Fosinopril/hydrochlorothiazide: single dose and steady-state pharmacokinetics and pharmacodynamics

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Aims Fosinoprilat, the active product of fosinopril, is eliminated by an hepatic pathway in addition to the renal pathway shared by other angiotensin converting enzyme inhibitors (ACEIs). This study aimed to determine whether impaired renal function affects the pharmacokinetics and pharmacodynamics of a combination of fosinopril and hydrochlorothiazide (HCTZ).

Methods The study had a parallel-group design comparing patients with renal impairment and body-mass-index-matched normal controls. The study was done in a University clinic in 13 patients with renal impairment (mean creatinine clearance 55.7 ± 15.6 ml min^{-1} 1.73 m^{-2}) and 13 age-, sex-, and body-mass-index-matched normal controls (mean creatinine clearance 102.4 ± 8.9 ml min^{-1} 1.73 m^{-2}). All patients and normal controls received fosinopril sodium 20 mg and HCTZ 12.5 mg as a daily oral administration on days 1–5. Non-compartmental pharmacokinetic parameters of fosinoprilat and HCTZ were determined from blood and urine samples obtained over 48 h starting on Day 1 (single dose) and Day 5 (steady state): maximum serum concentration (C_{max}), time to maximum serum concentration (t_{max}), area under the serum concentration-time curve during the dosing interval (AUC), cumulative urinary excretion (CUE) and the accumulation index (AI; ratio of AUC-day 5/AUC-day 1). Pharmacodynamic parameters were also measured over 24 h on day 1 and over 48 h on day 5: serum ACE activity and arterial blood pressure.

Results Fosinoprilat pharmacokinetic parameters on day 1 in renally impaired *vs* normal patients: $C_{max} = 387 \pm 0.19$ *vs* 324 ± 0.25 ng ml^{-1} ($P = 0.07$); $t_{max} = 3.5$ *vs* 3.0 h ($P = 0.58$); AUC $= 3510 \pm 0.29$ *vs* 2701 ± 0.35 ng ml^{-1} h ($P = 0.072$); CUE $= 5.08 \pm 2.70$ *vs* $7.40 \pm 2.56\%$ ($P = 0.009$). Fosinoprilat parameters on day 5: $C_{max} = 517 \pm 0.40$ *vs* 357 ± 0.19 ng ml^{-1} ($P = 0.007$); $t_{max} = 3.0$ *vs* 3.0 h ($P > 0.99$); AUC $= 4098 \pm 0.43$ *vs* 2872 ± 0.30 ng ml^{-1} h ($P = 0.027$); CUE $= 6.81 \pm 3.53$ *vs* $8.10 \pm 2.80\%$ ($P = 0.068$). AI $= 1.17 \pm 0.33$ *vs* 1.06 ± 0.23 ($P = 0.29$). In both groups ACE inhibition and blood pressure response were similar over 24 h and slightly greater 48 h after last dosing.

Conclusions In renally impaired subjects fosinopril and HCTZ can be coadministered without undue increases in fosinoprilat concentrations or any clinically significant pharmacodynamic effects. This is probably due to the dual excretory pathways for fosinoprilat.

Keywords: angiotensin converting enzyme inhibitor, fosinopril, fosinoprilat, hydrochlorothiazide, pharmacodynamics, pharmacokinetics, renal insufficiency

Introduction

Fosinopril sodium is a prodrug 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 a hepatic pathway in addition to the renal pathway shared by the other clinically available ACE inhibitors [1]. After oral administration, fosinopril is completely hydrolysed to fosinoprilat independent of renal or hepatic function and excretion is divided almost equally between renal and hepatic pathways [2]. In a previous study of patients with

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Received 9 April 1998, accepted 10 May 1999.

renal impairment, total clearance of fosinopril was maintained by an increase in hepatic clearance [3]. In another study in patients on chronic peritoneal dialysis, half-life ($t_{1/2}$) increased along with the area under the time-concentration curve (AUC$(0,\infty)$), but without a change in maximum drug concentration (C_{max}) [4].

Conflicting results have come from studies of the pharmacokinetics and pharmacodynamics of fixed combinations of an ACE inhibitor (ACEI) and hydrochlorothiazide (HCTZ). Two studies with lisinopril/HCTZ have shown no pharmacokinetic interaction [5, 6]. This result was also found in one study with enalapril/HCTZ [7], but, in another study, the level of enalaprilat achieved was increased significantly when enalapril was administered following HCTZ independent of the degree of renal impairment [8].

The conflicting data from prior studies with a combination ACEI/HCTZ raise questions about the influence of HCTZ on fosinoprilat pharmacokinetics. This study was designed to investigate the pharmacokinetics and pharmacodynamics of fosinoprilat when coadministered with HCTZ in normal patients and in patients with renal impairment.

Methods

This study compared the pharmacokinetics of an oral fosinopril sodium/HCTZ formulation in 13 patients with impaired renal function and 13 age-, body mass index-, and sex-matched control subjects. Eligible patients were of either sex, 18–70 years of age with a body mass index between 17 and 30. Normal subjects were defined as those with a creatinine clearance greater than 90 ml min^{-1} 1.73 m^{-2} while subjects with a creatinine clearance between 30 and 80 ml min^{-1} 1.73 m^{-2} were defined as renally impaired. Control subjects were matched for sex, for age (± 5 years) and for body mass index ($\leq$ 15% difference).

Subjects with a creatinine clearance of <30 or between 80 and 90 ml min^{-1} 1.73 m^{-2} were excluded from the study as were those with a sitting or standing diastolic blood pressure <60 or >105 mmHg or heart rate <60 or >100 beats min^{-1}. Any mildly hypertensive subjects on treatment were withdrawn from ACE inhibitors and diuretics for at least 2 weeks, and other antihypertensive medication for at least 1 day, before the first study-drug administration. No one was included with a history of significant alcohol intake or drug abuse or any significant disease other than renal impairment.

Excluded medications were any investigational drug within 60 days; barbiturates within 4 weeks; NSAIDs (including aspirin) in the 7 days before the determination of creatinine clearance or during the study period; oral hypoglycaemic agents or any other drugs, including over-the-counter preparations, within 1 week of the first study-drug administration. Insulin was allowed for diabetic control in one patient and paracetamol (acetaminophen) for analgesia. The study protocol was approved by the Ethics Committee of Universitair Ziekenhuis Antwerpen and all subjects and patients gave written consent to participate in the study.

Each subject received orally 20 mg fosinopril sodium and 12.5 mg hydrochlorothiazide each morning for 5 consecutive days with 250 ml of tap water at the time of administration and at 1 and 2 h following administration. Otherwise subjects were fasting from 8 h before until 4 h after drug administration. Blood samples for determination of fosinoprilat and HCTZ concentration and for ACE activity and cumulative urine collections were obtained before and up to 24 h (day 1) or 48 h (day 5) after dosing. The samples for fosinoprilat concentration and serum ACE activity were allowed to clot for 15 min at room temperature, centrifuged for 15 min and stored frozen at -20° C. Samples for plasma HCTZ concentration were placed on ice and within 30 min were centrifuged for 15 min under refrigerated conditions and stored frozen at -20° C. Urine from each sample period was stored at 4° C until its volume was determined, and then three 10 ml aliquots were frozen at -20° C.

Fosinoprilat concentrations in serum and urine were measured by a radioimmunoassay technique [9] with a lower limit of quantification of 1 ng ml^{-1} in both serum and urine. The precision of the quality control (QC) assay results ranged from 4 to 18% CV and from 7 to 16% CV for the serum and urine assays, respectively. At least two QC samples in each analytical run were within 15% or 20% of their nominal concentration for the serum or urine assay, respectively.

HCTZ concentrations in plasma and urine were determined by a Zymark Py/Technology^{TM} Robotic HPLC system developed at Bristol-Myers Squibb-Pharmaceutical Research Institute [10] following an extraction of the samples with ethyl acetate. This assay has a lower limit of quatitation of 10 and 100 ng ml^{-1} of HCTZ in plasma and urine, respectively. The accuracy of the assay was within 4.5% and 8.2% deviation for the plasma and urine assays, respectively. The between day was 2% RSD for the plasma assay and from 3.4 to 4.9% RSD for the urine assay.

ACE activity was assessed using a commercially available Ventrex Microvial^{TM} radioassay system [11]. ACE activity was expressed as activity units (% substrate hydrolysed min^{-1}).

The noncompartmental pharmacokinetic parameters of maximum serum concentration (C_{max}) and time to maximum serum concentration (t_{max}), area under the serum concentration-time curve during the dosing interval (AUC), and cumulative urinary excretion (CUE)

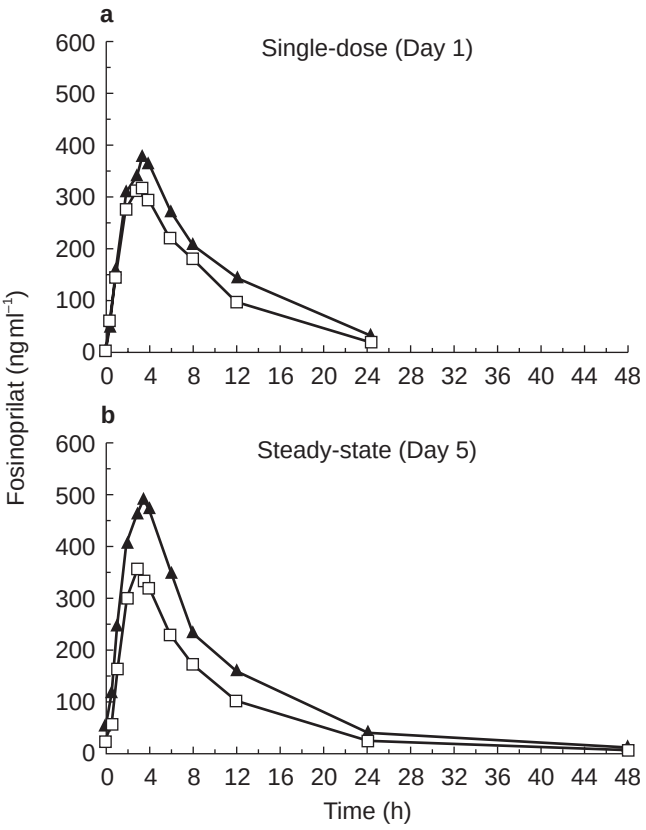

Figure 1 Mean fosinoprilat concentrations (ng ml^{-1}) in renally impaired subjects (▲) and matched normals (□) following a single oral dose of 20 mg fosinopril/12.5 mg HCTZ (a) and at steady state following 5 days of oral dosing (b): linear plot. Error bars indicating ± s.d. substantially overlap and have been omitted for purposes of clarity in the figure.

were calculated for days 1 and 5, and the accumulation index (AI: ratio of AUC-day 5/AUC-day 1) was derived. Non-compartmental methods of analysis were applied to individual serum concentration-time data points for fosinoprilat and HCTZ in both normal and renally impaired subjects following single dosing (first dose on day 1) and at steady state (final dose on day 5). Serum or plasma study-drug levels less than the lower level of quantification (<LLQ) were deemed to be equal to zero for all of the calculations.

The renally impaired subjects were match-paired with the normal subjects with respect to sex, age and body mass index. The homogeneity of the two groups was compared with respect to their entry characteristics by 2-sample *t*-test for height and weight, and by paired *t*-test for age and body mass index, using the matched pairs as the blocking factor.

C_{max}, AUC, %CUE and AI were analysed by statistically paired *t*-test. C_{max}, AUC and AI were log-transformed for analysis. t_{max} was analysed by Wilcoxon signed-rank test. The age and body-mass-index-matched pairs were used as the blocking factor in the above analyses.

Descriptive statistics were calculated for all quantitative data. The Wilcoxon rank-sum test and Wilcoxon signed-rank test were done using the StatXact software package [12]. All other statistical inferences were done using SAS software, version 6 [13]. A two-sided test at the 5% significance level was employed throughout. No formal adjustment was made on the probability value due to the multiplicity of inference.

Results

Demographics

There were no significant differences between the groups with regard to age, height, weight and body mass index (Table 1). All patients completed the study. Three of the matched pairs had an age difference of 6 or 7 years and two matched pairs had a body mass index of 16.1% and 17.5%. One meal was eaten within the proscribed 8 h predosing interval, and one renally impaired subject was entered with a creatinine clearance (26.9 ml min^{-1} 1.73 m^{-2}) less than that defined in the protocol.

In the normal group, mean creatinine clearance was 102.4 ± 8.9 ml min^{-1} 1.73 m^{-2} (range: 91.9–119.1), while in the renally impaired group mean creatinine clearance was 55.7 ± 15.6 ml min^{-1} 1.73 m^{-2} (range: 26.9–75.6).

Pharmacokinetics

The mean serum concentrations of fosinoprilat following a single-dose (day 1) of fosinopril and at steady state (day 5) are shown in Figure 1. There was no significant difference in serum pharmacokinetic parameters between the groups on day 1, but higher serum concentrations were observed in the renally impaired group at steady state. The geometric mean C_{max} for fosinoprilat for the renally impaired group was 19% greater than the corresponding value of C_{max} for the normal group on day 1 ($P=0.07$) and 45% greater at steady state ($P=0.007$) (Table 2). The geometric mean AUC for the 24 h dosing period in the renally impaired group was 30% ($P=0.072$) and 43% ($P=0.027$) greater than the

Table 1 Patient characteristics (Mean ± s.d. (Range)).

	Renally impaired patients (n = 13)	*Normal patients (n = 13)*
Age (years)	52 ± 12 (33–69)	52 ± 12 (32–70)
Sex	8 male, 5 female	8 male, 5 female
Height (cm)	169 ± 11 (150–186)	173 ± 9 (158–190)
Weight (kg)	72.0 ± 10.1 (53.5–85.0)	75.7 ± 8.0 (65–89)
BMI (kg m^{-2})	25.2 ± 3.0 (21.5–29.8)	25.3 ± 2.4 (22.2–29.5)

Table 2 Pharmacokinetic parameters (mean/median[a] ± s.d.[d]) of fosinoprilat following a single dose of fosinopril 20 mg/HCTZ 12.5 mg.

		Renally impaired subjects s.d.[d]	*Normal subjects* s.d.[d]	n[b]	SE[c]	P *value*
C_{max}	Day 1	387 ± 0.19	324 ± 0.25	12	0.088	0.07
(ng ml^{-1})	Day 5	517 ± 0.40	357 ± 0.19	12	0.11	>0.007
t_{max}	Day 1	3.5	3.0	12	NA[e]	0.58
(h)	Day 5	3.0	3.0	12	NA[e]	>0.99
AUCτ	Day 1	3510 ± 0.29	2701 ± 0.35	12	0.13	0.072
(ng ml^{-1} h)	Day 5	4098 ± 0.43	2872 ± 0.30	12	0.14	0.027
CUE (%)	Day 1	5.08 ± 2.70	7.40 ± 2.56[g]	11[f]	0.72	0.009
	Day 5	6.81 ± 3.53	8.10 ± 2.80[g]	11[f]	0.63	0.068

[a]Group comparisons were done for the geometric mean of C_{max} and AUCτ, the arithmetic mean for %CUE and the median for t_{max}.
[b]One matched pair was excluded from all fosinoprilat calculations because a fosinoprilat level of 180 ng ml^{-1} in one subject's urine sample prior to first administration of study drug.
[c]SE = standard error of the mean difference of the log-transformed data for C_{max} and AUC.
[d]s.d. = Standard deviation of the log-transformed data for C_{max} and AUC.
[e]NA = Not applicable.
[f]One matched pair was excluded from the calculation of CUE because fosinoprilat urine assay on day 1 was not done.
[g]With a fosinoprilat plasma elimination $t_{1/2} \approx 12$ h, the sampling period for urine was too short to cover total fosinoprilat urinary excretion.

corresponding values for the normal group on both days 1 and 5 (Table 2). Median t_{max} values were roughly equal on both days 1 and 5 (Table 2). The mean cumulative 24 h urinary excretion of fosinoprilat was 7.4% and 5.1% for the normal and renally impaired group on day 1 ($P=0.009$) and 8.1% and 6.8%, respectively, at steady state, a difference which approached significance ($P=0.068$) (Table 2). The geometric mean accumulation index was 1.17 and 1.06 in the renally impaired and normal subjects, respectively, a difference which was not significant (95% CI: 0.91–1.32, $P=0.29$) (Table 3).

The mean serum concentrations of HCTZ following a single-dose (day 1) of fosinopril/HCTZ and at steady state (day 5) are shown in Figure 2. There were clear differences between the groups both on day 1 and at steady state with geometric mean C_{max} values 35% ($P=0.031$) and 64% ($P=<0.001$) greater in the renally impaired group than in the normals and AUC values 85% and 124% (both $P=0.001$) greater than the normals on days 1 and 5 (Figure 2 and Table 4). Median t_{max} values were the same on both days 1 and 5 (Table 4). The mean percentage cumulative 24 h urinary excretion of hydrochlorothiazide was 62.6% and 39.9% for the normal and renally impaired group on day 1 ($P=<0.001$) and 71.7% and 60.0%, respectively, at steady state, a difference which approached significance ($P=0.068$) (Table 4). The geometric mean accumulation index was 1.40 in the renally impaired and 1.15 in the normal subjects, a difference which was borderline significant (95% CI: 1.00–1.47, $P=0.053$) (Table 3).

Table 3 Geometric mean accumulation indices for fosinoprilat and hydrochlorothiazide.

	Fosinoprilat		*HCTZ*	
	Renally impaired subjects	*Normal subjects*	*Renally impaired subjects*	*Normal subjects*
Geometric Mean	1.17	1.06	1.40	1.15
Minimum	0.66	0.72	0.92	0.89
Maximum	2.28	1.54	2.56	1.48
s.d.[a]	0.33	0.23	0.28	0.14
n[b]	12	12	13	13
95% confidence interval	0.91 to 1.32		1.00 to 1.47	
P value	0.29		0.053	

[a]s.d. = Standard deviation of the log-transformed data.
[b]One matched pair was excluded from all fosinoprilat calculations because of a fosinoprilat level of 180 ng ml^{-1} in one subject's urine sample prior to first administration of study drug.

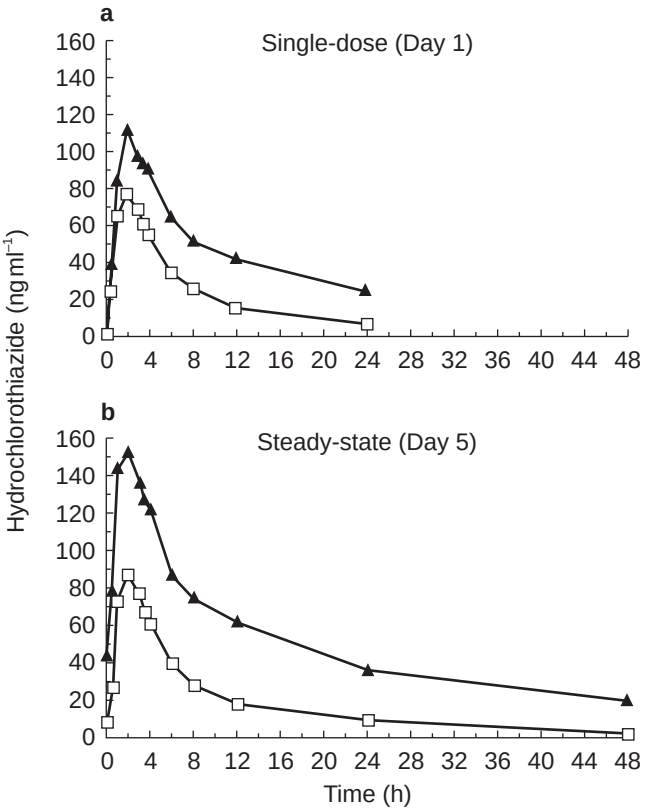

Figure 2 Mean hydrochlorothiazide concentrations (ng ml^{-1}) in renally impaired subjects (▲) and matched normals (□) following a single oral dose of 20 mg fosinopril/12.5 mg HCTZ (a) and at steady state following 5 days of oral dosing (b): linear plot. Error bars indicating ± s.d. do not overlap for the most part but have been omitted for purposes of clarity in the figure (see text).

Pharmacodynamics

Mean serum ACE activity over time was similar in both normal and renally impaired subjects (Table 5). Maximum inhibition of ACE activity was achieved in both groups on day 1 within 1 h of dosing and was maintained for at least 24 h. ACE activity in both groups began to return toward baseline levels between 12 h and 24 h on the same day (Table 5). By 48 h after the final dose on day 5, ACE activity was 44% and 25% of baseline levels for normal and renally impaired subjects, respectively.

Immediately prior to dosing, mean systolic blood pressure was slightly higher in the renally impaired than in the normal group (139 *vs* 132 mmHg; P = NS), while diastolic blood pressure was identical in the groups (82 *vs* 82 mmHg). At steady state dosing, mean blood pressure was maximally reduced at 8 h after dosing in both normals and those renally impaired and the pattern of blood pressure during the 24-h period was similar

Table 5. Summary statistics of serum ACE activity[a] following single and multiple doses of fosinopril and hydrochlorothiazide.

Time (h)	*Day*	*Renally impaired subjects* *Mean ± s.d.*[b]	*Normal subjects* *Mean ± s.d.*[b]
0	Day 1	5.9 ± 0.60	4.8 ± 0.56
	Day 5	0.2 ± 0.08	1.0 ± 0.13
1	Day 1	0.5 ± 0.25	0.6 ± 0.34
	Day 5	0.1 ± 0.04	0.0 ± 0.04
4	Day 1	0.0 ± 0.04	0.0 ± 0.04
	Day 5	0.1 ± 0.04	0.0 ± 0.03
12	Day 1	0.1 ± 0.04	0.0 ± 0.04
	Day 5	0.1 ± 0.04	0.0 ± 0.04
24	Day 1	0.4 ± 0.14	0.0 ± 0.10
	Day 5	0.8 ± 0.37	0.5 ± 0.10
48	Day 1	–	–
	Day 5	1.5 ± 0.20	2.1 ± 0.30

[a]ACE activity is reported as activity units (% substrate hydrolyzed min^{-1}).
[b]n = 13 for all mean values.

Table 4 Pharmacokinetic parameters (mean/median[a] ± s.d.[c]) of hydrochlorothiazide following dosing with fosinopril 20 mg/HCTZ 12.5 mg.

		Renally impaired subjects	*Normal subjects*	n	SE_b	P-*value*
C_{max}	Day 1	107 ± 0.40	79 ± 0.28	13	0.12	0.031
(ng ml^{-1})	Day 5	150 ± 0.40	91 ± 0.19	13	0.10	< 0.001
t_{max}	Day 1	2.0	2.0	13	NA[d]	0.42
(h)	Day 5	2.0	2.0	13	NA[d]	0.84
AUCτ	Day 1	1006 ± 0.51	544 ± 0.24	13	0.14	0.001
(ng ml^{-1} h)	Day 5	1406 ± 0.58	628 ± 0.24	13	0.17	0.001
CUE	Day 1	39.9 ± 20.8	62.6 ± 16.5	13	3.61	< 0.001
(%)	Day 5	60.0 ± 17.4	71.7 ± 11.1	12[e]	5.80	0.068

[a]Group comparisons were done for the geometrc mean of C_{max} and AUCτ, the arithmetic mean for %CUE and the median for t_{max}.
[b]SE = Standard error of the mean difference of the log-transformed data for C_{max} and AUC.
[c]s.d. = Standard deviation of the log-transformed data for C_{max} and AUC.
[d]NA = Not applicable.
[e]One matched pair was excluded from the calculation of CUE because of a missing sample.

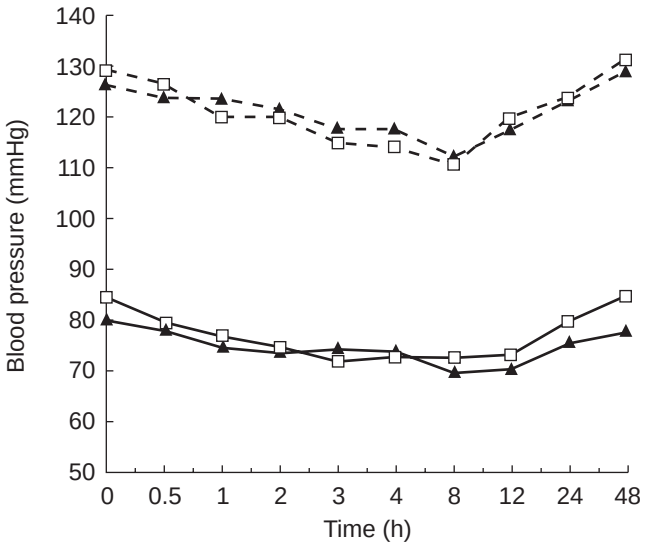

Figure 3 Mean systolic (closed symbols) and diastolic (open symbols) blood pressure in renally impaired subjects (–▲–, –□–) and matched (–△–, –□–) normals at steady state following 5 days of oral dosing of 20 mg fosinopril/12.5 mg HCTZ.

(Figure 3). At 48 h after the final dose mean diastolic blood pressure remained lower in the renally impaired ($P=0.038$) while systolic pressure was similar.

Safety

No serious clinical or laboratory adverse effects were noted. Mild or moderate adverse effects were noted in five normal patients and five renally impaired patients, predominantly headache and fatigue in both groups.

Discussion

This study was designed to investigate the pharmacokinetics of fosinoprilat in the presence of HCTZ in normal subjects and renally impaired patients and was carried out in the fasted state to avoid reductions in HCTZ plasma levels and urinary excretion associated with the fed state [14]. The patients were also free of other interfering medications or disease states other than renal impairment and matched for sex, age and body mass index with normal subjects. The study design allowed for both biochemical (ACE activity) and physiological (blood pressure response) measures of pharmacodynamics.

The pharmacokinetic results showed there were no clinically significant differences between the renally impaired patients and the normal subjects. Despite a similar percentage decrease in the CUE for both drugs in the renally impaired patients on day 5 (16% *vs* 16%), HCTZ accumulated more rapidly as indicated by the greater percentage increase for HCTZ than for fosinoprilat in C_{max} (65% *vs* 45%), in AUC (124% *vs* 43%) and in AI (22% *vs* 10%). This constitutes a modest increase in fosinoprilat levels and a more marked accumulation of HCTZ as would be expected with the alternative hepatic excretory pathway for fosinoprilat which does not exist for HCTZ. There were no pharmacodynamic consequence of the small buildup of fosinoprilat at steady state (day 5) over the 24 h dosing interval whether measured by ACE activity or blood pressure response (Figure 3 and 4). A pharmacodynamic difference appears only modestly 48 h after last dosing when there is slightly less ACE activity and slightly lower diastolic blood pressure in the renally impaired subjects compared to the normal subjects (Figure 3 and 4), although no placebo group was studied as a control for the blood pressure effect.

In a prior study in which fosinopril was compared with enalapril and lisinopril in chronic renal insufficiency, the percentage increase in AUC over the first 10 days of oral administration was 27% for fosinoprilat, 77% for enalapril and 161% for lisinopril [1]. That increase in fosinoprilat is less than the 43% increase in fosinoprilat AUC at steady state found in this study in renally impaired subjects but certainly emphasizes the importance of the secondary hepatic excretion pathway for fosinoprilat.

Reduction of creatinine clearance has been associated with extension of the plasma half-life of HCTZ and reduction of CUE and renal clearance [15, 16]. The results of this study are in line with those results and similar with respect to AUC [17] and CUE [14] to those found in previous studies of HCTZ pharmacokinetics. In the renally impaired subjects there was a consistent and significant increase in AUC, C_{max} and AI with a decreased CUE associated with the decreased creatinine clearance in that group.

Fixed combinations of an ACEI and HCTZ have been studied previously [5–8]. The coadministration of lisinopril and HCTZ showed no pharmacokinetic interaction in a study of normal subjects [6]. In another lisinopril/HCTZ study, the serum profiles of both drugs were comparable with observations from previous studies, showing similar higher concentrations in the elderly and in renally impaired patients and no evidence of an interaction between the drugs. One study with enalapril/HCTZ in elderly and renally impaired subjects showed a predictable increase in plasma concentration and a decrease in urinary elimination at lower rates of GFR which correlated predictably with the degree of renal impairment [7]. Another study, however, found that the administration of enalapril with HCTZ was associated with a significant increase in AUC and a significant reduction of the renal clearance of enalaprilat independent of the degree of renal impairment [8]. This result was attributed either to an initial reduction of GFR

by hydrochlorothiazide or to interference with the tubular secretion of enalaprilat [8]. In the present study, there was no such effect for fosinoprilat despite the higher levels of HCTZ. This may, again, reflect the presence of the alternative hepatic excretory pathway for fosinoprilat. Interestingly, and similar to the finding in the present study, the alterations mentioned above in the pharmacokinetics of either lisinopril [5] or enalapril [7, 8] appeared not to affect the pharmacodynamics of ACE inhibition.

It is desirable to be able to administer a drug to patients with renal impairment without concerns for differences in pharmacokinetics resulting from this condition. This study confirms that the pharmacokinetics of fosinopril in combination with HCTZ are only modestly affected by renal impairment and that the dual renal and hepatic excretory pathways of fosinoprilat, unlike the sole renal pathway of other ACE inhibitors, make possible its administration in combination with HCTZ and in the presence of renal impairment without the risk of undue increases in fosinoprilat concentrations and without adverse pharmacodynamic effects.

This work was supported by a grant from the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ.

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