Effect of fluconazole on the pharmacokinetics of eprosartan and losartan in healthy male volunteers

Objective: To investigate the effect of steady-state fluconazole administration on the disposition of eprosartan, losartan, and E-3174.

Methods: Sixteen healthy male subjects received 300 mg eprosartan every 12 hours, and 16 received 100 mg losartan every 24 hours on study days 1 to 20. All 32 subjects received 200 mg fluconazole every 24 hours beginning on day 11 and continuing through day 20. Serial blood samples were collected over one dosing interval on study days 10 and 20 for measurement of plasma concentrations of eprosartan, losartan, and E-3174 (the active metabolite of losartan).

Results: There was no significant difference in eprosartan area under the concentration-time curve from time 0 to time of last quantifiable concentration [AUC(0-t)] or maximum concentration (C_{max}) when administered alone and with fluconazole. After concomitant administration with fluconazole, losartan AUC(0-t) and C_{max} were significantly increased 66% and 30%, respectively, compared with those values for losartan alone. The AUC(0-t) and C_{max} for E-3174 were significantly decreased 43% and 56%, respectively, after administration of losartan with fluconazole.

Conclusions: Fluconazole significantly increases the steady-state AUC of losartan and inhibits the formation of the active metabolite of losartan, E-3174. In contrast, fluconazole administration has no effect on the steady-state pharmacokinetics of eprosartan. (Clin Pharmacol Ther 1997;62:417-25.)

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Eprosartan (SK&F 108566) is an angiotensin II receptor antagonist that is highly selective for the angiotensin II receptor subtype.[1] Eprosartan is rapidly absorbed; peak concentrations occur within 1 to 3 hours after oral administration. The drug is not metabolized through the cytochrome P450 system and is excreted into the bile and urine as either unchanged drug or as an acyl glucuronide conjugate.[2] In the treatment of patients with hypertension, eprosartan has a terminal elimination half-life in the range of 8 to 12 hours.

Losartan is the first selective angiotensin II receptor antagonist approved by the U.S. Food and Drug Administration for the management of hypertension. After oral administration, losartan is well absorbed and undergoes extensive first-pass metabolism with a systemic bioavailability of approximately 33%.[3] Unlike eprosartan, losartan undergoes hepatic metabolism with 14% of the losartan dose normally converted to an active carboxylic acid metabolite, E-3174.[3,4] The terminal elimination half-life of losartan (2 hours) is shorter than that of the metabolite (6 to 9 hours). E-3174 is 10 to 40 times more potent by weight than losartan and is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment.[3] In vitro studies indicate that both CYP2C9 and CYP3A4 are involved in the biotransformation of losartan to E-3174.[5] However, in vivo studies have shown that

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ketoconazole, a CYP3A4 inhibitor, has little to no inhibitory effect on the conversion of intravenously administered losartan to E-3174 and the plasma clearances of losartan and E-3174.[6] Therefore it is unlikely that CYP3A4 is an important in vivo pathway in the metabolism of losartan.

Fluconazole, an orally administered antifungal agent, is a potent inhibitor of CYP2C9.[7] Coadministration of fluconazole with phenytoin[8] and warfarin,[9] both known to be metabolized through CYP2C9,[10] has resulted in dramatic increases in plasma concentration as well as the pharmacodynamic effects of these agents. Inhibition of CYP2C9 activity by fluconazole may inhibit the conversion of losartan to its active metabolite and potentially alter the pharmacodynamic effects of losartan. The purpose of this study was to compare the steady-state pharmacokinetic parameters of eprosartan, losartan, and E-3174 before and during concomitant steady-state administration of fluconazole.

METHODS

Subjects. Thirty-two nonsmoking men provided written informed consent to participate in the study. All subjects were within 20% of ideal body weight (1983 Metropolitan Life Insurance Tables) and judged to be healthy on the basis of normal physical findings and clinical laboratory test results. The study was conducted in accordance with the Declaration of Helsinki and approved by the Millard Fillmore Hospital Institutional Review Board (Buffalo, N.Y.).

Design and procedures. Volunteers were randomly assigned to receive either eprosartan or losartan for 20 days (days 1 through 20) along with fluconazole treatment on days 11 through 20 in an open-labeled parallel-group study. A minimum dosing period of 10 days for each drug regimen was used to establish steady-state concentrations. Subjects were randomly assigned to one of two different treatment regimens. Sixteen subjects received 300 mg eprosartan orally every 12 hours for 20 days and 16 subjects received 100 mg losartan (Cozaar, Merck & Co., West Point, Pa.) orally once daily for 20 days. All oral doses of study medication were administered with 60 ml tepid water and were witnessed by a staff member in the clinical research center. Beginning on study day 11 of each regimen, subjects were administered 200 mg fluconazole (Diflucan; Pfizer, Inc., New York, N.Y.) orally once daily with the morning dose of study medication up to and including study day 20. All study drug regimens were initiated to provide steady-state plasma concentrations of eprosartan, losartan, E-3174, and fluconazole.

For the eprosartan treatment regimen, blood samples (5 ml) were obtained before dosing (0 hour) and at ½, 1½, 2, 2½, 3, 4, 5, 6, 8, 10, and 12 hours after eprosartan dosing on study days 10 and 20. For the losartan treatment regimen, blood specimens (8 ml) were obtained before dosing (0 hour) and at ½, 1, 1½, 2, 2½, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours after losartan dosing on study days 10 and 20. Blood specimens were collected into heparinized tubes and immediately chilled in an ice bath. Plasma was separated by means of refrigerated centrifugation and then transferred to polypropylene specimen containers. Specimens were immediately frozen and stored at approximately −20° C until analysis.

Sample analysis. Plasma samples were assayed for eprosartan concentrations with a sensitive and specific HPLC method.[11] In brief, chromatographic separation was performed by means of reversed-phase HPLC with a mixture of 50 mmol/L citrate (pH, 3.5) and tetrahydrofuran, 340:160 (vol/vol), as the mobile phase. Five hundred microliters of plasma was spiked with 25 μl of internal standard solution and 500 μl of 0.1 mol/L citrate buffer (pH, 3.5) and briefly vortex mixed. After centrifugation, the samples were applied to solid phase extraction cartridges (phenyl, 100 mg bed packing, Analytichem International, Harbor City, Calif.), conditioned with 2 ml methanol and 2 ml millipore water. The extraction cartridge was washed with 2 ml 0.05N acetic acid, and 1 ml ethyl acetate containing 0.1% triethylamine; each washing was followed by a 45 second drying period. The analytes were eluted with 2 ml methanol in 0.05 normal acetic acid (90:10, vol/vol). The eluent was evaporated to dryness, and the residue was redissolved in 125 μl of mobile phase. Fifty microliters of this solution was injected onto the analytical column (BDS-Hypersil, C18, 5 μm, 150 × 2 mm, Keystone Scientific, Bellefonte, Pa.). With a constant flow rate of 0.25 ml/min, eprosartan and internal standard were eluted with retention times of 9.5 and 13.0 minutes, respectively. Detection of eprosartan was achieved by means of ultraviolet absorbence at 300 nm. The calibration curve was linear up to 5000 ng/ml with a lower detection limit of 10 ng/ml. After a three-run validation, the mean within-run precision, between-run precision, accuracy, and recovery were determined to be 6.5%, 3.9%, 105.7%, and 71.8%, respectively.

Plasma samples were assayed for losartan and E-3174 concentrations by means of a sensitive and

Table I. Subject demographics

Group	*n*	*Parameter*	*Age (y)*	*Weight (kg)*	*Race*
Eprosartan	16	Mean	30.9	80.5	14 white, 2 black
		SD	9.9	12.5	
		Range	19-48	54.5-96.8	
Losartan	16	Mean	30.1	80.1	13 white, 2 black, 1 Asian
		SD	6.9	10.3	
		Range	21-48	66.8-100.0	
All subjects	32	Mean	30.5	80.3	27 white, 4 black, 1 Asian
		SD	8.4	11.3	
		Range	19-48	54.5-100.0	

specific HPLC with ultraviolet detection.[12] In brief, 1 ml plasma was spiked with 75 μl internal standard and acidified with 100 μl 1.0 mol/L sulfuric acid. Losartan, E-3174, and an internal standard were then extracted into methyl *tert*-butyl ether. The compounds were then back-extracted into 0.05 mol/L sodium hydroxide, acidified, and washed with hexane. Separation of the compounds was achieved by means of reverse-phase HPLC on an analytical column (Ultremex CN, 5 μm, 250 mm × 4.6 mm, Phenomenex, Torrance, Calif.) with a mixture of 0.01 mol/L sodium phosphate buffer (pH, 2.1) and acetonitrile, 18.5:81.5 (vol/vol) as mobile phase. At a constant flow rate of 2.0 ml/min, losartan, E-3174, and internal standard were eluted with retention times of 6.7, 7.6, and 5.8 minutes, respectively. Detection of losartan and E-3174 was achieved by means of ultraviolet detection at 254 nm. The calibration curve was linear over the range of 5.00 to 1000 ng/ml for both losartan and E-3174. After a six-run validation, the mean within-run precision, between-run precision, accuracy, and recovery for losartan were determined to be 4.2%, 5.6%, 94.5%, and 73.0%, respectively. After a six-run validation, the mean within-run precision, between-run precision, accuracy, and recovery for E-3174 were determined to be 5.5%, 4.7%, 107.2%, and 62.8%, respectively.

Data analysis. Noncompartmental analysis was used to characterize eprosartan, losartan, and E-3174 plasma concentration–time profiles. The maximum plasma drug concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) were determined directly from the concentration-time data. Area under the concentration-time curve (AUC) from time zero (predose) to the time of the last quantifiable concentration [AUC(0-t)] was calculated by means of the linear trapezoidal method for ascending concentrations, and the log-linear trapezoidal method for descending concentrations. The terminal elimination rate constant and half-life ($t_{1/2}$) for eprosartan, losartan, and E-3174 could not be determined in this study because of variability observed in the plasma concentrations in the terminal phase or the limited number of measurable plasma concentrations in the terminal phase. For eprosartan and E-3174, almost all samples had quantifiable concentrations, and thus the AUC(0-t) was equivalent to the AUC for the dosing interval.

All statistical analyses were carried out with SAS for Windows (version 6.08) running under Windows version 3.1. Sample size was based on estimates of within-subject variability for AUC of eprosartan, losartan, and E-3174 from previous pharmacokinetic studies. A sample size of 12 for each regimen was estimated to provide greater than 90% power to detect differences of at least 30% in AUC between days 20 and 10 for eprosartan, losartan, and E-3174. Point estimates were computed for the ratios of day 20 (eprosartan or losartan administered with fluconazole) versus day 10 (eprosartan or losartan given alone). After log-normal transformation, AUC and C_{max} for eprosartan, losartan, and E-3174 were analyzed separately by means of ANOVA including terms for subject and day. Point estimates and 95% confidence interval (CI) for the difference between day 20 and day 10 for each analyte were constructed with the residual variance. The point and interval estimates on the log-normal scale were exponentially back-transformed to give estimates of the ratio of day 20 to day 10. The t_{max} was analyzed nonparametrically for eprosartan, losartan, and E-3174 by means of Wilcoxon test for related groups data.[13] Point estimates and associated 95% CI for each analyte were constructed for the median difference between day 20 and day 10.

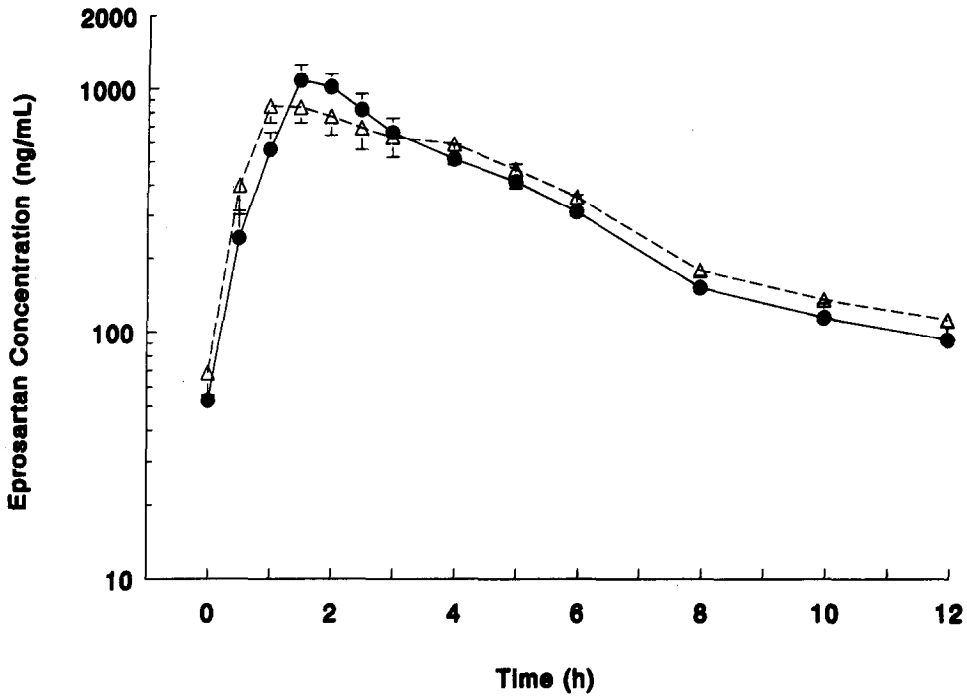

Fig. 1. Mean (SEM) steady-state eprosartan plasma concentration–time curves after twice daily oral administration of 200 mg eprosartan alone *(circles)* and with administration of 200 mg fluconazole *(triangles)* among healthy subjects.

RESULTS

A total of 32 subjects with a mean age of 31 years (age range, 19 to 48 years) and mean weight of 80.3 kg (weight range, 55 to 100 kg) participated in the study. Complete subject demographics are presented in Table I. Two subjects withdrew from the eprosartan group; one subject was asked to leave the study because of noncompliance with the dosing regimen, and another subject withdrew from the study because of insomnia after taking eprosartan plus fluconazole. This adverse experience resolved soon after study medication was discontinued. All adverse experiences were mild or moderate in severity. The most frequently reported adverse event was upper respiratory tract infection; four subjects in both the losartan and eprosartan groups had such infections. The number of adverse experiences reported were similar between and within regimens for both monotherapy and combination therapy with fluconazole. None of the changes in heart rate or blood pressure were considered clinically significant by the investigators.

Mean steady-state plasma concentration–time profiles for eprosartan administered with and without fluconazole are shown in Fig. 1. Mean steady-state plasma concentration–time profiles for losartan and E-3174 before and after fluconazole administration are presented in Figs. 2 and 3. Mean concentration-time profiles showed higher losartan concentrations and lower E-3174 concentrations when losartan was administered with fluconazole than when given alone. Mean concentration-time profiles for eprosartan were similar for administration with and without fluconazole.

After administration of eprosartan with fluconazole, day 20 AUC(0-t) values for eprosartan were increased an average of 4%. Values for C_{max} decreased an average of 11% compared with day 10 (without fluconazole) values. These results demonstrated no statistically significant differences in pharmacokinetic parameters when eprosartan was administered alone and with fluconazole.

After administration of losartan with fluconazole, day 20 losartan AUC(0-t) values increased an average of 66% compared with day 10 (without fluconazole) values. The 95% CI for the ratio of the geometric means did not contain the value 1.0, indicating fluconazole treatment resulted in a statistically significant increase in the AUC of losartan. The C_{max} increased an average of 30% after admin-

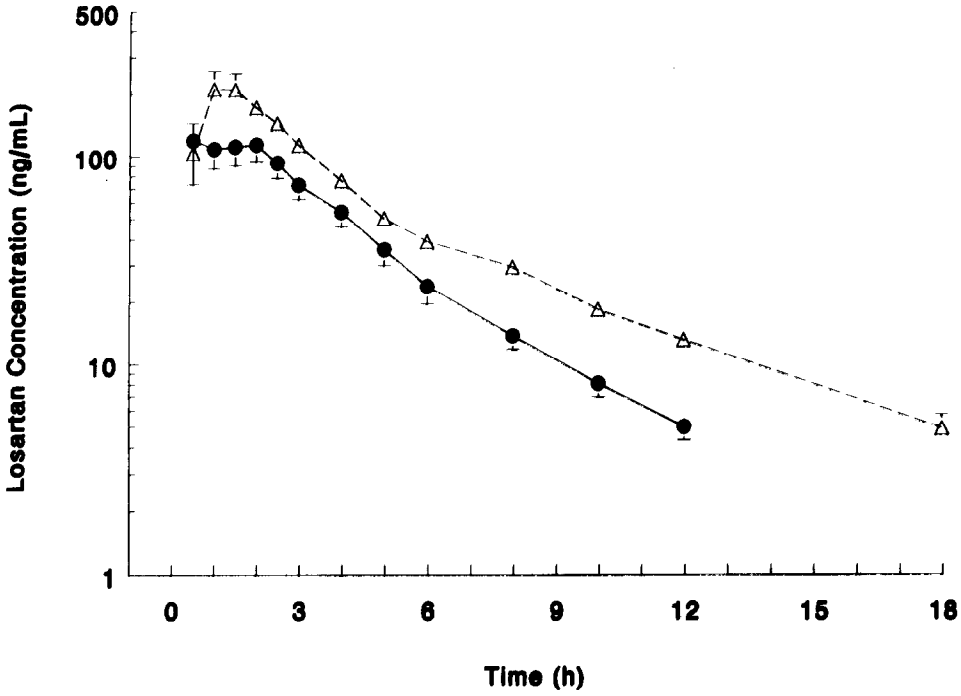

Fig. 2. Mean (SEM) steady-state losartan plasma concentration–time curves after once daily oral administration of 100 mg losartan alone *(circles)* and with administration of 200 mg fluconazole *(triangles)* among healthy subjects.

istration of losartan with fluconazole. However, the 95% CI for the ratio of the geometric means for C_{max} contained the value 1.0.

Compared with day 10 results, there was a mean decrease in E-3174 AUC(0-t) and C_{max} of 43% and 56%, respectively, after administration of losartan with fluconazole. The 95% CIs for the ratios of the geometric means for both AUC(0-t) and C_{max} did not contain the value 1.0. Therefore, fluconazole treatment caused a statistically significant decrease in both the AUC(0-t) and C_{max} of E-3174.

Fig. 4 displays AUC changes for losartan, E-3174, and eprosartan on day 10 (before fluconazole) and day 20 (with fluconazole). Compared with those on day 10, on day 20 the findings were that all 16 losartan-treated subjects demonstrated increased AUCs with a mean (95% CI) day 20 to day 10 ratio of 1.6 (1.44;1.92). Conversely, AUCs for E-3174 decreased on day 20 compared with day 10 for all 16 subjects, with a mean (95% CI) day 20 to day 10 AUC ratio of 0.57 (0.52;0.62). Although not displayed graphically, C_{max} for E-3174 decreased among all 16 subjects after fluconazole administration. Among the eprosartan-treated group, the day 20 AUC was higher than the day 10 AUC for six subjects, lower for five subjects, and approximately the same for three subjects. The mean (95% CI) day 20 to day 10 AUC ratio was 1.04 (0.87;1.25). Summary results of the arithmetic mean (SD) for AUC(0-t) and C_{max} and the median (range) for t_{max} for eprosartan, losartan, and E-3174 with and without fluconazole therapy are presented in Table II. The results of the statistical analyses are summarized in Table III.

Fluconazole administration had no statistically significant effect on t_{max} for eprosartan, losartan, or E-3174. In this study, the within-subject coefficients of variation for eprosartan, losartan, and E-3174 AUC values were 23%, 19%, and 12%, respectively. These values are similar to the value used in the sample size calculation; therefore no gross inadequacy was indicated in terms of the sample size used in this study.

DISCUSSION

The pharmacologic effects of losartan are related to both losartan and its active metabolite E-3174. However, studies with healthy volunteers challenged with angiotensin II infusions suggest that higher concentrations of the more potent metabolite that

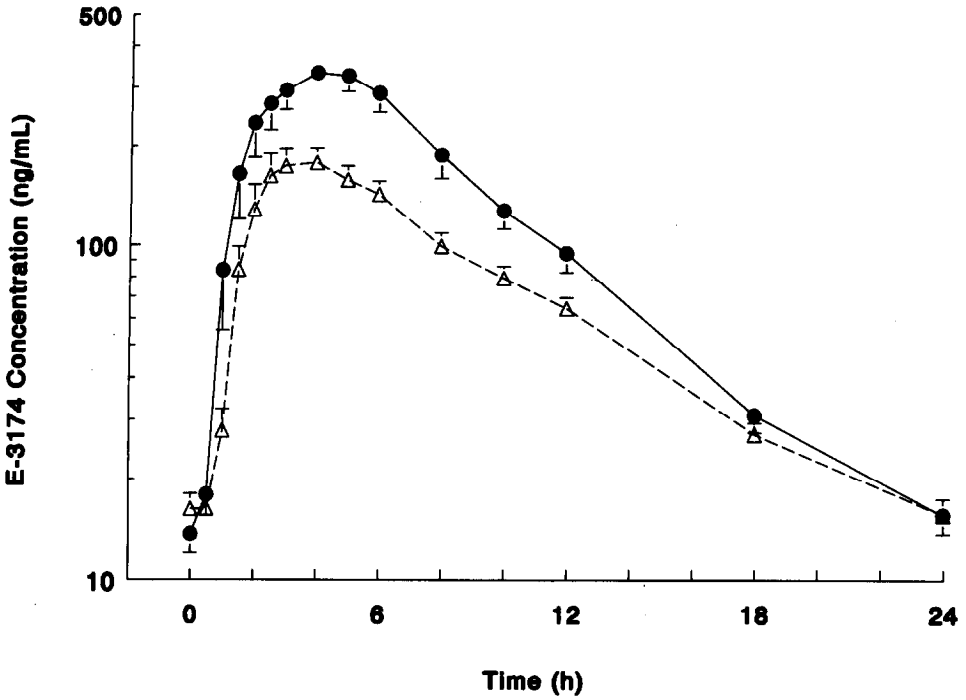

Fig. 3. Mean (SEM) steady-state E-3174 plasma concentration–time curves after once daily oral administration of 100 mg losartan alone *(circles)* and with administration of 200 mg fluconazole *(triangles)* among healthy subjects.

Table II. Summary statistics for eprosartan, losartan, and E-3174 with and without fluconazole

	AUC(0-t) *(ng · hr/ml)**	C_{max} *(ng/ml)**	t_{max} *(hr)*	
			Median	*Range*
Eprosartan without fluconazole	4331 ± 1967	1254 ± 547	1.74	1.00-4.00
Eprosartan with fluconazole	4504 ± 2096	1133 ± 464	1.50	0.50-4.00
Losartan without fluconazole	484 ± 114	246 ± 125	1.50	0.50-4.00
Losartan with fluconazole	818 ± 261	323 ± 157	1.50	0.50-2.50
E-3174 without fluconazole	2857 ± 770	425 ± 122	3.00	2.00-6.00
E-3174 with fluconazole	1676 ± 620	195 ± 85.5	3.50	2.50-6.03

AUC(0-t), Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, peak plasma concentration.
*Mean ± SD.

remain in the body for a longer period of time than the parent are associated with the overwhelming contribution of the pharmacodynamic actions of the drug.[14] In light of the important role of E-3174 in the action of losartan, it is important to characterize the disposition of losartan when it is coadministered with drugs that alter the activity of cytochrome P450 enzymes. In vitro experiments performed on human liver microsomes have demonstrated that biotransformation of losartan to E-3174 is catalyzed by the specific cytochrome P450 isoforms CYP3A4 and CYP2C9.[5] However, an in vivo study recently demonstrated little to no effect on the conversion of intravenously administered losartan to E-3174 with the coadministration of ketoconazole, a known CYP3A4 inhibitor, concluding that it is unlikely that CYP3A4 is an important metabolic pathway in the in vivo metabolism of losartan.[6] These data suggest that CYP2C9 is the primary P450 enzyme responsible for the in vivo conversion of losartan to E-3174. Data from clinical trials also suggest that a small percentage of the population (<1%) demonstrate decreased conversion of losartan to E-3174.[15] Sequencing of the coding regions of the *CYP2C9* gene from two subjects taking

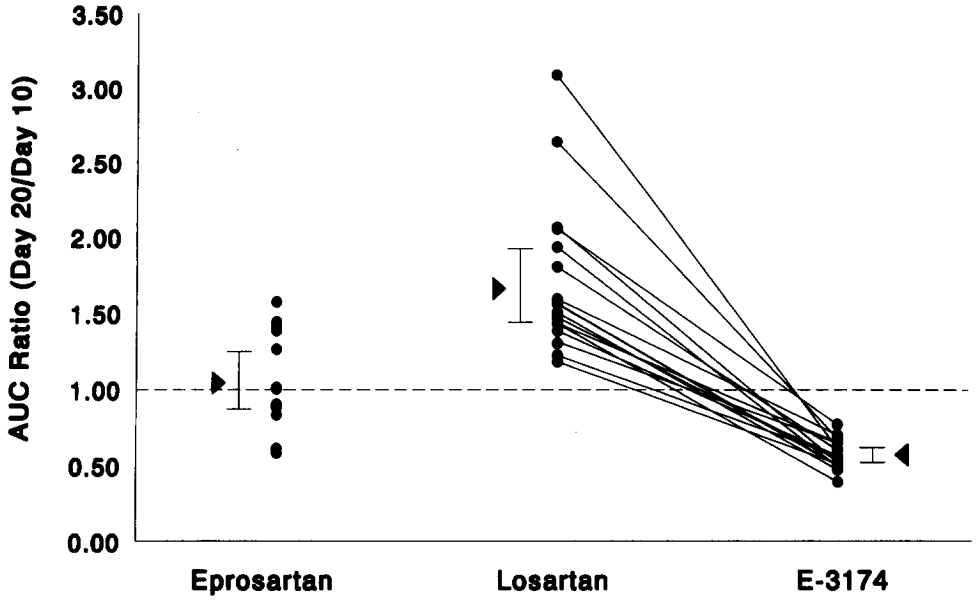

Fig. 4. Individual area under the concentration-time curve (AUC) ratios for day 20 to day 10 for losartan, E-3174, and eprosartan. *Circles* represent individual AUC ratios. *Arrowheads* are the geometric means of AUC ratios. *Bars* are the 95% confidence limits about the geometric mean ratios. AUC ratios for losartan and E-3174 for a given subject are connected by a solid line. Day 20 is measurement during treatment with fluconazole, and day 10 is measurement before treatment with fluconazole.

Table III. Point estimates and 95% confidence intervals of pharmacokinetic parameters for eprosartan, losartan, and E-3174 with and without fluconazole

	AUC(0-t)		*C_{max}*		*t_{max}*	
	Point estimates	*95% CI*	*Point estimates*	*95% CI*	*Point estimates*	*95% CI*
Eprosartan	1.04	0.87, 1.25	0.89	0.67, 1.19	0.00	−0.52, 0.50
Losartan	1.66	1.44, 1.92	1.30	0.92, 1.84	−0.13	−0.75, 0.50
E-3174	0.57	0.52, 0.62	0.44	0.39, 0.49	0.25	−0.74, 0.99

t_{max}, Time to reach C_{max}; CI, confidence interval.
AUC and C_{max} data are the geometric means and 95% CI on the ratio day 20 to day 10. t_{max} data are the median and 95% CI on the difference between day 20 and day 10.

losartan who were found to convert less than 1% of losartan to E-3174 demonstrated that both subjects were homozygous for a mutation causing an Ile to Leu substitution at residue 359, exon 7.[15] How this mutation affects enzyme function remains to be determined, but decreased conversion of losartan to E-3174 may result in clinically important alterations in pharmacodynamic activity.

Unlike losartan, eprosartan is eliminated primarily in the urine or the bile as unchanged drug or an acyl glucuronide conjugate and is not metabolized through the cytochrome P450 system. Therefore, coadministration with drugs that alter the activity of cytochrome P450 enzymes would not be expected to affect the disposition or efficacy of eprosartan.

Fluconazole is a potent and reversible inhibitor of the cytochrome P450 enzyme system.[16] The effect of fluconazole on the cytochrome P450 enzyme system appears to be dose related because doses of 50 mg fluconazole a day for 7 days did not alter antipyrine metabolism,[17] and 100 mg fluconazole a day for 14 days did not affect cyclosporine (CYP3A4) metabolism.[18] However, at doses of 200 mg fluconazole a day, cyclosporine (1NN, ciclosporin) increased con-

centrations twofold.[19] Coadministration of fluconazole with phenytoin[8] and warfarin,[9] both substrates of CYP2C9,[10] demonstrated dramatic increases in plasma concentration and the pharmacodynamic effects of these agents. Concomitant administration of 200 mg fluconazole a day for 14 days with phenytoin increased mean phenytoin AUC 75%.[8] Four hundred mg fluconazole a day increased *(S)*-warfarin AUC nearly threefold and markedly increased both the intensity and duration of the effect of warfarin on prothrombin time.[9]

This study showed that therapeutic doses of 200 mg a day fluconazole exert an inhibitory effect on the conversion of losartan to its active metabolite E-3174, without having any effect on the pharmacokinetics of eprosartan. Comparison of pharmacokinetic parameters between study day 20 (with fluconazole) and study day 10 (without fluconazole) resulted in statistically significant changes for losartan but not eprosartan. Losartan AUC(0-t) was significantly increased by 66% with concomitant fluconazole therapy. Although not statistically significant, losartan C_{max} demonstrated a mean increase of 30% after administration with fluconazole. Fluconazole did not affect the absorption time of losartan because the median t_{max} was 1.5 hours with and without fluconazole administration. Unlike losartan, E-3174 AUC(0-t) and C_{max} significantly decreased by a mean of 43% and 56%, respectively. As with losartan, fluconazole did not influence t_{max} of the metabolite. There were no significant differences in the pharmacokinetic parameters of eprosartan when administered alone and with fluconazole. Eprosartan AUC(0-t) increased 4% and C_{max} decreased 11%, both of which were not statistically significant.

The inhibition of CYP2C9 by fluconazole is likely to be the primary factor causing losartan AUC(0-t) to increase significantly and E-3174 AUC(0-t) and C_{max} to decrease significantly with concomitant fluconazole therapy. Despite elevations in losartan plasma concentrations after CYP2C9 inhibition, lower E-3174 plasma concentrations would be expected to decrease the angiotensin II receptor antagonist activity because of the greater potency of the metabolite. The relation between losartan and E-3174 concentrations and blood pressure response has been evaluated after administration of exogenous angiotensin II to healthy volunteers.[14] Inhibition of the blood pressure response was dose dependent, and the profile of angiotensin II blockade more closely paralleled plasma concentrations of E-3174 than those of losartan. These data suggest that as plasma concentrations of E-3174 decrease, the effect on blood pressure response and duration of action also decrease.[14] It has been estimated that a 30% change in AUC for either losartan or E-3174 is the minimal change necessary to produce a clinically important effect on a patient with hypertension.[14,20] Although changes in blood pressure were not observed in this study with healthy volunteers, changes in the AUC of losartan and E-3174 as large as those observed in this study may result in altered blood pressure control among patients with high blood pressure. However, there has not been any report in the literature of a statistically significant interaction between losartan and fluconazole.

The oral doses of eprosartan and losartan administered in this study were safe and well tolerated by the healthy male subjects who participated. Coadministration of fluconazole with losartan produced a statistically significant increase in steady-state AUC of losartan and decrease in the steady-state AUC of E-3174, presumably by means of inhibition of CYP2C9. In contrast, fluconazole administration did not alter the steady-state pharmacokinetics of eprosartan. No dosage adjustment of eprosartan is warranted with concomitant fluconazole therapy.

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