 hours post-dosing for candesartan and 1.00, 2.00, 2.30, 3.00, 3.30, 4.00, 4.30, 5.00, 5.30, 6.00, 7.00, 8.00, 10.0, 12.0, 20.00, 24.00, 36.00, 48.00 hours post-dosing for felodipine.

Drug analysis

Blood samples were cooled in an bath and centrifuged at 3,000 rpm for at least 10 min at approximately 4°C. At least 3 mL of the plasma were dispensed into polypropylene tubes. Sample tubes were frozen at -70°C as soon as possible, and maintained to that temperature until analysis. All samples from a single volunteer were analyzed on the same day in order to avoid interassay variation.

Candesartan and felodipine were extracted from human plasma by simple and single step liquid-liquid. Plasma concentrations of candesartan were determined by the HPLC coupled with tandem mass spectrometry (LC/MS/MS), using losartan as internal standard (IS). Both the compounds were tuned in positive mode for multiple reaction monitoring (MRM). In MRM mode, 439.51 → 309.50 and 421.37 → 179.04 were selected as transition ions for candesartan and IS, respectively. Plasma concentrations of felodipine was determined by the HPLC coupled with tandem mass spectrometry (LC/MS/MS), using nimodipine as internal standard (IS). Both the compounds were tuned in positive mode for multiple reaction monitoring (MRM). In MRM mode, 382.20 → 144.75 and 417.00 → 121.00 were selected as transition ions for felodipine and IS, respectively.

Method validation

Quantitation was based on determination of relationship between candesartan/ felodipine peaks areas and I.S. peaks areas. Selectivity was evaluated by extracting plasma samples of plasma from six different volunteers, including a lipemic and hemolysed plasma. Recoveries of candesartan/ felodipine at the three QC concentrations and I.S. were determined by comparing peak areas of spiked plasma samples with the peak area in solutions prepared with the same nominal concentration. For precision (as relative standard deviation, R.S.D.) and accuracy (as relative error, R.E.) studies, samples were prepared at three QC and were analysed in the same day (intraday precision and accuracy), and analysed in 3 consecutive days (inter-day precision and accuracy).

The calibration range of was 2.00-500.00 ng/mL (candesartan) and 0.05-4.00 ng/mL (felodipine). The validated method linearity > 0.98.

The method was validated according to ANVISA (National Health Surveillance Agency of Brazilian Government) criteria and used to determine the concentration of candesartan/ felodipine in volunteers plasma.

Pharmacokinetic analysis and statistical analysis

The first-order terminal elimination rate constant (Ke) was estimated by linear regression from the points describing the elimination phase on a log-linear plot, using the software SAS® Institute (Version 9.1.3). Elimination half-life (T_{1/2}) was derived from this rate constant (T_{1/2} = ln (2)/Ke). The maximum observed plasma concentration (C_{max}) and the time taken to achieve this concentration (T_{max}) were obtained directly from the curves. The areas under the candesartan/felodipine plasma concentration versus time curves from 0 to 48 hours (AUC_{0-48}) were calculated by applying the linear trapezoidal rule. Extrapolation of these areas to infinity (AUC_{0-∞}) was done by adding the value C_{48}/Ke to the calculated AUC_{0-48} (where C_{48}=plasma concentration calculated from the log-linear regression equation obtained for the estimation of Ke 48 hours after dose).

The bioequivalence between both formulations was assessed by calculating individual C_{max}, AUC_{0-48}, AUC_{0-∞} and C_{max}/AUC_{0-48} ratios (test/reference) together with their mean and 90% confidence intervals (CI) after log transformation of the data. The inclusion of the 90% CI for the ratio in the 80% to 125% range was analyzed by nonparametric (SAS® Institute Version 9.1.3) and parametric (ANOVA) methods.

Results

Tolerability analysis

Candesartan and felodipine was well tolerated at the administered dose. All the biochemical parameters did not any clinical relevant alterations. No adverse effects serious were either reported or observed.

Pharmacokinetic and statistical analysis

The mean (± SD) plasma concentration-time profiles are presented in Figure 1 (candesartan) and Figure 2 (felodipine) and the pharmacokinetic parameters of both substances are summarized in Table 1 and Table 2.

The mean of C_{max} of candesartan was 148.24 ng/mL in reference product and 158.36 ng/mL in test product. Both occurred 4.50 h after application. C_{max} of felodipine was on average 1.57 ng/mL in reference product and 1.45 ng/mL in test product and occurred 4.00 h after administration (reference) and 5.50 h (test). For candesartan,
the geometric means of AUC\(_{0-t}\) as a measure of extent of absorption amount to 1502.12 ng.h/mL (reference) and 1509.70 ng.h/mL (test). The geometric means of AUC\(_{0-t}\) of felodipine are 23.06 ng.h/mL (reference) and 24.41 ng.h/mL (test). The values of AUC\(_{0-t}\) for candesartan are 1389.61 ng.h/mL (reference) and 1392.01 ng.h/mL (test). In the felodipine evaluation the amounts of AUC\(_{0-t}\) are 19.38 ng.h/mL (reference) and 17.29 ng.h/mL (test). No significant differences with respect to drug absorption were found. Elimination half-lives and elimination rate constancy were well comparable between the different preparations.

The resulting 90% confidence intervals of the parameters ratios for AUC\(_{0-t}\), AUC\(_{\text{max}}\) and C\(_{\text{max}}\) as well as for differences in t\(_{1/2}\) are summarized in Table 03.

### Discussion

Over the past few decades, reducing blood pressure in patients with hypertension has been shown to decrease the risk for cardiovascular accident, chronic renal failure, and the overall morbidity and mortality of cardiovascular disease [13]. However, first-line antihypertensive monotherapy is effective in reducing blood pressure to the normal range in 60% of patients, leaving the remainder with inadequately controlled hypertension and at continued risk. For these patients, combination therapy usually results in better blood pressure control. Furthermore, increasing the dose of most antihypertensive agents used as monotherapy results in limited efficacy and poorer tolerability [41]. Combination therapy produced significantly greater decreases in blood pressure than either medication alone, which suggests a clinical additive effect. The validated method was successfully applied to assay human plasma samples from the pharmacokinetic interaction study of formulation of candesartan and felodipine in 36 healthy volunteers. A rapid, sensitive and reliable LC/MS/MS method for the determination of candesartan and felodipine has been successfully developed and validated using liquid-liquid extraction as sample preparation procedure. This assay method demonstrated acceptable sensitivity, precision, accuracy, selectivity, recovery and stability, and less absolute and relative matrix effect. The validated method was successfully applied to assay human plasma samples from the pharmacokinetic interaction study of candesartan and felodipine.

In this study combination of candesartan and felodipine was evaluated. The mean ratio of parameters C\(_{\text{max}}\) and AUC\(_{\text{max}}\) and 90% confidence intervals of correspondents were calculated to determine the pharmacokinetic interaction. The point estimator and the 90% confidence intervals for the AUC\(_{0-t}\) ratio (test/reference: 102.51% [90.00% - 116.77%]) indicate high similarity of both formulations.

### Table 1: Mean pharmacokinetic parameters of candesartan and felodipine of test and reference formulation.

| Parameter (unit) | TEST | REFERENCE |
|------------------|------|-----------|
| AUC\(_{0-t}\) (ng/mL) | 1392.01 | 1389.61 |
| AUC\(_{\text{max}}\) (ng/mL) | 1509.70 | 1502.12 |
| C\(_{\text{max}}\) (ng/mL) | 158.36 | 148.24 |
| t\(_{1/2}\) (median/amp) (h) | 4.50 | 4.50 |
| Kel (1/h) | 0.05 | 0.06 |
| T\(_{1/2}\) (median/amp) (h) | 14.29 | 11.26 |

### Table 2: Geometric mean parameters of candesartan and felodipine of test and reference formulation.

| Parameter | TEST | REFERENCE |
|-----------|------|-----------|
| AUC\(_{0-t}\) (ng/mL) | 1311.45 | 1279.29 |
| AUC\(_{\text{max}}\) (ng/mL) | 1425.50 | 1382.84 |
| C\(_{\text{max}}\) (ng/mL) | 147.32 | 133.45 |

### Table 3: Ratios mean and the 90% geometric confidence interval of test and reference formulation.

| Parameter | Ratio T/R (%) | Lower Limit | Upper Limit | Power (%) | Coefficient of Variation | Ratio T/R (%) | Lower Limit | Upper Limit | Power (%) | Coefficient of Variation |
|-----------|---------------|-------------|-------------|-----------|-------------------------|---------------|-------------|-------------|-----------|-------------------------|
| AUC\(_{0-t}\) | 102.51 | 90.00 | 116.77 | 72.81 | 32.46 | 102.69 | 89.46 | 117.88 | 99.99 | 34.46 |
| AUC\(_{\text{max}}\) | 103.09 | 91.12 | 116.62 | 77.35 | 30.68 | 107.55 | 94.13 | 112.87 | 99.99 | 32.21 |
| C\(_{\text{max}}\) | 110.40 | 93.94 | 129.74 | 29.50 | 40.81 | 96.17 | 82.07 | 112.69 | 99.99 | 39.95 |
| T\(_{1/2}\) (diff) (h) | -0.50 | -1.00 | 0.50 | - | - | -0.50 | -2.00 | 0.50 | - | - |
with respect to the extent of candesartan exposure together in a combination package feldopine. Similarity not was also observed for 90% confidence intervals for the Cmax ratio (test/reference: 110.40% [93.94% - 129.74%]) indicating pharmacokinetic interaction candesartan together in a combination package feldopine. Regarding the AUC ratio of feldopine, the point estimator is 102.69% and the 90% confidence interval 89.46% - 117.88%. Furthermore, not feldopine pharmacokinetic interaction together in a combination package candesartan is observed the point estimator and 90% confidence of Cmax of this active agent (96.17% [82.07% - 112.69%]).

The major variable in this respect, AUC, was not significantly affected by feldopine and candesartan with concomitant administration. The Cmax of candesartan was not significantly affected by co-administration of feldopine, whereas increase of only 10ng/mL ± 12ng/mL Cmax was found. Based on these data and in presence in the market of isolated feldopine and feldopino formularizations used in combination in medical practice, it is concluded that there are no risk with concomitant administration between feldopine and candesartan.

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