Fosinopril: Pharmacokinetics and pharmacodynamics in congestive heart failure

Fosinoprilat, the active product of fosinopril, is eliminated by a hepatic pathway, in addition to the renal pathway shared by other angiotensin converting enzyme inhibitors. Congestive heart failure (CHF) may elevate drug plasma concentrations caused by a reduction in steady-state volume of distribution (V_{SS}) and/or an impairment of clearance. This study compared the pharmacokinetics and pharmacodynamics of fosinopril (intravenous and oral) in 10 patients with established CHF and 10 age-, sex-, and weight-matched normal control subjects. There were no statistically significant differences between the patients with CHF and the control patients with respect to maximum drug concentration (C_{max}) or area under the plasma concentration–time curve from 0 to infinity. Absolute bioavailability was approximately 29%. V_{SS} was similar, and protein binding was 99% in both groups. The oral half-life of fosinoprilat was significantly longer than the intravenous half-life for both the patients with CHF and normal subjects, without statistically significant differences between the study groups. Median time to reach C_{max} occurred at 4 hours in each group and corresponded to maximum angiotensin converting enzyme inhibition, which was essentially complete through 12 hours and markedly reduced through 24 hours. Thus these data indicate that patients with CHF can receive fosinopril without undue increases in fosinoprilat concentrations. This probably is due to the dual excretory pathways. (CLIN PHARMACOL THER 1995; 58:660-5.)

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Fosinopril sodium is a pro-drug of the angiotensin converting enzyme (ACE) inhibitor fosinoprilat. Fosinoprilat differs from other currently available ACE inhibitors in two ways: (1) it is the only phosphinic acid ACE inhibitor, and (2) it is eliminated by an hepatic pathway, in addition to the renal pathway shared by the other clinically available ACE inhibitors.[1] After oral administration, fosinopril is completely hydrolyzed to fosinoprilat, independent of renal or hepatic function. In healthy volunteers, absolute bioavailability of fosinoprilat is 29%, the steady-state volume of distribution (V_{SS}) is 10 L, protein binding is above 95%, and excretion is divided almost equally between the renal and hepatic pathways.[2]

Congestive heart failure may be associated with elevated drug plasma concentrations because of reduced V_{SS} or impaired clearance.[3] In a previous study of patients with renal impairment, total clearance of fosinopril was maintained by an increase in hepatic clearance.[4] In another study in patients receiving long-term peritoneal dialysis, half-life ($t_{1/2}$) increased along with the area under the concentration–time curve [AUC(∞)] but without a change in maximum drug concentration (C_{max}).[5] Nonetheless, on the basis of these studies one cannot predict whether or not the pharmacokinetics of fosinopril would be affected in congestive heart failure, in which both renal and hepatic excretory pathways may be affected.

This study was designed to investigate the pharmacokinetics and pharmacodynamics of fosinopril in patients with established congestive heart failure and to

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Table I. Time of serum samples and urine collections relative to dosing for determination of fosinoprilat concentrations, protein binding, and ACEA

		Minutes					*Hours*												
	Time 0	*4*	*10*	*20*	*30*	*40*	*1*	*1½*	*2*	*3*	*4*	*5*	*6*	*8*	*12*	*16*	*24*	*30*	*48*
Oral	x				x		x		x	x	x	x	x	x	x	x	x	x	x
Intravenous	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x
ACEA	x						x				x				x		x		x
Protein Binding	x						x				x								
Urine	x												x		x		x		x

0, Prior to dosing; oral, collection times after oral administration of fosinopril; intravenous, collection times after intravenous administration of fosinoprilat; ACEA, collection times for angiotensin converting enzyme activity.

determine whether these parameters are significantly altered when compared to age-, sex-, and weight-matched healthy control subjects.

METHODS

This was an open-label, randomized, balanced, two-way crossover study that compared the pharmacokinetics and pharmacodynamics of oral fosinopril sodium and intravenous fosinoprilat in 10 patients with congestive heart failure and 10 age-, weight-, and sex-matched control subjects. Eligible patients with congestive heart failure were of either sex, 18 to 80 years old, and 50 to 110 kg in weight. All patients had New York Heart Association (NYHA) class II or III heart failure due to ischemia, cardiomyopathy, or hypertension. Valvular or hypertrophic cardiomyopathic disease was excluded by echocardiographic tests. Patients had to have taken diuretics for at least 2 weeks; digoxin was allowed at a constant dose but was not required. An echocardiographic left ventricular ejection fraction within 30 days of the study had to be ≤40%.

Control subjects were matched for sex, for age ±5 years, and for weight ±6.8 kg. An echocardiographic left ventricular ejection fraction ≥55% and blood pressure <180/95 mm Hg was required. Pregnancy, lactation, significant organ disease, or allergy or drug hypersensitivity were reasons for exclusion. Other reasons for exclusion were suspected or documented renal artery stenosis, serum creatinine >1.8 mg/dl, BUN >45 mg/dl, serum K^+ >5.5 mEq/L, or hepatic disease with AST or ALT ≥2 times the upper limit of normal. β-Blockers and calcium antagonists were allowed for blood pressure control, but other vasodilators (except for nitroglycerin) were excluded, as was warfarin or other agents that induce drug-metabolizing enzymes.

Each subject received 10 mg oral fosinopril sodium or 7.5 mg intravenous fosinoprilat in a randomized sequence, with at least a 96-hour washout between doses. Blood samples for determination of fosinoprilat concentration, ACE activity, and protein binding, as well as cumulative urine collections, were obtained at times indicated in Table I. The samples for fosinoprilat concentration and serum ACE activity were allowed to clot for 30 minutes in an ice bath, centrifuged for 15 minutes, and stored frozen at −20° C. Samples for serum protein binding were clotted and centrifuged in the same manner as that used for serum fosinopril concentration and placed in a Centrifree Micropartition System (Amicon Corporation, Beverly, Mass.) held at 45 degrees from vertical, centrifuged in a fixed 35-degree angle rotor for 10 minutes at 1000*g*, then stored at −20° C. The sample was assayed with use of HPLC combined with atmospheric pressure ionization tandem mass spectrometry,[6] which was revalidated at a lower standard curve range for the quantitative determination of fosinopril and fosinoprilat in human serum. Maximum specificity was achieved with use of multiple reaction monitoring on a triple quadrupole mass spectrometer. The standard curves were fitted by a quadratic equation weighted by 1/x over the concentration range of 1.2 to 300 ng/ml for all analytes. The lower limit of quantitation was determined to be 1.2 ng/ml. SQ 27,133 was used as an internal standard for fosinoprilat and SQ 33,055 for fosinopril. ACE activity was assessed with use of a commercially available Ventrex Microvial radioassay system (Hycor Biomedical Inc., Garden Grove, Calif.).[7]

Urine from each sample period was stored at 5° C until its volume was determined, and then a 20 ml aliquot was frozen at −20° C. Serum samples were extracted with use of 1.0 ml of serum and were prepared robotically on BenchMate extraction stations. Urine samples were centrifuged and the supernatant transferred directly to HPLC vials. Concentrations of fosinoprilat in urine were assessed by the methods modified as described above for serum samples.[6] The standard curves were fitted by a quadratic equation weighted by 1/x over the concentration range of 7.8 to

Table II. Patient characteristics

	Control patients (n = 10)	*Patients with congestive heart failure (n = 10)*
Age (yr)	65 ± 10.3 (48-80)	65 ± 10.1 (51-78)
Height (cm)	172 ± 17.7 (155-218)	175 ± 16.2 (152-213)
Weight (kg)	76 ± 12.8 (55-95)	75 ± 13.8 (49-98)
Race	9 white, 1 black	8 white, 2 black
Sex	8 male, 2 female	8 male, 2 female
NYHA CHF class	—	8 class II, 2 class III
Echo EF (%)	60 ± 4.9	32 ± 5.3
End-systolic LV vol (ml)	39 ± 11.6 (20-64)	90 ± 50.6 (47-205)
End-diastolic LV vol (ml)	99 ± 29.7 (70-175)	129 ± 64.2 (75-274)

Data are mean values ± SD; range is given in parentheses.
NYHA, New York Heart Association; CHF, congestive heart failure; EF, ejection fraction; LV, left ventricular.

1000 ng/ml for all analytes. The lower limit of quantitation was determined to be 15.6 ng/ml. Analyses were carried out in randomized sequence with use of fosinoprilat's thiophenyl analog, SQ 27,133, as an internal standard for fosinoprilat.

The pharmacokinetic variables AUC(∞), serum $t_{1/2}$, cumulative urinary excretion (expressed as a percent of dose), and renal clearance (CL_R) were summarized for each condition group (patients with congestive heart failure or control subjects) and treatment group combination. Noncompartment methods of analysis were applied to individual serum concentration–time data points in each profile for both the oral and intravenous treatment. Nonrenal clearance (CL_{NR}), total clearance (CL), and V_{SS} were summarized for the intravenous data only, and maximum serum concentration (C_{max}) and time to maximum serum concentration (t_{max}) were summarized for the oral data only. Absolute bioavailability (F), calculated as the ratio of the $AUC(\infty)_{oral}/AUC(\infty)_{iv}$, was summarized for each group.

The variables AUC, $t_{1/2}$, cumulative urinary excretion, and CL_R as well as the pharmacodynamic variables, were evaluated in the context of an ANOVA model appropriate for a crossover design. Specific comparisons of the oral treatment versus intravenous treatment within patients with congestive heart failure and within control subjects, as well as the comparisons of patients with congestive heart failure versus control subjects within the oral treatment and within the intravenous treatment, were made with use of customized hypothesis tests from this ANOVA model.

All analyses were performed with use of SAS software, version 6.07 (SAS Institute, Cary, N.C.). All tests of significance were performed at the 5% significance level.

RESULTS

The demographics of the study groups are shown in Table II. The data indicate no significant differences between the groups with regard to age, height, weight, sex, and race, whereas cardiac status, as indicated by symptoms and echocardiographic function and dimensions, was different. All patients completed the study. There were five minor protocol violations. Two occurred in patients with congestive heart failure (one had undergone previous cholecystectomy and one had an enrollment echocardiogram slightly before (10 days) the specified time) and three occurred in control subjects (two had undergone cholecystectomy and one had right bundle branch block without evidence of heart disease). The results in the patients who had undergone cholecystectomy were similar to the others.

The concentration-time relationship for both orally administered fosinopril and intravenously administered fosinoprilat is shown in Fig. 1. Patients with congestive heart failure have similar mean fosinoprilat concentrations compared with control subjects, both at C_{max} and throughout the sampling period for both intravenous and oral administration. Similarly, there were no statistically significant differences between patients with congestive heart failure and control subjects in any of the pharmacokinetic parameters tested (Table III). Mean AUC(∞) and C_{max} were slightly higher in patients with congestive heart failure. But these differences were not statistically significant.

Absolute bioavailability was approximately 29% in each study group (Table IV). The V_{SS} was also similar, and protein binding was 99% in both groups (Table III). The oral $t_{1/2}$ of fosinoprilat was significantly longer than the intravenous $t_{1/2}$ for both the patients with congestive heart failure and normal subjects. There was no statistically significant difference

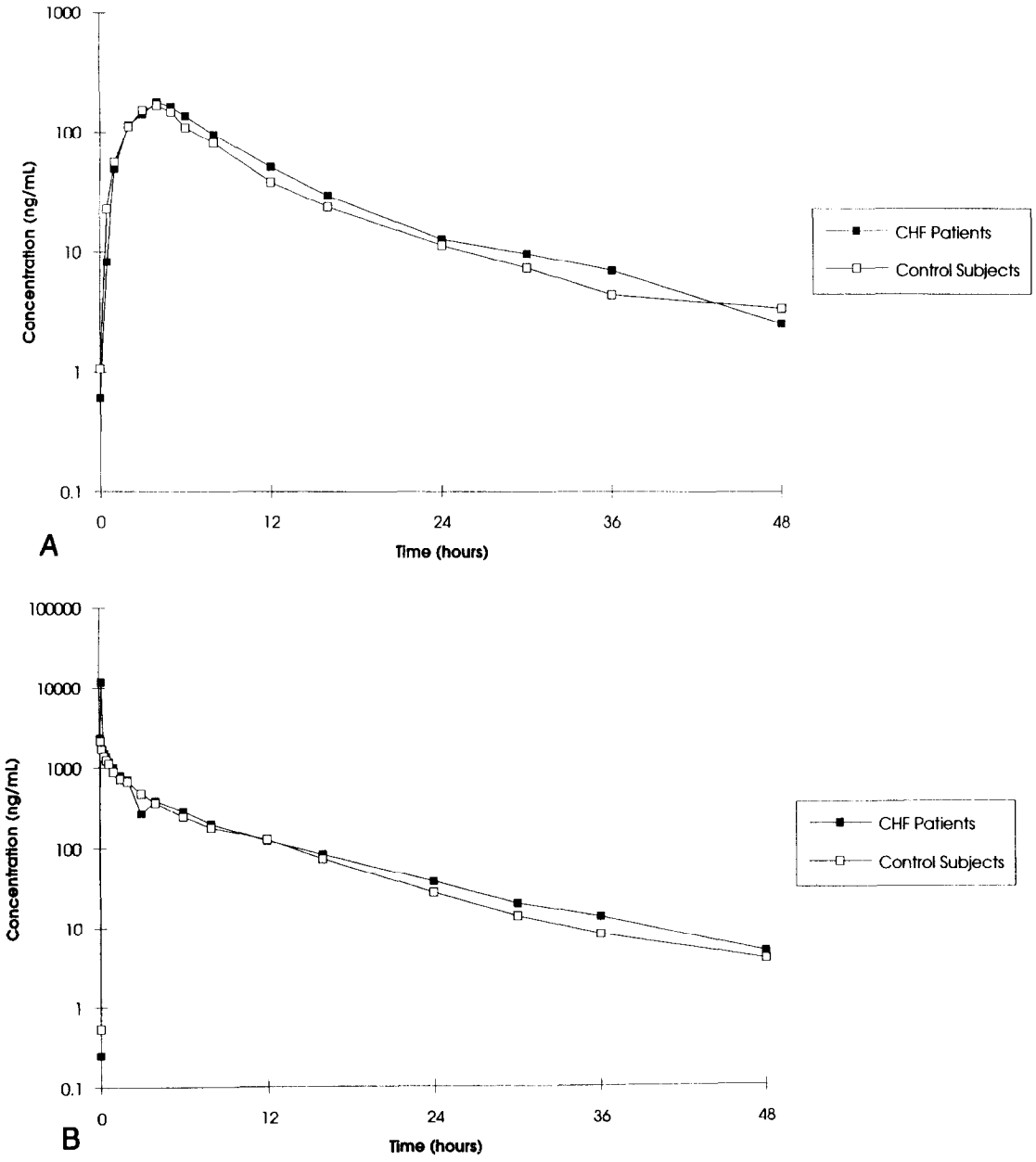

Fig. 1. A, Mean fosinoprilat concentrations (in nanograms per milliliter) in patients with congestive heart failure (CHF) and in matched control subjects after a 10 mg oral fosinopril dose (log-linear plot). **B,** Mean fosinoprilat concentrations (in nanograms per milliliter) in patients with congestive heart failure and in matched control subjects after a 7.5 mg intravenous fosinoprilat dose (log-linear plot).

in $t_{1/2}$ between the study groups, although numerically longer $t_{1/2}$ values were observed in the patients with congestive heart failure and control subjects after oral dosing.

Median t_{max} occurred at 4 hours in each study group. This value is similar to that previously reported for healthy subjects[8] and corresponds to maximum ACE inhibition, which was essentially complete through 12 hours and markedly reduced through 24 hours (Table V).

No serious clinical or laboratory adverse effects were noted. Mild or moderate adverse effects were noted in three patients with heart failure (two patients had dizziness and one patient had palpitations), and

Table III. Oral and intravenous pharmacokinetics

	Oral		*Intravenous*	
	Control	*CHF*	*Control*	*CHF*
AUC(0-t) (ng hr/ml)	1489 ± 619	1716 ± 808	5620 ± 2355	6392 ± 2638
AUC(∞) (ng hr/ml)	1562 ± 655	1808 ± 810	5702 ± 2409	6447 ± 2681
$t_{1/2}$ (hr)	11.0 ± 5.2	14.2 ± 7.3	9.4 ± 3.8	7.6 ± 1.9
C_{max} (ng/ml)	177 ± 64	196 ± 67	—	—
t_{max} (hr)				
Median	4.0	4.0	—	—
Range	(3.0-6.0)	(2.0-6.0)	—	—
V_{SS} (ml)	—	—	9911 ± 3018	8502 ± 3536
Protein binding (%)	99.1 ± 0.3	99.2 ± 0.5	99.4 ± 0.4	99.4 ± 0.2

Data are mean values ± SD; range is given in parentheses. CHF, Congestive heart failure; AUC, area under the serum concentration–time curve; $t_{1/2}$, half-life; C_{max}, maximum concentration; t_{max}, time to reach C_{max}, V_{SS}, steady-state volume of distribution.

Statistically significant differences: AUC intravenous > oral for control and CHF; cumulative urinary excretion intravenous > oral for control and CHF; $t_{1/2}$ oral > intravenous for CHF. No other differences were statistically significant.

Table IV. Bioavailability and excretion

	Control	*CHF*
Bioavailability (%)	28.6 ± 10.4	29.2 ± 11.8
% Urinary excretion (oral dosing)	7.6 ± 3.5	7.5 ± 3.2
% Urinary excretion (intravenous dosing)	36.2 ± 12.6	41.0 ± 12.6
CL (intravenous) (ml/hr)	1544 ± 650	1360 ± 570
CL_R (oral) (ml/hr)	519 ± 153	452 ± 183
CL_R (intravenous) (ml/hr)	540 ± 209	577 ± 305
% of CL	36.6% ± 12.9%	42.4% ± 15.2%
CL_{NR} (intravenous) (ml/hr)	1004 ± 534	793 ± 384
% of CL	63.4% ± 12.9%	57.6% ± 5.2%

Data are mean values ± SD.

CL, Total clearance; CL_R, renal clearance; CL_{NR}, nonrenal clearance.

Statistically significant differences: CL_R intravenous > oral for CHF. No other differences were statistically significant.

four control subjects (three patients had diarrhea or vomiting and one patient had skin irritation). Thus, two of 10 patients with heart failure reported dizziness, a previously cited effect of ACE inhibitors.[9] None required treatment.

DISCUSSION

It is desirable to be able to administer a drug to patients with congestive heart failure without concern for differences in pharmacokinetics resulting from this condition. This study confirms that the pharmacokinetics of fosinopril and its effects on ACE activity are not affected by heart failure. The patients with congestive heart failure enrolled in this study had clinically significant heart failure, as indicated by their NYHA class II or III designation, as well as objective echocardiographic evidence of left ventricular dilatation and diminished left ventricular function. In contrast, the control subjects had normal cardiovascular, renal, and hepatic function.

Table V. ACE inhibition as a percentage of initial ACE activity

Time after dosing	*Oral (%)*		*Intravenous (%)*	
	Control	*CHF*	*Control*	*CHF*
±4 hours	98 ± 3	99 ± 3	99 ± 2	100 ± 1
12 hours	95 ± 5	97 ± 4	98 ± 3	98 ± 2
24 hours	84 ± 12	86 ± 7	91 ± 16	94 ± 7
48 hours	53 ± 14	57 ± 21	57 ± 19	72 ± 19

Data are mean values ± SD.

No statistically significant differences were identified between CHF and control subjects.

Bioavailability, V_{SS}, and $t_{1/2}$ were not different between the patients with congestive heart failure and the control subjects. Mean AUC(∞), C_{max}, and CL_{NR} were numerically slightly higher in patients with congestive heart failure. However, these differences were not statistically different. This appears to underscore the advantage of dual excretory pathways.

Because most ACE inhibitors are excreted through the renal pathway, usually by tubular secretion, their elimination $t_{1/2}$ increases progressively with renal impairment. For this reason, the dose administered and the interdosing interval should be adjusted in patients with significant renal dysfunction. Patients with heart failure may also have reduced renal function and slower clearance of ACE inhibitors such as enalapril, captopril, or lisinopril.[10] Thus patients with moderate or severe heart failure may also require adjustment of the dose of those ACE inhibitors.[11,12] However, practical guidelines for dosage adjustment or measurements of serum drug concentrations have not been found to be useful in the usual clinical practice. The

data presented here indicate that ACE inhibition with dual excretion pathways may not need dosage adjustment in heart failure.

References

1. Sica DA, Cutler RE, Parmer RJ, Ford NF. Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril and enalapril in patients with chronic renal insufficiency. Clin Pharmacokinet 1991;20:420-7.
2. Singhvi SM, Duchin KL, Morrison RA, Willard DA, Everett DW, Frantz M. Disposition of fosinopril sodium in healthy subjects. Br J Clin Pharmacol 1988;25:9-15.
3. Shammas FV, Dickstein K. Clinical pharmacokinetics in heart failure. An updated review. Clin Pharmacokinet 1988;15:94-113.
4. Hui KK, Duchin KL, Kripalani KJ, Chan D, Kramer PK, Yanagawa N. Pharmacokinetics of fosinopril in patients with various degrees of renal function. CLIN PHARMACOL THER 1991;49:457-67.
5. Gehr TW, Sica DA, Grasela DM, Fakhry I, Davis J, Duchin KL. Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. Eur J Clin Pharmacol 1991;41:165-9.
6. Wang-Iverson D, Ivashkiv E, Jemal M, Cohen AI. Simultaneous determination of SQ 28,555 and SQ 27,519 in serum by ionspray mass spectrometry [Abstract]. Presented at the Annual American Society for Mass Spectrometry Meeting, Nashville, Tennessee, May 1991.
7. Rohatgi PK, Ryan JW. Simple radioassay for measuring serum activity of angiotensin-converting enzyme in sarcoidosis. Chest 1980;78:69-76.
8. Duchin KL, Waclawski AP, Tu JI, Manning J, Frantz M, Willard DA. Pharmacokinetics, safety, and pharmacologic effects of fosinopril sodium, an angiotensin-converting enzyme inhibitor in healthy subjects. J Clin Pharmacol 1991;31:58-64.
9. Kostis JB, Shelton B, Gosselin G, et al. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). Am Heart J [In press].
10. Kostis JB. Angiotensin converting enzyme inhibitors; II: clinical use. Am Heart J 1988;116:1591-605.
11. Shionoiri H. Pharmacokinetic drug interactions with ACE inhibitors. Clin Pharmacokinet 1993;25:20-58.
12. Cody RJ. Optimising ACE inhibitor therapy of congestive heart failure: insights from pharmacodynamic studies. Clin Pharmacokinet 1993;24:59-70.