Effect of Food on the Bioavailability of Lisinopril, a Nonsulfhydryl Angiotensin-Converting Enzyme Inhibitor

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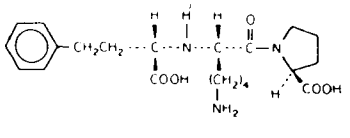
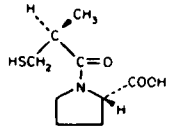
Abstract □ A randomized, two-way, crossover study was performed on 18 normal volunteers to assess the influence of food on the bioavailability of lisinopril, (1-[N^2-[(*S*)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline), a long-acting nonsulfhydryl angiotensin converting enzyme inhibitor. A single, 20-mg oral dose of lisinopril was administered to volunteers in the fasting state or following a standardized breakfast. Treatment periods were separated by 2-week intervals. No significant differences existed between fasting and fed regimens in the mean ± SD area under the serum concentration–time curve (AUC_{0-120h}; 1231 ± 620 versus 1029 ± 254 ng · h · ml $^{-1}$), peak lisinopril serum concentration (86 ± 48 versus 69 ± 19 ng/mL), or time to peak lisinopril serum concentration (6.2 ± 1.1 versus 6.8 ± 1.0 h). Five-day urinary excretion of lisinopril was not altered by food (5.3 ± 3.0 versus 5.1 ± 2.0 mg). Based on the urinary data, the mean ± SD bioavailability of lisinopril was not different following fasting or fed regimens (27 ± 15 versus 26 ± 10%). Unlike with captopril, food did not affect the bioavailability of lisinopril.

The influence of food and diet on the bioavailability of various drugs has been the subject of recent reviews.[1-3] Food may influence drug absorption as a result of physiological changes in the GI tract or physical or chemical interactions between particular food components and drug molecules. Depending on the type and degree of interaction, drug absorption may be reduced, delayed, not affected, or increased by concomitant food intake. It has been reported that the presence of food in the GI tract reduces the absorption of captopril, a marketed oral angiotensin converting enzyme (ACE) inhibitor, by 30–40%.[4] This reduction in bioavailability may be partially due to the binding of the sulfhydryl group of captopril to the thiol groups present in food. Compromised absorption of captopril could influence the magnitude or duration of the antihypertensive effect of this drug.[5] Recently, we reported that the bioavailability of enalapril, a new nonsulfhydryl ACE inhibitor, was not affected by a standardized breakfast.[6] Lisinopril (1-[N^2-[(*S*)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline) is a new, long-acting, orally-active ACE inhibitor which has been shown to reduce blood pressure in patients with mild to moderate hypertension.[7,8] The oral bioavailability of lisinopril, though lower than that of enalapril, may be greater than the bioavailability of captopril since lisinopril and enalapril lack the sulfhydryl moiety. The purpose of this study was to investigate the influence of food consumption on the rate or extent of absorption of orally administered lisinopril in healthy volunteers.



1

Lisinopril



2

Captopril

Experimental Section

Subjects—Eighteen healthy, normotensive subjects (age 21–37 years) volunteered to participate in this study. They were judged to be in good health on the basis of history, physical examination, routine laboratory data, standard electrocardiogram, and diastolic blood pressure (<90 mmHg). All subjects weighed ± 10% of their ideal body weight for their age and height. No medication other than lisinopril (1-[N^2-[(*S*)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline) was taken by the subjects from 1 week prior to the study until its completion. The protocol was approved by the Committee on Human Research of Thomas Jefferson University. The drug was supplied as 20-mg tablets by the Merck Sharp and Dohme Research Laboratories, Rahway, NJ.

Study Design—This was an open, randomized, two-way, crossover study in which lisinopril was administered as two 20-mg tablet doses separated by a 14-d washout period. Subjects fasted from midnight of the night prior to experimentation. On the first day of each treatment period, individuals received lisinopril either in a fasting state or immediately following a standardized breakfast. The lisinopril dose was taken with 350 mL of tap water for subjects in the fed state and 500 mL for subjects in the fasted state. The breakfast (524 kcal) consisted of one fried egg, two pieces of toast or bread, 20 g of orange marmalade or jelly, two strips of bacon, 150 mL of skimmed milk, and 100 mL of orange juice. This was considered a balanced fat meal (15% protein, 40% fat, and 45% carbohydrate) and was consistent with the average American diet.[9] The subjects were required to eat everything that was served to them and no other food or beverage intake was permitted. All volunteers resumed their normal diets 4 h following dosing.

Blood samples (7 mL) were drawn in nonheparinized tubes at 0, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 h post-drug administration. Urine was collected at −1–0, 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36, 36–48, 48–72, 72–96, and 96–120 h following each treatment. Blood pressure and pulse rate were measured in the supine and sitting positions at regular intervals for 24 h following drug administration. Adverse effects were monitored throughout the study.

Drug Measurement and Statistical Methods—Lisinopril (1-[N^2-[(*S*)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline) was measured in serum and urine using a modification of the fluorescent enzymatic method of Tocco et al.[10] The assay was considered to be accurate and reproducible at lisinopril concentrations of 0.7 ng/mL in serum and 100 ng/mL in urine. Concentrations below the minimum detection limit (MDL) of the assay were considered zero for the purpose of data analysis. The interassay coefficient of variation in serum and in urine at the MDL concentrations were 10 and 11%, respectively. All parameters were compared by using a paired *t* test; $p < 0.05$ was considered significant. When no significant difference existed in the plasma and urinary data for lisinopril in the fasted versus fed states, a power analysis was performed to determine how confident we could be that a 25% difference did not exist.[11]

Results

The time-course of the mean lisinopril serum concentration following a meal and in the fasting state resulted in similar profiles (Fig. 1). The mean urinary excretion rates of lisinopril for the first 60 h postadministration are shown in Fig. 2 and indicate a similar lisinopril excretion rate–time profile for the fasting and fed regimens. Table I depicts

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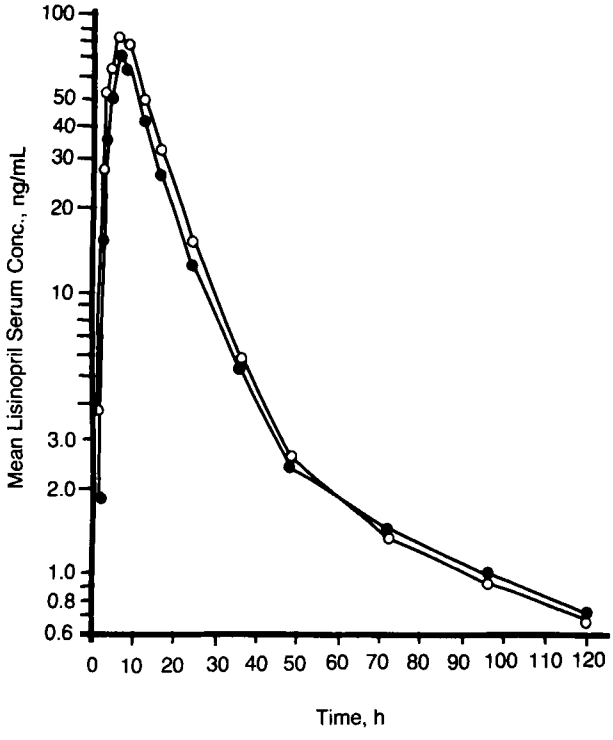

Figure 1—*Mean lisinopril serum concentrations as a function of time following the administration of a 20-mg oral dose of lisinopril to* (○) *fasting and* (●) *fed volunteers (n = 18).*

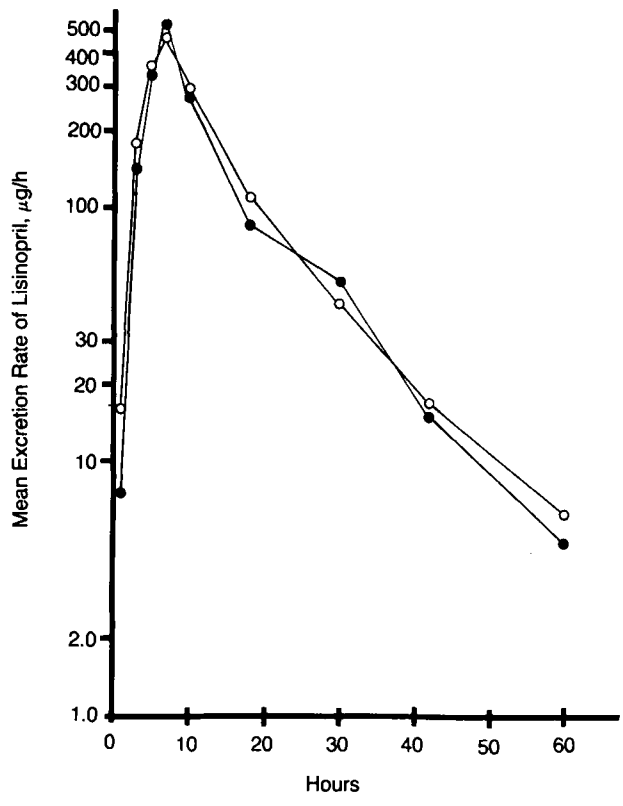

Figure 2—*Mean lisinopril urinary excretion rate as a function of time following a 20-mg oral dose of lisinopril to* (○) *fasting and* (●) *fed volunteers (n = 18).*

selected mean (± SD) serum and urine parameters for lisinopril following each treatment regimen.

No statistical difference was observed in the mean ± SD peak serum concentration (C_{max}) of lisinopril following the fasting and fed states (86 ± 48 versus 69 ± 19 ng/mL; NS). Similarly, the time to peak concentration (t_{max}) was not affected by food (6.2 ± 1.1 versus 6.8 ± 1.0 h; NS). The mean ± SD area under the serum concentration–time curves (AUC_{0-120}) for lisinopril during the fasting and fed regimens were essentially the same (1231 ± 620 versus 1029 ± 254 ng · h · mL^{-1}; NS). Power analysis of the AUC_{0-120} data revealed that we could be >80% confident that a 25% difference in AUC_{0-120} did not exist. Mean urinary recovery of lisinopril (0–120 h) was 27 and 26% of the dose for the fasting and fed regimens, respectively. No difference was found between the two treatments for any of the urine parameters reported. There was no significant difference in mean supine diastolic blood pressures (SDBP) between the fasting and fed regimens before or at any time point after lisinopril administration. The supine diastolic blood pressure decreased maximally from predose values by 6 h following dosing with both regimens (54 ± 10 versus 68 ± 10 mm Hg, $p < 0.001$ in the fasting state). This suppression lasted up to 12 h in some volunteers. No adverse effects were reported.

Table I—Mean Serum and Urine Parameters for Lisinopril in 18 Normal Volunteers Following Ingestion of a 20-mg Tablet in the Fasted and Fed States[a]

Parameters	Fasting (Mean + SD)	Fed (Mean + SD)	Power Analysis $(1 - \beta)$[b]
C_{max}, ng/mL	86 ± 48	69 ± 19	0.70
t_{max}, h	6.2 ± 1.1	6.8 ± 1.0	0.99
AUC_{0-120}, ng · h · mL^{-1}	1231 ± 620	1029 ± 254	0.80
Total urinary recovery 0–5 d, mg	5.31 ± 3.0	5.1 ± 2.0	0.60
Fraction of dose in urine (% of administered dose)	27.2 ± 15.4	25.7 ± 10	0.60

[a] No significant differences (NS) were found for any parameter between fasting and fed states. [b] Power analysis was based on detection of a 25% change between the two regimens at $\alpha = 0.05$ for the paired comparison.

Discussion

Lisinopril is a long-acting, nonsulfhydryl ACE inhibitor, which has been shown to be more potent and have a longer duration of action than captopril in healthy volunteers.[8] Recently, Rotmensch et al.[7] reported on the safety, tolerance, and efficacy of single, increasing doses of lisinopril in patients with mild to moderate essential hypertension. In the present study, the effect of a standardized breakfast on the serum concentration–time profile and urinary recovery of lisinopril following the administration of single doses of lisinopril was evaluated.

A 30% decrease in drug absorption in the presence of food has been demonstrated for captopril, a currently marketed ACE inhibitor.[4] In the present study, a standard breakfast produced no significant alteration in the C_{max}, t_{max}, AUC_{0-120}, or 5-d urinary recovery following administration of lisinopril in 18 healthy volunteers. Maximum inhibition of ACE, as reflected by enzyme activity in serum, appears to be required for the full therapeutic effect of ACE inhibitors.[7,12] Since serum ACE activity is directly related to the circulating drug concentration, maximal ACE inhibition may not occur if drug absorption is impaired by food.

Comparison of lisinopril serum concentration versus time curves through computation of AUC_{0-120} values is most appropriate when the AUCs are computed on the basis of unbound lisinopril concentrations. This is because of the high affinity, low capacity nature of lisinopril binding to ACE.

This binding produces a nonlinear serum binding pattern for lisinopril in serum (Ulm et al.[13]). This nonlinear binding has been reported for enalaprilat following administration of enalapril in human volunteers.[14–16] While lisinopril AUCs based on unbound drug were not computed in the present study, it is not likely to be of consequence since little intrasubject variation existed in the time course of total lisinopril serum concentrations between each treatment sequence.

We have demonstrated that an enalaprilat concentration of ~14 ng/mL is required for 90% ACE inhibition.[17,18] More recently, we reported maximal ACE inhibition and maximal blood pressure lowering effects for lisinopril at serum concentrations of ≥10 ng/mL.[7] In the current study, lisinopril serum concentrations remained above 10 ng/mL for at least 24 h following each 20-mg dose in most subjects, regardless of diet.

Renal excretion has been reported as the major elimination pathway for both enalaprilat and lisinopril in humans.[15–19] The results of Ulm et al.[15] indicate the lack of significant metabolism of these agents, apart from the presystemic bioactivation of enalapril to enalaprilat following oral administration of enalapril maleate. Based on our urinary data, the mean bioavailability of 26–27% for lisinopril is consistent with previously reported data.[15]

In conclusion, the serum and urine kinetic parameters for lisinopril were similar following oral administration of a single 20-mg dose to 18 healthy volunteers under fasting and fed conditions. Administration of lisinopril with food did not appreciably alter its absorption or bioavailability. The results of this study suggest that the time course of lisinopril serum concentrations should not be significantly altered by food intake during chronic therapy with this agent.

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