Enantioselectivity in the Pharmacokinetic Interaction Between Fluvastatin and Lercanidipine in Healthy Volunteers

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Hypertension and dyslipidemia are independent risk factors for cardiovascular mortality and are frequently present in the same patient. Fluvastatin (FV), used to reduce cholesterol levels, and lercanidipine (LER), used to control blood pressure, are marketed as racemic mixtures. Therapeutic activities are 30-fold higher for (+)-3R,5S-FV and 100- to 200-fold higher for S-LER compared with their respective antipodes. The present study describes the enantioselective pharmacokinetic interaction between LER and FV in healthy volunteers. A crossover randomized study was conducted in 3 phases on 8 volunteers treated with a single oral racemic dose of LER (20 mg) or FV (40 mg) or LER plus FV. Serial blood samples were collected from 0 to 24 hours. Plasma concentrations of the LER and FV enantiomers were determined by liquid chromatography/tandem mass spectrometry, and pharmacokinetic parameters were evaluated using the WinNonlin software. The Wilcoxon and Mann-Whitney tests ($P < .05$) were used to analyze enantiomer ratios and the pharmacokinetic drug interaction. Data are expressed as medians. In monotherapy, the kinetic disposition of both FV and LER was enantioselective. AUC values were significantly higher for (–)-3S,5R-FV than for (+)-3R,5S-FV (358.20 vs 279.68 ng·h/mL) and for S-LER compared with R-LER (13.90 vs 11.88 ng·h/mL). The pharmacokinetic parameters of FV were not enantioselective when combined with LER (AUC: (–)-3S,5R-FV: 325.21; (+)-3R,5S-FV: 316.44 ng·h/mL). There was a significant reduction in S-LER (8.06 vs 13.90 ng·h/mL) and R-LER (6.76 vs 11.88 ng·h/mL) AUC values when FV was coadministered. In conclusion, the interaction between FV-LER might be clinically relevant because AUC values of (+)-3R,5S-FV were increased when LER was coadministered, and AUC values of the 2 LER enantiomers were reduced when FV was coadministered.

Keywords: *Lercanidipine; fluvastatin; drug-drug interaction; enantiomers; pharmacokinetics; healthy volunteers*

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Hypertension and hypercholesterolemia frequently coexist and substantially increase the risk of cardiovascular disease events and mortality. Prevalence estimates for the concomitant diseases range from 15% to 31% in the United States. Nevertheless, treatment and control of combined hypertension and hypercholesterolemia are suboptimal.[1,2]

Lercanidipine (LER) is a third-generation vasoselective dihydropyridine (Figure 1), which acts by blocking L-type calcium channels in cell membranes.[3] Lercanidipine, at a single daily dose, exerts a prolonged antihypertensive effect lasting 24 hours and seems to be well tolerated, with a low rate of adverse events.[4] It has a chiral center at position 4 of the dihydropyridine ring. An in vitro binding displacement study has shown a 100- to 200-fold higher affinity of S-LER for the L-type calcium channel compared with R-LER. Previous studies have suggested that the overall antihypertensive activity of

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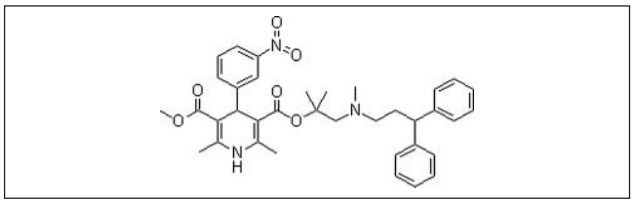

Figure 1. Molecular structure of lercanidipine.

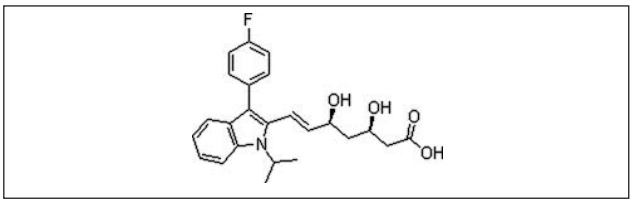

Figure 2. Molecular structure of fluvastatin.

LER might be attributed to the S-enantiomer because R-LER did not affect blood pressure at doses much higher than those at which the racemate and S-LER are active.[4,5] Following racemate administration to healthy volunteers, AUC and C_{max} values for S-LER are on average 1.2 times higher than those observed for R-LER.[6] After oral administration, LER undergoes extensive and saturable first-pass metabolism by CYP3A4 to largely inactive metabolites.[4,5]

Fluvastatin (FV) is a synthetic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor used for the treatment of hypercholesterolemia (Figure 2). Moderate reduction in serum cholesterol levels of about 20% to 30% is achieved with daily doses of 20 to 40 mg of the rapid-release formulation.[7] Fluvastatin is marketed as a racemic mixture of the (+)-3R,5S and (–)-3S,5R enantiomers. However, the therapeutic activity is 30-fold higher for (+)-3R,5S-FV. In vitro data have shown that about 50% to 80% of the metabolic clearance of FV is mediated by CYP2C9.[8] The pharmacokinetics of the 2 FV enantiomers depends on the CYP2C9 genotype. The AUC values of the active 3R,5S-FV enantiomer are 3-fold higher in carriers of CYP2C9*3/*3 than in carriers of CYP2C9*1/*1, and AUC values of the inactive 3S,5R-FV enantiomer are more than 4-fold higher.[8]

The combination of the dihydropyridine calcium channel blocker, LER, and the HMG-CoA reductase inhibitor, FV, provides an important step forward toward managing cardiovascular risk. An ideal combination would be administered once daily, with established safety, efficacy, and cardiovascular benefits.

In view of the clinical relevance of the combination of the antihypertensive drug LER and the hypocholesterolemic agent FV, considering that for both drugs, the pharmacological effect resides only on one of the enantiomers and the potential pharmacokinetic interaction in terms of CYP3A- and CYP2C9-dependent metabolism, the present crossover randomized study describes the stereoselectivity in the kinetic disposition of the 2 drugs administered alone or in combination. There are no studies in the literature regarding the drug interaction of the individual enantiomers of FV or LER.

PATIENTS AND METHODS

Eight healthy female volunteers ranging in age from 19 to 33 years (median: 23, confidence interval [CI]: 21.0-28.8) and weighing 54 to 70 kg, with a median body mass index of 21.3 kg/m^2 (CI: 18.7-23.4), were investigated after clinical and physical examination. The study was approved by the Ethics Committee of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil, and was conducted in accordance with good clinical practice (protocol 9576/2006). Each volunteer gave written consent to participate after receiving written and verbal information about the study. The volunteers were required to abstain from any medication and alcohol for 15 days prior to the study.

Clinical Protocol

Each volunteer received in a random sequence 3 different drug regimens lasting for 24 hours, which were separated by washout periods of at least 7 days. The drugs were administered as single oral doses as follows: 20 mg racemic LER (Zanidip, 10-mg tablets, Medley, Campinas, Brazil) or 40 mg racemic FV (Lescol, Novartis, Taboão da Serra, São Paulo, Brazil) or a combination of 20 mg racemic LER and 40 mg racemic FV with 200 mL water after an overnight fast. Three and 12 hours after dosing, a light breakfast and dinner were given to each volunteer, respectively. Serial blood samples (10 mL) were collected through an intravenous catheter at predose (0 hours) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10, 12, and 24 hours postdose. The blood samples were transferred to tubes containing heparin (Liquemine, 5000 IU, Roche, São Paulo, Brazil) and were protected from light. The samples were centrifuged (10 minutes at 2000 *g*), and plasma was separated and stored at –70°C until the time of chromatographic analysis.

Sample size estimation after the study was based on pharmacokinetic variability measured in the healthy volunteers included in the present investigation. For

S-LER, the mean area under the curve (AUC) (n = 8) was 14.66 ng·h/mL (SD 10.81 ng·h/mL). To detect differences higher than 50% between the 2 groups, an 80% power and 5% type I error would be achieved with a minimum sample size of 7 per group. For (+)-3R,5S-FV, the mean AUC (n = 8) was 406.19 ng·h/mL (SD 176.50 ng·h/mL). To detect differences higher than 50% between the 2 groups, an 80% power and 5% type I error would be achieved with a minimum sample size of 6 per group.

Stereoselective Analysis of Lercanidipine

Plasma concentrations of R- and S-LER were determined by an enantioselective liquid chromatography/tandem mass spectrometry (LC/MS/MS) method in a Quattro Micro triple quadrupole mass spectrometer (Micromass, Manchester, UK) using an electrospray interface in the positive ion mode as described by Jabor et al.[9] Briefly, 25 μL of the internal standard (0.66 μg/mL amiodarone) and 50 μL sodium hydroxide solution (0.1 mol/L) were added to the plasma samples (1.0 mL), and the LER enantiomers were extracted with 4.5 mL of a mixture of hexane-isopropanol (99:1, v/v) by shaking in a vortex mixer for 2 minutes. After centrifugation, the organic phases were collected and evaporated to dryness, and the residues were dissolved in 50 μL hexane-ethanol (95:5, v/v) plus 0.1% (v/v) diethylamine. Aliquots (20 μL) of the final extracts were analyzed by LC/MS/MS on a Chiralpak AD column (250 × 4.6 mm i.d., 10-μm particle size; Chiral Technologies, Inc, Exton, Pennsylvania) using a LiChrospher 100 RP-18 guard column (4 × 4 mm i.d., 5 μm; Merck, Darmstadt, Germany) and a mobile phase consisting of a mixture of hexane-ethanol-diethylamine (95:5:0.1, v/v/v) at a flow rate of 1.3 mL/min. Tandem mass spectrometry detection was carried out by postcolumn infusion consisting of the addition of an aqueous solution of 10 mmol/L ammonium acetate in ethanol (5:95, v/v). For multiple-reaction monitoring (MRM), the ammonium adducts $[M + NH_4]^+$ and their respective product ions were monitored using 2 functions: 612.40 > 100.10 (0.0–5.0 minutes) for the LER enantiomers and 646.30 > 100.30 (5.0-8.0 minutes) for the internal standard. The quantification limit was 0.025 ng/mL for each LER enantiomer. Linearity of the method was observed over a range of 0.025 to 50 ng/mL for each LER enantiomer. Precision and accuracy showed a coefficient of variation and relative errors of less than 15%. No matrix effects were observed.

Stereoselective Analysis of Fluvastatin

Plasma concentrations of (–)-3S,5R-FV and (+)-3R,5S-FV were determined by an enantioselective LC/MS/MS method in a Quattro Micro triple quadrupole mass spectrometer (Micromass) using an electrospray interface in the negative ion mode as described by Di Pietro et al.[10] Briefly, 25 μL of the internal standard (1 μg/mL warfarin), 1 mL 0.75 M acetate buffer (pH 5.0), and 5 mL diisopropyl ether were added to 0.5-mL aliquots of human plasma. The samples were extracted in a horizontal shaker for 30 minutes and centrifuged at 2000 *g* for 5 minutes. The organic phases were collected and evaporated to dryness, and the residues were dissolved in 50 μL of the mobile phase. Aliquots (20 μL) of the final extracts were analyzed by LC/MS/MS on a Chiralcel OD-R chiral column (Chiral Technologies, Inc; 250 × 4.6 mm i.d., particle size of 10 μm) equipped with a LiChrospher 100 CN precolumn (4 × 4 mm i.d., particle size of 5 μm; Merck). The mobile phase consisted of a mixture of acetonitrile, methanol, and water (24:36:40, v/v/v) containing 0.1% formic acid and was used at a flow rate of 0.7 mL/min. The column was kept at a temperature of 30 ± 1°C. The analyses were performed in the selected reaction monitoring (SRM) mode. Two transitions (410.6 > 348.2 for the FV enantiomers and 307.1 > 161.6 for the internal standard) were monitored. All analytical procedures were performed under yellow light because of the photosensitivity of FV. The quantification limit was 0.75 ng/mL for each FV enantiomer. Linearity of the method was observed over a range of 0.75 to 625 ng/mL for each FV enantiomer. Precision and accuracy showed a coefficient of variation and relative errors of less than 15%. No matrix effects were observed.

Pharmacokinetic and Statistical Analysis

The pharmacokinetic parameters were calculated based on the plasma enantiomer concentration versus time curves using the WinNonlin program, Version 4.0 (Pharsight Corp, Mountain View, California).

The experimental data were analyzed statistically using the Graphpad Instat software for the calculation of the mean, the median, and 95% confidence interval. Data were compared using a nonparametric test for paired data (comparison between enantiomers), with the level of significance set at $P \leq .05$.

Table I Stereoselective Kinetic Disposition of Fluvastatin (FV) in Healthy Volunteers (n = 8) Treated With Single Doses of Racemic Drug (40 mg)

	FV		Lercanidipine + FV	
Parameter	**(–)-3S,5R-FV**	**(+)-3R,5S-FV**	**(–)-3S,5R-FV**	**(+)-3R,5S-FV**
C_{max}, ng/mL	338.44*	220.71	335.37	286.58
	345.89	234.67	356.79	284.67
	(167.89-508.19)	(102.02-305.75)	(208.37-613.77)	(145.69-666.17)
t_{max}, h	0.60	0.79	0.68	0.65
	0.65	0.76	0.68	0.71
	(0.44-0.87)	(0.51-1.00)	(0.51-0.91)	(0.51-0.87)
$AUC_{0-\infty}$, ng·h/mL	358.20*	279.68	325.21	316.44**
	406.19	306.74	381.23	425.67
	(258.58-553.80)	(170.35-443.14)	(219.16-787.55)	(235.33-780.28)
$t_{1/2}$, h	2.59	3.45	2.42	2.27
	2.65	3.13	2.22	2.16
	(1.59-3.71)	(2.11-4.16)	(1.46-2.98)	(1.04-3.29)
K_{el}, h^{-1}	0.27	0.20	0.26	0.25
	0.31	0.30	0.33	0.38
	(0.19-0.44)	(0.06-0.55)	(0.21-0.42)	(0.18-0.54)
CL/F, L/h/kg	0.86*	1.11	0.95	0.97**
	0.88	1.23	0.81	0.83
	(0.56-1.21)	(0.76-1.70)	(0.51-1.11)	(0.48-1.17)
V_d/F, L/kg	2.70*	5.61	2.58	2.25**
	2.81	5.78	2.95	2.30
	(1.66-4.68)	(2.94-8.05)	(1.16-3.97)	(1.06-3.55)
$AUC_{\pm}^{0-\infty}$	0.77		1.03**	
	0.74		1.03	
	(0.63-0.84)		(0.79-1.27)	

Values are reported as the median, mean (95% confidence interval).
Wilcoxon test, $P \leq .05$. *Between enantiomers. **Between groups.

RESULTS

The kinetic disposition of FV administered as monotherapy or in combination with LER is shown in Table I. The pharmacokinetics of FV are enantioselective when administered as monotherapy, with observation of higher values of C_{max} (338.44 vs 220.71 ng/mL) and AUC (358.20 vs 279.68 ng·h/mL) for the enantiomer (–)-3S,5R-FV. On the other hand, the combination with LER resulted in a loss of enantioselectivity in FV pharmacokinetics.

The kinetic disposition of LER is not enantioselective when administered as monotherapy to healthy volunteers (Table II). The combination of FV resulted in higher values of AUC (8.06 vs 6.76 ng·h/mL) for the enantiomer S-LER.

DISCUSSION

This crossover randomized study investigated 8 healthy women treated with single doses of racemic LER, FV, or a combination of both. No adverse reactions were observed during the study period. There are no data in the literature regarding the influence of gender on the kinetic disposition of the drugs studied.

The kinetic disposition of FV administered as monotherapy was enantioselective for the parameters AUC, V_d/F, CL/F, and C_{max}, with the observation of plasma accumulation of the (–)-3S,5R-FV enantiomer (Figure 3). The ± AUC ratio of 1.03 (Table I) agrees with the results reported by Kirchheiner et al,[7] who observed ratios ranging from 1.1 to 1.6 in healthy volunteers with CYP2C9 genotypes, excluding those identified as *3/*3, who presented ratios close to 2. Di Pietro et al[10] reported a ± AUC ratio of 1.8 in a study on a healthy volunteer genotyped as CYP2C9 *1/*1.

The combination of single doses of LER and FV resulted in a loss of enantioselectivity in the pharmacokinetics of FV, with a ± AUC ratio close to 1 (Figure 4 and Table I). The mechanism to explain the

Table II Stereoselective Kinetic Disposition of Lercanidipine (LER) in Healthy Volunteers (n = 8) Treated With Single Dose of Racemic Drug (20 mg)

	LER		LER + Fluvastatin	
Parameter	**S-(LER)**	**R-(LER)**	**S-(LER)**	**R-(LER)**
C_{max}, ng/mL	1.41*	1.18	1.36	1.13
	2.75	2.09	2.14	1.75
	(0.69-4.82)	(0.59-3.59)	(0.23-4.06)	(0.24-3.26)
t_{max}, h	1.70	1.76	1.27	1.09
	1.96	1.82	1.33	1.49
	(1.23-2.68)	(1.34-2.30)	(0.92-1.73)	(0.64-2.34)
$AUC_{0-\infty}$, ng·h/mL	13.90	11.88	8.06*,**	6.76**
	18.32	16.64	10.03	8.51
	(6.29-30.35)	(5.25-28.02)	(4.82-15.23)	(3.45-13.56)
$t_{1/2}$, h	3.06	3.43	3.05	3.65
	3.77	3.61	3.19	3.48
	(2.42-5.13)	(2.25-4.98)	(2.23-4.15)	(2.47-4.50)
K_{el}, h^{-1}	0.26	0.20	0.23	0.22
	0.22	0.26	0.25	0.23
	(0.17-0.33)	(0.15-0.30)	(0.15-0.29)	(0.16-0.36)
CL/F, L/h/kg	11.17	13.00	19.65*	23.83**
	15.92	17.60	24.09	27.83
	(4.76-27.09)	(4.73-30.48)	(6.92-41.27)	(12.06-43.61)
V_d/F, L/kg	82.15	84.85	95.50*	119.12
	94.23	98.13	100.41	132.56
	(27.01-132.66)	(29.06-132.69)	(39.92-175.98)	(51.15-239.35)
$AUC^{0-\infty}_{S/R}$	1.06		1.24	
	1.04		1.21	
	(0.93-1.33)		(1.02-1.43)	

Values are reported as the median, mean (95% confidence interval) (n = 8).
Wilcoxon test, $P \leq .05$. *Between enantiomers. **Between groups.

loss of enantioselectivity in the kinetic disposition of FV might be the capacity of LER to preferentially inhibit the metabolism of (+)-3R,5S-FV. This mechanism is suggested based on the data of Table I showing that LER significantly reduces only the clearance of the (+)-3R,5S-FV enantiomer. These results are relevant considering that the (+)-3R,5S-FV eutomer is approximately 30 times more potent as an inhibitor of HMG-CoA reductase than its distomer.[7,11] However, there are no studies in the literature regarding the involvement of the same or different enzymes in the metabolism of the 2 FV enantiomers.

In the present study, we also evaluated the influence of administration of a single dose of FV on the pharmacokinetics of the 2 LER enantiomers. When the volunteers were treated only with LER, the S/R AUC ratios were close to 1 (Figure 5 and Table II), a finding not characterizing enantioselectivity in the pharmacokinetic parameters depending on AUC, CL/F, and V_d. Jabor et al[12] reported S/R AUC ratios ranging from 1.09 to 1.40 in male volunteers treated with a single dose of racemic LER.

The administration of a single dose of FV resulted in enantioselectivity in the pharmacokinetic parameters of LER, with the observation of a reduction in clearance and V_d and an increase in the AUC for the S-LER enantiomer compared with R-LER (Figure 6 and Table II). The administration of a single dose of FV also resulted in a reduction of approximately 42% in the AUC of both LER enantiomers. These changes are probably due to the displacement of the 2 LER enantiomers from their plasma protein binding sites because induction of metabolism is not expected because FV was administered as a single dose. Because many substrates of CYP3A4 are also substrates of P-glycoprotein and because LER is a substrate of CYP3A4, one may also speculate that FV induces intestinal P-glycoprotein and consequently reduces the bioavailability of LER.[13]

The interaction between FV and LER might be of clinical relevance because the plasma concentrations

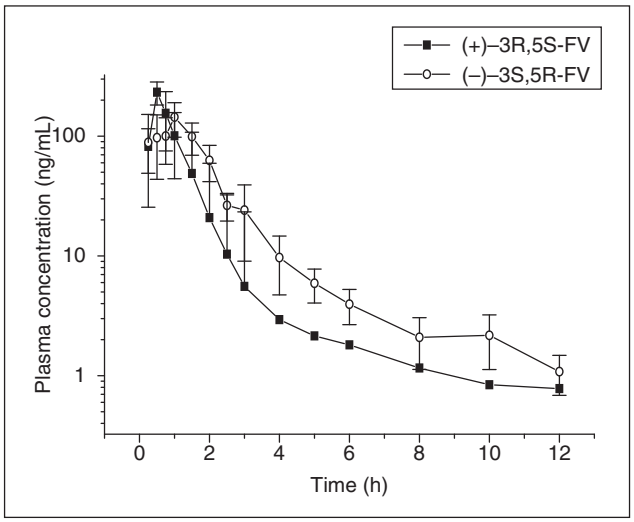

Figure 3. Pharmacokinetic profile of the fluvastatin (FV) enantiomers represented by the mean plasma concentrations observed and their respective standard error of the mean (n = 8) after administration of racemic fluvastatin alone (phase 2).

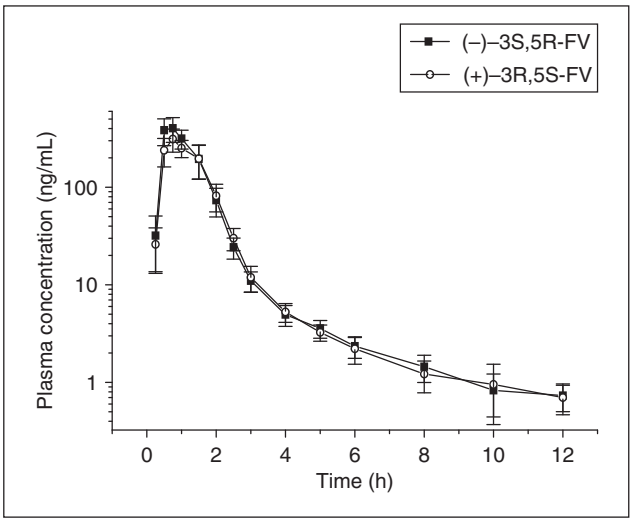

Figure 4. Pharmacokinetic profile of the fluvastatin (FV) enantiomers represented by the mean plasma concentrations observed and their respective standard error of the mean (n = 8) after the combined administration of racemic fluvastatin and racemic lercanidipine (phase 3).

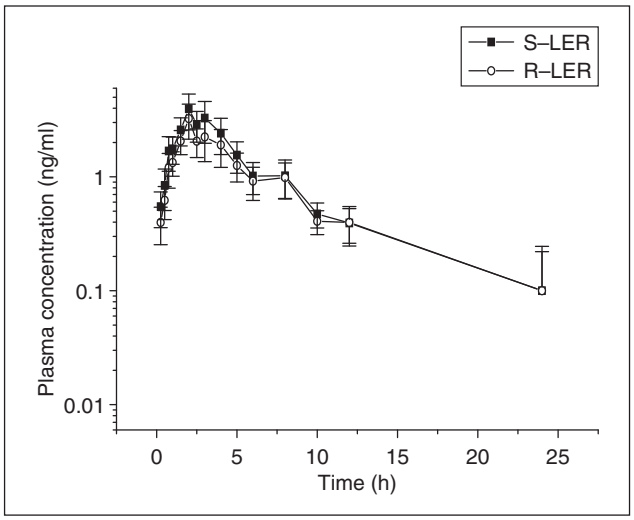

Figure 5. Pharmacokinetic profile of the lercanidipine (LER) enantiomers represented by the mean plasma concentrations observed and their respective standard error of the mean (n = 8) after administration of racemic lercanidipine alone (phase 1).

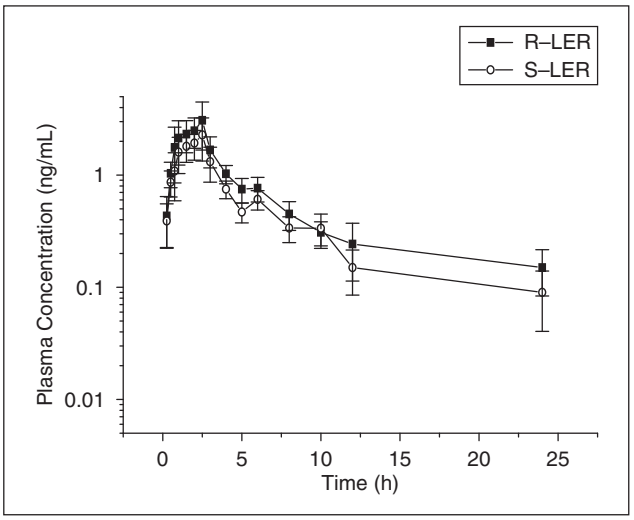

Figure 6. Pharmacokinetic profile of the lercanidipine (LER) enantiomers represented by the mean plasma concentrations observed and their respective standard error of the mean (n = 8) after the combined administration of racemic fluvastatin and racemic lercanidipine (phase 3).

of the enantiomer with higher antihypertensive activity (S-LER) were reduced by almost half.

In conclusion, the interaction between FV and LER induces changes in the pharmacokinetics of both FV and LER. The administration of a single dose of LER results in the loss of enantioselectivity in the kinetic disposition of FV because of the enantioselective inhibition of the metabolism of (+)-3R,5S-FV, which presents higher biological activity, thus increasing the risk of manifestations of myotoxicity. The administration of a single dose of FV causes enantioselectivity in the kinetic disposition of LER, with the observation of reduced clearance of the S-LER eutomer when compared with the R-LER distomer. In addition, the

administration of a single dose of FV reduces the plasma concentrations of both LER enantiomers by approximately half. These findings suggest that when LER and FV are used in association, higher reduction of cholesterol values could be observed due to higher plasma concentrations of eutomer (+)-3R,5S-FV. Otherwise, this association could be related to less reduction in blood pressure values considering the reduction of about 40% in the plasma concentrations of S-LER.

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REFERENCES

1. Preston RA, Harvey P, Herfert O, et al. A randomized, placebo-controlled trial to evaluate the efficacy, safety, and pharmacodynamic interaction of coadministered amlodipine and atorvastatin in 1660 patients with concomitant hypertension and dyslipidemia: the respond trial. *J Clin Pharmacol.* 2007;47:1555-1569.

2. Wong ND, Lopez V, Tang S, Williams GR. Prevalence, treatment, and control of combined hypertension and hypercholesterolemia in the United States. *Am J Cardiol.* 2006;98:204-208.

3. Barrios V, Escobar C, Navarro A, Barrios L, Navarro-Cid J, Calderón A. Lercanidipine is an effective and well tolerated antihypertensive drug regardless the cardiovascular risk profile: the LAURA study. *Int J Clin Pract.* 2006;60:1364-1370.

4. Testa R, Leonardi A, Tajana A, Risacassi R, Magliocca R, Sartani A. Lercanidipine (Rec15/2375): a novel 1,4-dihidropiridine calcium antagonist for hypertension. *Cardiovasc Drug Rev.* 1997;15:187-219.

5. McClellan KJ, Jarvis B. Lercanidipine: a review of its use in hypertension. *Drugs.* 2000;60:1123-1140.

6. Barchielli M, Dolfini P, Farina B, et al. Clinical pharmacokinetics of lercanidipine. *J Cardiovasc Pharmacol.* 2000;29: 3609-3617.

7. Kirchheiner J, Kudlicz D, Meisel C, et al. Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (–)-3S,5R-fluvastatin and (+)-3R, 5S-fluvastatin in healthy volunteers. *Clin Pharmacol Ther.* 2003;74:186-194.

8. Fischer V, Johanson L, Heitz F, et al. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor fluvastatin: effect on human cytochrome P-450 and implications for metabolic drug interactions. *Drug Metab Dispos.* 1999;27:410–416.

9. Jabor VAP, Coelho EB, Ifa DR, Bonato PS, Santos NAG, Lanchote VL. Enantioselective determination of lercanidipine in human plasma for pharmacokinetics studies by normal-phase liquid chromatography–tandem mass spectrometry. *J Chromatogr B.* 2003;796:429-437.

10. Di Pietro G, Coelho EB, Geleilete TM, Marques MP, Lanchote VL. Chiral evaluation of fluvastatin in human plasma high-performance liquid chromatography electrospray mass spectrometry. *J Chromatogr B.* 2006;832:256-261.

11. Kathawala FG. HMG-CoA reductase inhibitors: an exciting development in the treatment of hyperlipoproteinemia. *Med Res Rev.* 1991;11:121-146.

12. Jabor VAP, Coelho EB, Lanchote VL. Enantioselective pharmacokinetics of lercanidipine in healthy volunteers. *J Chromatogr B.* 2004;813:343-346.

13. Klotz U. Interaction potential of lercanidipine, a new vasoselective dihydropyridine calcium antagonist. *Drug Res.* 2002;52: 155-161.