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The pharmacokinetics and pharmacodynamics of fosinopril in haemodialysis patients*

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Summary. The pharmacokinetics and pharmacodynamics of fosinoprilat, the diacid of fosinopril sodium (a new angiotensin-converting enzyme (ACE) inhibitor), were investigated in six haemodialysis patients. Intravenous ^{14}C-fosinoprilat (7.5 mg), oral ^{14}C-fosinopril sodium (10 mg) and oral fosinopril sodium (10 mg) were administered in an open-label, randomized study.

Mean maximum concentration (C_{max}), clearance (CL), volume of distribution at steady-state (V_{ss}), mean residence time (MRT_{iv}), and $t_{1/2}$ values after IV administration of ^{14}C-fosinoprilat were 2,042 $\mu g \cdot ml^{-1}$, 11.3 $ml \cdot min^{-1}$, 11.0 l, 16.3 h and 28.3 h, respectively. Following oral administration of ^{14}C-fosinopril, mean C_{max}, time to maximum plasma concentration (t_{max}), and fosinoprilat bioavailability values were 197 $ng \cdot ml^{-1}$, 5.2 h and 29.2 %. Para-hydroxy fosinoprilat and fosinoprilat glucuronide comprised approximately 15 % and 2 % of radioactivity recovered in faeces. Four hours of haemodialysis only cleared approximately 1.5 % of the administered dose. The maximum effect (E_{max}) model was fitted to the percentage inhibition of serum ACE activity vs. fosinoprilat concentration data in three patients. E_{max} ranged from 95.3 to 102.5 %, and IC_{50} (the fosinoprilat concentration required to produce 50 % of E_{max}) ranged from 2.6 to 4.2 $ng \cdot ml^{-1}$.

Pharmacokinetic variables of the patients were similar to those in patients with moderate to severe renal dysfunction. Dosage modifications or supplemental dosing following dialysis are unnecessary.

Key words: Fosinopril; ACE inhibitors, haemodialysis, pharmacokinetics, pharmacokinetics-pharmacodynamics

Fosinopril, a new phosphinic acid-containing angiotensin-converting enzyme inhibitor (ACEI), has been used to treat hypertensive patients [1–5]. Following oral administration, fosinopril is rapidly hydrolyzed almost completely to the pharmacologically active diacid, fosinoprilat, and 20 to 30 % is conjugated to inactive glucuronide and active para-hydroxy analogs [6]. Fosinoprilat is primarily eliminated unchanged through the renal and hepatic routes. Since 50 % of the active drug is eliminated by the kidney, fosinopril's use in patients with renal failure might prove problematic. Our study was designed to determine the interdialytic disposition and biotransformation profiles of fosinopril and fosinoprilat in patients receiving chronic haemodialysis. In addition, the clearance of fosinoprilat during haemodialysis, plasma renin activity (PRA), plasma aldosterone concentration, blood pressure, and ACE activity were assessed following oral administration of fosinopril.

Patients and methods

Six hypertensive haemodialysis patients were studied; 4 m, 2 f; 4 black, 2 white; mean age, 40 (13) y; mean weight, 73 (16) kg; Exclusion criteria included pregnancy or lactation; heart, liver or collagen vascular disease; a history of alcohol or drug abuse or a demonstrated allergy to ACEIs.

Experimental design

The study was approved by the Committee on the Conduct of Human Research at the Medical College of Virginia. All patients gave informed written consent and were admitted to the Clinical Research Center at the Medical College of Virginia for two 6-day periods and one 2-day period; study periods were separated by at least 14 days. All non-essential medications were withheld for 24 h before and 48 h following study drug administration.

Each patient received 10 mg of ^{14}C-fosinopril orally as a dry-filled capsule and 7.5 mg of ^{14}C-fosinoprilat intravenously (IV). Following dosing, blood samples were collected over the ensuing 96 h, and then haemodialysis was restarted. Faecal samples were collected for 120 h after dosing. On a third dosing day 10 mg of fosinopril sodium, as a dry-filled capsule, was given orally 6 h before a haemodialysis session. Each oral dose was administered with 250 ml of tap water. Patients fasted for about 8 h before and 4 h following drug administration.

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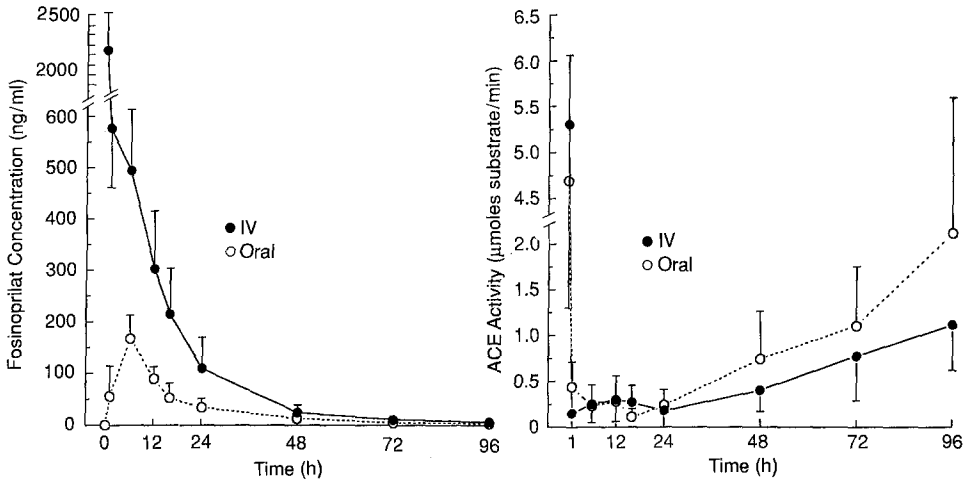

Fig. 1. Serum fosinoprilat concentration ($ng \cdot ml^{-1}$) (*left panel*) and serum angiotensin converting enzyme (ACE) activity (μmol of substrate $\cdot min^{-1}$) (*right panel*) following the intravenous administration of 7.5 mg of ^{14}C-fosinoprilat and oral administration of 10 mg of ^{14}C-fosinopril to 6 haemodialysis patients. Values are expressed as mean with SD

Sitting blood pressures and radial pulse rates were recorded immediately before and at 0.5, 1, 3, 4, 6, 8, 12, 24, 48, 72 and 96 h after administration of ^{14}C-fosinopril and ^{14}C-fosinoprilat. Baseline faecal samples were collected during the 24 h before dosing.

Venous blood samples were collected before and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 48, 72 and 96 h after administration of ^{14}C-fosinopril and ^{14}C-fosinoprilat. Plasma samples and the simultaneously collected faecal samples were frozen at –20 °C until assayed for fosinopril, fosinoprilat and fosinoprilat metabolite concentrations.

For estimation of fosinoprilat dialysis clearance following 10 mg of fosinopril sodium, "arterial" and venous blood were simultaneously collected at the start of haemodialysis and at 1, 2, 3 and 4 h after initiation of dialysis in 4 of 6 patients. Dialysates were collected for h 0–1, 1–2, 2–3 and 3–4 during a standard 4-h haemodialysis session and subsequently assayed for fosinoprilat concentration. A plasma sample collected during dialysis was also assayed for urea nitrogen content.

Plasma protein binding was determined from venous blood samples collected from each patient 2 and 6 h after administration of radiolabeled drug.

Haemodialysis methods. Hollow fiber dialyzers (Baxter Healthcare, Inc., Deerfield, IL) (3 Travenol® CF 15–11, 1.0 m^2; 1 Travenol® CF 12–11, 0.8 m^2) were used with a single-pass dialysate system. Dialysate flow rate was 550 $ml \cdot min^{-1}$, blood flow was maintained at 250 $ml \cdot min^{-1}$, and ultrafiltration was minimized.

Analytical methods. Plasma samples and faecal homogenates were analysed using a sensitive and specific thin-layer radio-chromatographic (TLRC) assay for fosinoprilat [6, 7] with a limit of detection of 2 $ng \cdot ml^{-1}$. These plasma and faecal samples were also assayed for fosinopril, fosinoprilat and fosinoprilat metabolites with high pressure liquid chromatography (HPLC) [7] with a Whitman M9-ODS-3 reverse phase column.

Concentrations of nonradiolabeled fosinoprilat in serum and dialysate were determined by a radioimmunoassay (RIA) [8]. Intra-assay variability was 7.6 % for a low control (6.7 $ng \cdot ml^{-1}$) and 3.3 % for a high control (41 $ng \cdot ml^{-1}$); inter-assay variability was 6.0 % for the low control and 5.8 % for the high control. The limit of detection was 1 $ng \cdot ml^{-1}$.

Plasma renin activity was determined using a RIA that measures generation of angiotensin I in vitro (GammaCoat ×, Clinical Assays, Cambridge, MA) [9]. Plasma aldosterone concentrations were determined using a solid-phase RIA (Coat-A-Count®, Diagnostic Products Corp., Los Angeles, CA) [9]. Serum angiotensin-converting enzyme activity was measured using a radioassay procedure (Ventrex, Portland, ME) [10].

Pharmacokinetic analysis. HPLC and TLRC data were used to calculate the relative distribution of unchanged fosinopril, fosinopril's biotransformation product, fosinoprilat, and fosinoprilat's metabolites in plasma and faeces. Fosinoprilat concentrations determined by RIA were used to calculate haemodialysis clearance.

Pharmacokinetic parameters of fosinoprilat were calculated using model-independent area and moment analysis [11]. After oral dosing, the time to maximum plasma concentration (t_{max}) and maximum plasma concentration (C_{max}) were determined from visual inspection of the plasma concentration vs time curves of individual patients. Mean absorption time (MAT) was calculated as MRT_{po}–MRT_{iv}. The bioavailability of fosinoprilat was estimated from the ratio of dose-normalized AUC values for fosinoprilat following oral fosinopril and intravenous fosinoprilat.

Haemodialysis clearance was calculated using the following equation:

$$CL_{HD} = Q_D \cdot D_E / A$$

where Q_D = dialysate flow rate ($ml \cdot min^{-1}$), D_E = concentration of fosinoprilat in dialysate effluent (ng/ml), and A = fosinoprilat arterial concentration (blood entering the dialyzer) ($ng \cdot ml^{-1}$).

The cumulative amount of fosinoprilat eliminated in dialysis fluid was determined by multiplying the fosinoprilat 1 concentration (in aliquots of hourly dialysate collections) by the dialysate volume per collection period and then summing the individual hourly excretion amounts.

Pharmacodynamic analysis. An E_{max} model [12] was used to relate fosinoprilat plasma concentrations to percentage ACE inhibition from baseline:

$$E = (E_{max} \cdot F)/(IC_{50} + F)$$

where E is the percentage of ACE inhibition from baseline and F is the fosinoprilat concentration. E_{max} is the maximum possible effect, and IC_{50} is the fosinoprilat concentration required to produce 50 % of E_{max}.

Results

Mean plasma fosinoprilat concentrations after intravenous and oral administration of ^{14}C-fosinoprilat and ^{14}C-fosinopril are depicted in Fig. 1. The means (SD) of the model-independent pharmacokinetic parameters for fosinoprilat after intravenous and oral administration of ^{14}C-fosinoprilat, respectively, are shown in Tables 1 and 2.

Binding of radioactivity to plasma proteins ranged from 93.2 to 98.4 % (mean (SD), 96.5 (0.6)%) for all determinations made 2 and 6 h after IV administration of ^{14}C-

Table 1. Model-independent pharmacokinetic parameters for fosinoprilat after IV administration of 7.5 mg of ^{14}C-fosinoprilat to 6 haemodialysis patients

Patient	C_{max} (ng/ml)	AUC ($ng \cdot h \cdot ml^{-1}$)	$t_{1/2}$ (h)	MRT (h)	Clearance ($ml \cdot min^{-1}$)	V_{ss} (l)
1	2095.6	12364.5	22.2	12.1	10.1	7.3
2	2113.4	9149.4	51.0	18.2	13.7	14.9
3	1964.8	16272.6	25.8	19.3	7.7	8.9
4	2643.3	15172.0	18.7	16.1	8.2	8.0
5	1805.9	8647.8	32.7	16.1	14.5	14.0
6	1629.7	9220.1	19.2	16.0	13.5	13.0
Mean	2042.1	11804.4	28.3	16.3	11.3	11.0
SD	346.8	3326.0	12.3	2.5	3.0	3.3
CV (%)	17.0	28.2	43.5	15.3	26.6	30.0

$t_{1/2}$, Half-life; C_{max}, peak concentrations; AUC, area under the plasma concentration-time curve; MRT_{iv}, mean residence time; V_{ss}, steady-state volume of distribution; CV, coefficient of variation

Table 2. Model-independent pharmacokinetic parameters for fosinoprilat after oral administration of 10 mg of ^{14}C-fosinopril to haemodialysis patients

Patient	C_{max} ($ng \cdot ml^{-1}$)	t_{max} (h)	AUC ($\mu g \cdot h \cdot ml^{-1}$)	MAT[a] (h)	MRT_{po} (h)	$t_{1/2}$ (h)	Bioavailability [%]
1	250.0	6	4.13	16.4	28.5	37.9	33.4
2	246.0	4	2.89	0.8	19.0	35.2	31.6
3	235.0	2	2.01	< 0	15.7	28.5	12.3
4	159.1	4	3.51	10.0	26.1	24.4[b]	23.1
5	145.0	6	3.05	15.4	31.5	42.5	35.3
6	148.0	9	3.66	6.5	22.5	16.7	39.6
Mean	197.2	5.2	3.21	9.8	23.9	32.2	29.2
SD	51.4	2.4	0.73	6.5	6.0	10.0	9.9
CV (%)	26.1	46.2	22.9	66.3	25.1	31.1	33.9

[a] MAT, Mean absorption time

[b] Excluded from calculation of mean value because the correlation coefficient was < 0.9 during terminal portion of log Conc vs time curve

fosinoprilat. A similar value was measured (96 (0.5)%) after oral administration of ^{14}C-fosinopril.

Over the 120 h following IV administration of ^{14}C-fosinoprilat, 37.9 (13.8)% of radioactivity was recovered in the faeces. The faecal recovery after oral administration of ^{14}C-fosinopril (27.5 (28.5)%) varied from patient to patient. Because constipation is common in haemodialysis patients, 120 h may have been insufficient time to recover all administered radioactivity.

The plasma biotransformation profile was determined following both the IV administration of ^{14}C-fosinoprilat and the oral administration of ^{14}C-fosinopril. Following IV administration, fosinoprilat accounted for 94.3 (2.5)% at 1 h and 70.3 (1.1)% of the circulating radioactivity at 24 h. Para-hydroxy fosinoprilat accounted for 1.8 (0.8)% of the radioactivity at 1 h and 6.6 (5.7)% at 24 h. Fosinoprilat glucuronide was undetectable at 1 h and accounted for 1.1 (2.0)% of the radioactivity at 24 h following IV administration. Unknown compounds accounted for approximately 4 % of the total radioactivity at 1 h and 21 % at 24 h following IV administration. Following oral administration of ^{14}C-fosinopril, fosinoprilat accounted for 74.1 (5.4)% of the total radioactivity at 2 h, 73.3 (5.6)% at 4 h, and 74.6 (4.9)% at 9 h. Para-hydroxy fosinoprilat accounted for 2.1 (0.5)%, 4.4 (1.6)%, and 6.0 (1.6)%; and fosinoprilat glucuronide accounted for 12.5 (4.3)%, 14.5 (2.2)%, and 8.9 (2.2)% of the total radioactivity at those specified time points. Fosinopril was virtually undetectable 2 h post-dose and accounted for 1.9 (0.5)% of total radioactivity.

After IV administration of ^{14}C-fosinoprilat, most of the radioactivity (84.5 (4.7)%) in pooled faeces was from fosinoprilat. Para-hydroxy fosinoprilat accounted for most of the remaining radioactivity (12.1 (3.2)%). After the oral administration of ^{14}C-fosinopril, fosinoprilat accounted for 77.8 (4.9)%, para-hydroxy fosinoprilat for 17.0 (4.4)%, and fosinoprilat glucuronide for 2.4 (0.5)% of the total radioactivity in pooled faeces.

Mean fosinoprilat haemodialysis clearance was 4.4 (1.4) $ml \cdot min^{-1}$ with a corresponding mean urea nitrogen clearance of 200 (34.3) $ml \cdot min^{-1}$. Only 1.5 (0.5)% of the fosinopril dose was cleared during the 4-h haemodialysis session.

As expected, PRA increased and plasma aldosterone concentration and serum ACE activity decreased following administration of either fosinoprilat or fosinopril. Maximum PRA increases from baseline were 246 (218)% following ^{14}C-fosinoprilat administered intravenously and 173 (119)% following ^{14}C-fosinopril administered orally. Plasma aldosterone concentrations decreased as much as 23 (26)% following IV administration of ^{14}C-fosinoprilat and 42 (18)% following oral administration of ^{14}C-fosinopril. Fig. 1 depicts serum ACE inhibition for 96 h after intravenous administration of ^{14}C-fosi-

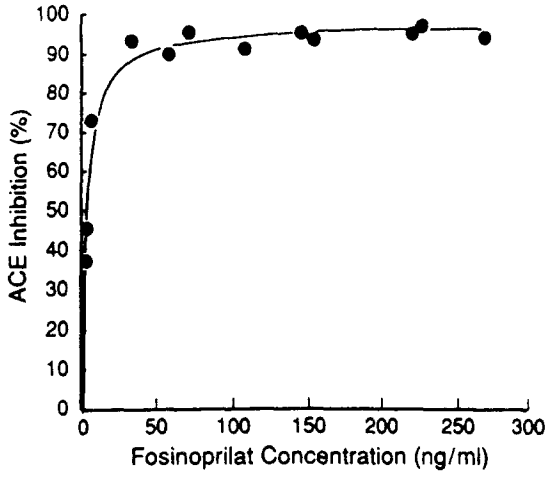

Fig. 2. Relationship between % inhibition of serum ACE activity from baseline and serum fosinoprilat concentration ($ng \cdot ml^{-1}$) for a representative haemodialysis patient. The curve has been generated utilizing the E_{max} model

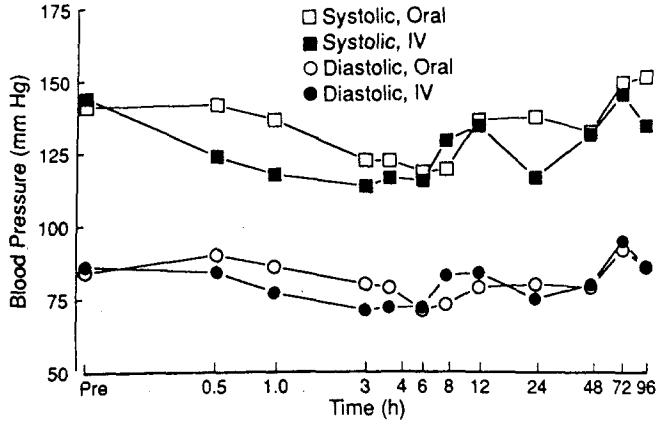

Fig. 3. Mean systolic and diastolic blood pressure following the intravenous administration of 7.5 mg of ^{14}C-fosinoprilat and oral administration of 10 mg of ^{14}C-fosinopril to 6 haemodialysis patients. Values are expressed as mean

noprilat and oral administration of ^{14}C-fosinopril. Due to the prolonged inhibition of serum ACE activity, the E_{max} model was only appropriate to describe three patients' data (2 following IV fosinoprilat and 2 following oral fosinopril). Individual E_{max} values ranged from 95.3 to 102.5 % and IC_{50} values ranged from 2.58 to 4.15 $ng \cdot ml^{-1}$. Fig. 2 depicts a typical E_{max} curve from a representative haemodialysis patient.

Fig. 3 depicts mean systolic and diastolic blood pressure after single IV doses of ^{14}C-fosinoprilat or oral administration of ^{14}C-fosinopril. Three h after IV administration of ^{14}C-fosinoprilat, mean blood pressure decreased maximally to 114/71 mmHg, a decrease of 30/15 mmHg from baseline. Six h after oral administration of ^{14}C-fosinopril, mean blood pressure decreased maximally to 119/71 mmHg, a decrease of 22/13 mmHg.

No adverse events occurred during this study. No abnormalities in liver function, electrolytes, urinalysis or haematology profiles were detected.

Discussion

^{14}C-fosinoprilat and ^{14}C-fosinopril were administered to healthy volunteers [6, 7] and to patients with renal impairment [7] in similar studies. In healthy volunteers given fosinoprilat intravenously, clearance was equally divided between hepatic and renal routes of elimination [6, 7]. Singhvi et al [6] collected plasma data for 16 h post dosing. Hui et al [7] used a protocol similar to ours and collected plasma data for 96 h post dosing. In that study total body clearance of fosinoprilat remained constant for patients with varying renal dysfunction (creatinine clearance from 11 to 72 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$). The constant clearance was probably related to hepatic elimination with a greater biliary than renal secretion of fosinoprilat and to metabolism to para-hydroxy fosinoprilat.

Following oral administration of ^{14}C-fosinopril to haemodialysis patients, the bioavailability of fosinoprilat in our study was comparable to bioavailability of 29 % in young, healthy subjects [6] and to the 22 % to 28 % in patients with renal impairment [7]. The t_{max} of 5.2 (2.4) h after oral fosinopril dosing was somewhat longer than the 2.7 h in healthy subjects [6] but closer to the 4 h in patients with renal impairment [7]. Because one subject's t_{max} was 9 h and plasma was not sampled between 6 and 9 h, t_{max} data may have been skewed. C_{max} and estimates of AUC, MRT_{po} and MAT in patients from our study were similar to those estimates in patients with renal impairment not requiring dialysis [7]. After IV administration of ^{14}C-fosinoprilat, estimates for AUC V_{SS} and MRT_{iv} in patients from our study were also similar to those estimates in renally impaired patients [7].

After IV administration of ^{14}C-fosinoprilat, almost all circulating drug remained as fosinoprilat at 1 h. With time that percentage decreased, and the proportion of para-hydroxy fosinoprilat increased. Following the oral administration of ^{14}C-fosinopril, fosinoprilat accounted for most of the radioactivity in the plasma and faeces. Fosinoprilat-glucuronide accounted for 9 % to 15 % of the circulating radioactivity, proportions similar to those in the plasma of patients with severe renal impairment [7] and lower than concentrations of 20 % to 27 % in healthy subjects [6]. Fosinoprilat accounted for approximately 75 % of the circulating radioactivity, less than that in patients with more modest renal impairment (80 % to 90 %) [6]. The lower plasma concentrations of fosinoprilat and fosinoprilat-glucuronide were offset by higher plasma concentrations of para-hydroxy fosinoprilat. Those data suggest that metabolism of fosinopril to para-hydroxy fosinoprilat is greater in haemodialysis patients than in subjects with normal renal function. In faeces, fosinoprilat and para-hydroxy fosinoprilat accounted for almost all radioactivity, and that finding is similar to findings in healthy subjects [6].

During the interdialytic period, recovery of radioactivity was incomplete after both IV and oral administration. More time may have been required to recover the entire dose in the patients due to the high incidence of constipation in this patient population. Similarly, in a study of haemodialysis patients who received ^{14}C-captopril orally, only about 40 % of the dose was recovered over 96 h [13].

Despite the reduced recovery, biliary excretion is an important route of elimination of fosinoprilat.

Total body clearance of fosinoprilat following intravenous administration was similar to clearance in subjects with a wide range of renal impairment (11 to 72 $ml \cdot min^{-1}$) and approximately half that in normal subjects [7]. Because of an increase in hepatic clearance [7], the total body clearance of fosinoprilat remains constant as renal function deteriorates. Since a large percentage of unchanged fosinopril is found in the faeces, biliary secretion appears to become progressively more important in the elimination of that compound as renal function worsens. Fosinopril is unique in this regard, since the total body clearance of virtually all other ACE inhibitors decreases and AUC increases as renal function progressively deteriorates [13–26].

The removal of fosinoprilat by haemodialysis was insignificant. Arterial and venous fosinoprilat concentrations decreased slightly during a 4-h haemodialysis session. High plasma protein binding, similar to that in normal subjects [6], explains the negligible haemodialysis clearance. The lack of clearance contrasts with the substantial haemodialysis clearance of other ACE inhibitors, captopril [13], enalapril [15, 16] and lisinopril [15].

Although a strong relationship has been demonstrated between serum ACE inhibitor concentration and inhibition of ACE activity [17, 18, 27], the antihypertensive effects have not correlated well with those concentrations [12, 28, 29]. Therefore, optimal ACE inhibitor dosage regimens have been difficult to determine solely on the basis of pharmacokinetic data. In our study, fosinoprilat sustained inhibition of serum ACE activity well beyond the time necessary for blood pressure to return to baseline. In the four patients with evaluable data, IC_{50} concentrations were similar to those in peritoneal dialysis patients [8] and to those in animal studies [30]. Those low values indicate that serum ACE activity is highly sensitive to the action of fosinopril. Serum fosinoprilat concentrations were much higher than the IC_{50} for prolonged periods following drug administration; thus, some disparity may exist between serum and tissue ACE activity following ACE inhibitor administration [31].

Despite the absence of excretory function of the kidneys, the renin-angiotensin-aldosterone axis remained responsive in our haemodialysis patients as exemplified by increases in PRA and decreases in aldosterone concentrations following administration of fosinopril. Indeed, the axis remains responsive in haemodialysis patients [32, 33] and may be an important pathogenic factor in the development of hypertension in haemodialysis patients [34], particularly those patients with "dialysis refractory" hypertension [35–38]. Blood pressure decreased after drug administration, and maximum decreases seemed to correlate with peak drug concentrations. However, without a placebo treated group, the single dose antihypertensive effect of fosinopril is difficult to assess.

In summary, the pharmacokinetic parameters of fosinopril in haemodialysis patients are similar to the parameters in patients with mild to severe renal dysfunction. Increases in fractional hepatic elimination have been implicated in maintaining the clearance of fosinopril in spite of decreasing renal function. These data suggest that dose modifications are unnecessary in patients with renal dysfunction, although chronic dosing studies are necessary to confirm this. The haemodialysis clearance of fosinopril is not clinically significant; hence, supplemental dosing following haemodialysis is not needed.

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