Effects on the Pharmacokinetics and Pharmacodynamics in the Elderly of Coadministering Ramipril with Water, Apple Juice, and Applesauce

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INTRODUCTION

Ramipril (Altace®) is an angiotensin converting enzyme (ACE) inhibitor that is indicated for the treatment of hypertension when used alone or in combination with thiazide diuretics. In one large international study in patients with clinical evidence of transient or ongoing heart failure, oral administration of ramipril initiated between the second and ninth day after myocardial infarction was shown to substantially reduce premature death from all causes (1–2).

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. Hepatic cleavage of the ester group converts ramipril to its active diacid metabolite, ramiprilat (3–4). The parent drug is almost completely metabolized to ramiprilat, peak plasma concentrations of which are reached 2 to 4 hours after dosing (5). Ramipril itself has an elimination half-life of approximately 2 hours, while ramiprilat has a long terminal elimination phase of approximately 13 to 17 hours due to tight enzyme binding. Other metabolites of ramipril are inactive. Ramiprilat has approximately six times the ACE inhibitory activity of ramipril, and is therefore considered to be the active species (6).

Ramipril is administered in the form of hard gelatin capsules, which are usually swallowed whole. Ramipril is the only ACE inhibitor available in capsule form; other drugs in its class are available as tablets. The target patient population for ramipril includes the elderly, many of whom have difficulty swallowing an intact capsule or tablet formulation (7–8). Therefore, the primary objective of this study was to evaluate the bioequivalence of the capsule formulation of ramipril and the contents of the capsule coadministered with three specified foods or liquids in order to establish an alternative mode of administration for such patients. A secondary objective of the study was to compare cardiovascular pharmacodynamic parameters (manual blood pressure recordings) between treatments. Routine safety evaluations were also performed.

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ABBREVIATIONS: AUC(0–24): Area under the curve (0–24 hours); AUC(0–48): Area under the curve (0 to 48 hours); GLC: Gas-liquid chromatography; RIA: Radioimmunoassay.

MATERIALS AND METHODS

Study Subjects

This study was conducted at Pharmaco LSR, Austin, Texas. The protocol was approved by Research Consultants Review Committee, Austin, TX (an accredited institutional review board). The study was carried out according to the tenets of the Declaration of Helsinki, and all patients gave informed consent before receiving study treatments. Twenty-three healthy elderly male volunteers were enrolled in the study after providing written informed consent. The age range of the subjects was 65 to 79 years, with a mean age of 71 years. All subjects were in good health, as determined by physical examination and standard clinical laboratory tests.

Within the 3 months before the study, subjects received no known investigational drug, and no drug with a potential for toxicity to a vital organ. Subjects were excluded from the study if they had recent symptoms of a major internal disease, had donated blood within 2 months before the study, had a history of alcohol abuse or hypersensitivity to foods or drugs, or a history or current occurrence of any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs. All subjects had a negative urine screen test for illicit drugs. During the period of study, subjects did not receive any nonstudy medications, and they did not consume any ethanol-containing beverages within 2 days of each study drug administration.

On the day before each dosing, food and fluid intake were standardized to reduce variability in test results and to achieve a controlled baseline. On each dosing day and immediately following blood sampling on nondosing days, subjects underwent standard fast-feed regimens.

Treatments

Subjects were randomized to receive a single 5-mg dose of each of the following treatments according to an open-labeled, balanced Latin-square crossover design: ramipril capsule taken with 120 ml water, contents of a ramipril capsule sprinkled onto 120 ml applesauce, contents of a ramipril capsule dissolved in 120 ml of apple juice, and contents of a ramipril capsule dissolved in 120 ml of water. Preparation of the doses was carried out immediately before dosing. Two weeks separated each study drug administration.

Blood Sample Collection and Analysis

Venous blood samples (10 ml) for the determination of ramipril and ramiprilat were collected in heparinized tubes immediately before dosing, and again at 15 and 30 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hours after each dosing. Plasma was harvested from the samples after centrifugation, and was frozen until assayed. Assays for ramipril and ramiprilat in plasma were carried out by use of a radioimmunoassay (RIA) procedure (method on file, Hoechst AG, Frank-

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furt, Germany). Standard curves were constructed over the range 0 to 100 ng/ml for both ramipril and ramiprilat. The limit of quantitation was 0.1 ng/ml for ramipril and 0.5 ng/ml for ramiprilat. The coefficient of variation ranged from 3 to 4% over the range 1 to 30 ng/ml of ramiprilat.

Complete 48-hour urine specimens for the determination of ramipril, ramiprilat, and total drug (ramipril, ramiprilat, diketopiperazine ester, plus diketopiperazine acid) in urine were collected immediately before ramipril administration, at 2-hourly intervals up to 8 hours after dosing, for the interval 8 to 12 hours after dosing, and at 12-hourly intervals from 12 to 48 hours after dosing. After recording the pH and volume of each fresh specimen, portions (10 ml) of each sample were frozen until assayed. Urinary assays for parent drug and three metabolites (ramipril, ramiprilat, diketopiperazine ester, and diketopiperazine acid) were carried out by a gas-liquid chromatography (GLC) procedure (method on file, Hoechst AG, Frankfurt, Germany). Standard curves were constructed over the calibration range 0 to 1,000 ng/ml. The minimum level of quantitation was 20 ng/ml for ramipril and each of the three metabolites assayed.

Clinical Assessments

Manual blood pressure measurements for the determination of pharmacodynamic response were carried out immediately before dosing, and again at 30 minutes, and at 1, 2, 4, 6, 8, 12, 24, and 48 hours after each dosing. Blood samples for the determination of complete blood count with differential, glucose, cholesterol, total protein, albumin, uric acid, creatinine, urea nitrogen, bilirubin, globulin, alkaline phosphatase, ALT, AST, γ-glutamyl transferase (GGT), triglycerides, LDH, sodium, potassium, calcium, chloride, and inorganic phosphorus were drawn before and 48 hours after each ramipril administration. Subjects were interviewed throughout the period of study to determine whether they had experienced any clinical events.

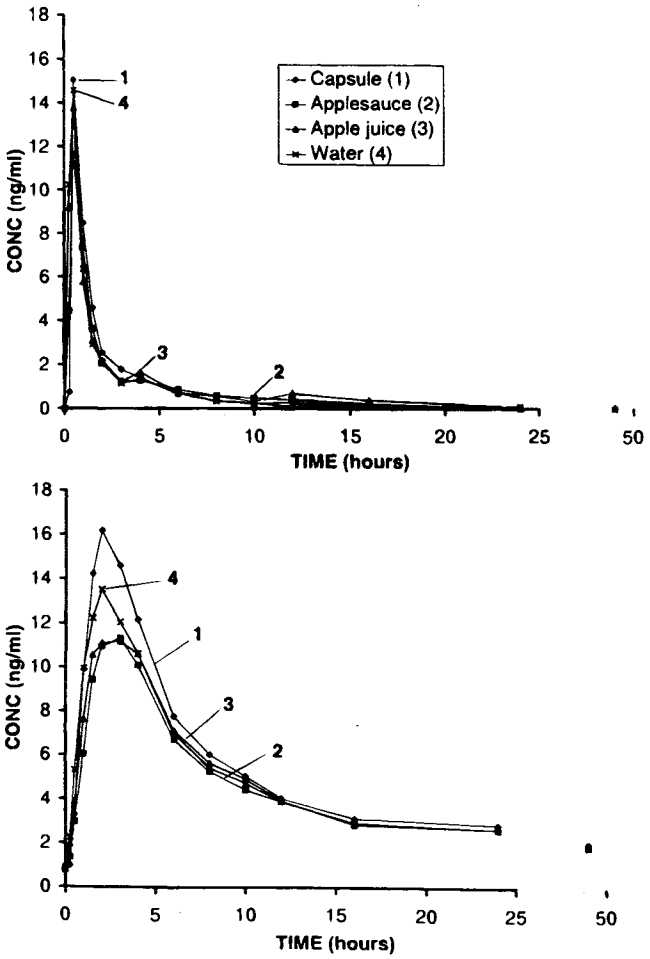

Fig. 1. Mean plasma concentrations of ramipril (top) and ramiprilat (lower) after a single 5-mg dose of ramipril in healthy elderly men.

Data Analysis

Pharmacokinetic parameters were determined for ramipril and ramiprilat in plasma, and for ramiprilat and total drug excreted in urine. The terminal elimination rate constants (k_{el}) were determined from the slope of a line fitted to the linear portion of the distribution/elimination phase of the logarithmic concentration-time curves. The value of $t_{1/2}$ was calculated from the apparent elimination rate constant as follows:

$$t_{1/2} = 0.693/k_{el}$$

Areas under the plasma concentration-time curves [AUC(0–24) and AUC(0–48)] were determined by trapezoidal rule. Total urinary excretion for ramiprilat and for ramipril plus its metabolites (total drug) was determined for the 48-hour period after dosing.

For the log transformed parameters C_{max} and AUC, bioequivalence was based on calculation of the two one-sided 90% confidence limits around the ratio of the test treatment mean to the standard treatment mean (9). An analysis of variance model appropriate to a four-period crossover design was used, as follows:

$$\text{value} = \mu + \alpha + \pi(\alpha) + \beta + \delta + \epsilon$$

where μ is the grand mean, α is the effect of sequence group, $\pi(\alpha)$ is the effect of subjects within sequence group, β is the treatment effect, δ is the period effect, and ϵ is the residual error term from the ANOVA model used to test the significance of the treatment and period effects. The ANOVA test was carried out using SAS.

The following two pharmacodynamic parameters were derived from manual blood pressure measurements: maximum drop from baseline, and area under the blood pressure lowering effect curve. These pharmacodynamic variables were calculated using PCNONLIN software (Version 4.0, SCI Software). The mean and standard error of the mean were calculated for these parameters.

Adverse signs and symptoms were analyzed by inspection of data listings and data summarized as treatment emergent signs and symptoms. Laboratory data were analyzed by clinical evaluation of predefined changes from baseline.

RESULTS

A total of 23 subjects were included in the pharmacokinetic and pharmacodynamic assessments for all treatments except the intact capsule: 1 subject discontinued from the study before receiving this particular treatment, which was to be the final dose of ramipril in this subject.

Table I. Mean ± SD Plasma Pharmacokinetic Parameters of Ramipril and Ramiprilat After a Single 5-mg Dose of Ramipril in Healthy Elderly Men

	Capsule		With Applesauce		Dissolved in Apple Juice		Dissolved in Water	
	N	Mean + SD	N	Mean + SD	N	Mean + SD	N	Mean + SD
Ramipril								
C_{max}(ng/ml)	22	16.4 ± 5.8	23	11.8 ± 5.0	23	14.1 ± 6.9	23	16.0 ± 5.3
t_{max}(h)	22	0.67 ± 0.28	23	0.54 ± 0.14	23	0.63 ± 0.74	23	0.47 ± 0.15
AUC(0–24)(ng/ml·h)	22	21.9 ± 12.3	23	22.5 ± 20.9	23	25.5 ± 18.6	23	22.3 ± 16.6
AUC(0–48)(ng/ml·h)	22	21.9 ± 12.3	23	22.5 ± 20.9	23	27.5 ± 23.0	23	23.7 ± 18.8
$t^1/_2$(h)	15	1.93 ± 1.60	15	1.78 ± 1.66	18	1.75 ± 1.73	18	1.49 ± 1.53
Ramiprilat								
C_{max}(ng/ml)	22	17.5 ± 13.9	23	12.5 ± 9.4	23	12.7 ± 10.4	23	14.7 ± 11.0
t_{max}(h)	22	2.73 ± 1.45	23	3.26 ± 1.81	23	2.94 ± 1.35	23	2.59 ± 1.06
AUC(0–24)(ng/ml·h)	22	138.9 ± 68.7	23	116.2 ± 60.2	23	121.3 ± 65.7	23	126.0 ± 67.2
AUC(0–48)(ng/ml·h)	22	197.4 ± 89.8	23	170.3 ± 73.7	23	176.7 ± 82.9	23	180.8 ± 89.9
$t^1/_2$(h)	22	6.92 ± 3.65	23	9.90 ± 11.4	23	9.79 ± 8.65	23	7.95 ± 4.99

Pharmacokinetic results in plasma are presented for ramipril and ramiprilat. Results for the parent drug were similar to those for the active metabolite.

The plasma concentration-time profiles and pharmacokinetic parameters for ramipril after administration of the four treatments are shown in Figure 1 and Table I. The mean times to peak plasma concentration of ramipril were similar between treatments, ranging from 0.5 to 0.7 hours. The peak concentrations of ramipril ranged from 12 to 16 ng/ml. Although values for both C_{max} and t_{max} were somewhat greater for the intact capsule form of ramipril, AUCs were neither clinically nor statistically different between treatments. Differences between the marketed capsule and other treatments in mean C_{max} were no greater than 30%, and differences for the mean AUCs no greater than 14%. For a prodrug such as ramipril, which is dosed on a chronic basis, such differences are not considered to be of clinical importance. The 90% confidence intervals for the ratios of each of the three investigational treatments to

Table II. 90% Confidence Intervals (CI) for Plasma Pharmacokinetic Parameters of Ramipril and Ramiprilat. Ratios of the Intact Capsule to Three Experimental Treatments

	With Applesauce		Dissolved in Apple Juice		Dissolved in Water	
	Ratio	90% C.I.	Ratio	90% C.I.	Ratio	90% C.I.
Ramipril						
C_{max}(ng/ml)	69.6%	60.6 to 80.0%	81.6%	71.0 to 93.8%	98.0%	85.2 to 112.6%
AUC(0–48)(ng/ml·h)	86.7%	68.1 to 110.4%	109.8%	86.2 to 139.8%	101.0%	79.3 to 128.7%
Ramiprilat						
C_{max}(ng/ml)	71.8%	64.1 to 80.5%	73.8%	65.8 to 82.7%	84.4%	75.3 to 94.6%
AUC(0–48)(ng/ml·h)	86.1%	79.3 to 93.6%	88.3%	81.3 to 95.9%	88.5%	81.4 to 96.1%

Table III. Mean ± Standard Error of the Mean (SEM) for Blood Pressure Pharmacodynamic Parameters After a Single 5-mg Dose of Ramipril in Healthy Elderly Men

	Capsule		With Applesauce		Dissolved in Apple Juice		Dissolved in Water	
	N	Mean + SEM	N	Mean + SEM	N	Mean + SEM	N	Mean + SEM
Maximum Change From Baseline (mmHg)								
Supine systolic	20	23.8 ± 2.0	23	26.1 ± 1.5	23	23.1 ± 2.4	21	27.0 ± 2.4
Standing systolic	20	25.2 ± 2.3	23	23.0 ± 2.0	18	23.8 ± 3.0	23	25.5 ± 3.1
Supine diastolic	21	14.0 ± 0.9	22	18.0 ± 1.7	22	16.7 ± 1.3	23	15.0 ± 1.5
Standing diastolic	21	14.7 ± 1.9	22	15.1 ± 1.5	20	14.6 ± 1.4	20	15.1 ± 1.4
Area under the Blood Pressure Lowering Effect Curve 0 to 12 Hours (mmHg·h)								
Supine systolic	18	153.6 ± 19.8	23	174.5 ± 20.1	20	167.0 ± 21.3	19	208.2 ± 21.0
Standing systolic	18	176.2 ± 22.6	20	153.7 ± 19.1	15	190.1 ± 26.6	21	177.7 ± 33.6
Supine diastolic	20	86.3 ± 11.2	20	127.7 ± 15.2	19	118.7 ± 11.1	20	101.5 ± 15.9
Standing diastolic	14	110.8 ± 18.2	18	80.5 ± 13.4	16	87.8 ± 15.8	16	103.9 ± 14.8

capsule in log transformed C_{max} and AUC(0–48) are presented in Table II.

The plasma concentration-time profiles and pharmacokinetic parameters for ramiprilat are shown in Figure 1 and Table I. Mean peak ramiprilat concentrations of 13 to 18 ng/ml occurred approximately 3 hours after dosing. Mean values for ramiprilat C_{max} and AUCs were slightly greater for the intact capsule than other treatments; however, these differences were small, and were not considered to be clinically noteworthy. The 90% confidence intervals for the ratios of the investigational treatments to capsule in log transformed AUC(0–48) demonstrate bioequivalence (Table II). Although the 90% confidence intervals for ramiprilat C_{max} were slightly outside the established range, these findings are not expected to affect clinical response.

The total urinary excretion of ramiprilat over the collection period was similar between treatments (0.4 to 0.5 mg), with no clinically noteworthy or statistically meaningful differences (data not shown). Additionally, excretion of total drug in urine was approximately 1 mg in all cases. The excretion data indicated bioequivalence between the intact capsule and its contents coadministered with water, apple juice, or applesauce.

The effect on cardiovascular pharmacodynamic parameters was determined from manual blood pressure measurements. Pharmacodynamic parameters are summarized in Table III. Results were similar between treatments, with indistinguishable differences in pharmacodynamic response, as demonstrated by area under the blood pressure lowering effect curve and maximum drop from baseline. The results suggest that coadministration of ramipril with any of the investigative treatments produces a comparable pharmacodynamic effect.

There were no clinically important medical events and no noteworthy changes in clinical laboratory parameters.

DISCUSSION

The results of this study show that coadministration of ramipril with water, apple juice, or applesauce resulted in equivalent systemic exposures to ramiprilat (the active species) as determined by plasma AUCs. Additionally, the amount of drug excreted in urine, when measured by either ramiprilat alone or by total drug (ramipril plus metabolites), was equivalent across treatments. Each of the four treatments resulted in comparable pharmacodynamic response when measured by maximum reduction in blood pressures and area under the blood pressure effect curve. This finding corroborates the pharmacokinetic results, showing an equivalent therapeutic effect between treatments. Ramipril was well tolerated when administered as the intact capsule or the capsule contents coadministered with water, apple juice, or applesauce.

These results indicate that the ramipril capsule can be opened and the contents sprinkled onto a small amount of applesauce or mixed in water or apple juice with no expected effect on clinical response. This finding represents a distinct advantage for those patients who have difficulties in swallowing ramipril in capsule form or other ACE inhibitors in tablet form.

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