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Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis 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 after the oral administration of 10 mg of fosinopril sodium to 6 chronic ambulatory peritoneal dialysis (CAPD) patients. The results from 1 patient are reported separately because of the presence of concomitant liver dysfunction.

The mean $t_{1/2}$, C_{max}, t_{max}, and AUC values for 5 of the CAPD patients were 19.5 h, 202 ng · ml^{-1}, 4.8 h, and 3.19 μg · h · ml^{-1}, respectively. Values for 1 CAPD patient with liver dysfunction were $t_{1/2}$ of 65.4 h, C_{max} of 182 ng · ml^{-1}, t_{max} of 9 h, and AUC of 18.1 μg · h · ml^{-1}. Peritoneal clearance of fosinoprilat was negligible, ranging from 0.07 to 0.23 ml · min^{-1}.

Serum ACE activity remained significantly suppressed at 24 and 48 h after fosinopril sodium administration with mean decreases from baseline of 94.2% and 70.6%, respectively. ACE activity was suppressed to an even greater degree in the patient with liver dysfunction, remaining 97% inhibited 72 h after drug administration. Plasma renin activity (PRA) increased and plasma aldosterone concentrations decreased following drug administration. Mean arterial pressure did not change appreciably throughout the study. Dosage reductions may not be necessary in the majority of dialysis patients.

Key words: Fosinopril; fosinoprilat, CAPD, ACE-inhibitor, pharmacokinetics, pharmacodynamics, peritoneal dialysis

Fosinopril sodium (SQ 28,555) represents a new class of orally effective, phosphorous containing angiotensin-converting enzyme (ACE) inhibitors which has been proven effective in the treatment of essential hypertension [1]. During or following absorption, fosinopril sodium is rapidly and extensively hydrolyzed to its pharmacologically active diacid, fosinoprilat (SQ 27,519) [2]. To date, two additional minor metabolites of fosinopril sodium have been identified, a glucuronide conjugate and a p-hydroxy analog of the active diacid [2].

Excretion of fosinoprilat occurs approximately equally via renal and hepatic routes in patients without dysfunction of these organs [2]. After intravenous administration of SQ 27,519-[^{14}C] to normal subjects, the 0 to 96 h recovery of radioactivity in urine averaged 44% of the dose. Faecal recovery under similar circumstances was 46% of the administered dose [2]. Since biliary clearance of fosinoprilat represents only 50% of total body clearance, it is important to investigate the pharmacokinetics and pharmacodynamics in patients with renal insufficiency. Accordingly, 6 chronic ambulatory peritoneal dialysis (CAPD) patients were studied.

Patients and methods

Six CAPD patients (5 M, 1 F) were studied after having given written informed consent (Table 1). These studies were approved by the Committee on the Conduct of Human Research of Virginia Commonwealth University. All patients were clinically stable and without evidence of either acute or chronic peritonitis. One patient

Table 1. Clinical characteristics of CAPD patients

Patient	Age (y)	Weight (kg)	Sex	Inulin clearance (ml · min^{-1})	Meds	Disease
C.M.	39	55	F	2.3		NS
R.B.	38	67	M	0		CGN
H.J.	31	75	M	3.8	2	unknown
J.M.	66	82	M	3.9	5	NS
J.J.	46	88	M	4.6	1,3,4	DN
L.W.[a]	54	79	M	0	1,6	HTN

[a] abnormal liver function
NS = nephrosclerosis; CGN = chronic glomerulonephritis; DN = diabetic nephropathy; HTN = hypertension; 1 = metoprolol; 2 = propranolol; 3 = diltiazem; 4 = isosorbide dinitrate; 5 = hydralazine; 6 = decadurabolin

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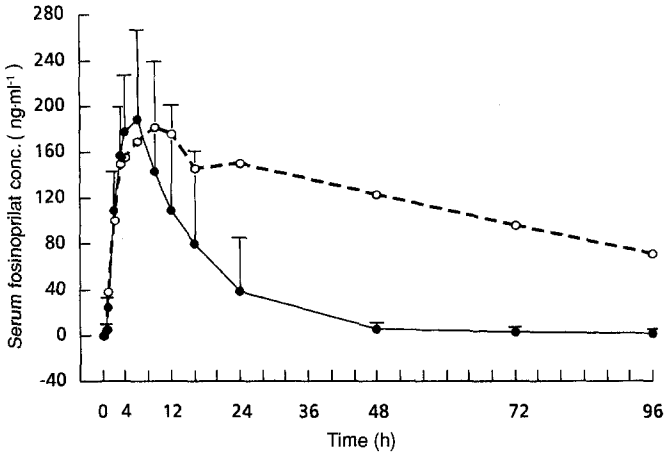

Fig. 1. Serum fosinoprilat concentrations ($ng \cdot ml^{-1}$) following the oral administration of fosinopril sodium (10 mg) to 5 CAPD patients (·) and 1 CAPD patient (L. W., o) with concomitant liver dysfunction. Values are expressed as mean with SD

(L. W.) was studied in the presence of enzymatic liver dysfunction and his pharmacokinetic data are reported separately. Approximately one week prior to study he had received an intramuscular injection of the anabolic steroid, decadurabolin. His serum bilirubin subsequently rose from 0.6 to 1.7 $mg \cdot dl^{-1}$ (normal range, 0–1.5 $mg \cdot dl^{-1}$), SGOT increased from 25 to 56 $IU \cdot l^{-1}$ (normal range, 0–40 $IU \cdot l^{-1}$), and GGT increased to 162 $IU \cdot l^{-1}$ (normal range, 0–55 $IU \cdot l^{-1}$), all prior to the administration of fosinopril sodium. Following discontinuation of decadurabolin, his liver function tests completely normalized.

Each patient was admitted to the General Clinical Research Center of the Medical College of Virginia on the evening prior to study day 1 to allow for collection of baseline biological samples. Patients were managed with their routine peritoneal dialysis prescription which consisted of three, 2-l daytime dialysate exchanges and one, 2-l overnight exchange. Daytime exchanges contained either 1.5 or 2.5% dextrose and the overnight exchange either 2.5 or 4.25% dextrose. Patients fasted for at least 8 h prior to and for 4 h following drug administration. All antihypertensive medications were withheld the day prior to and throughout the study.

A single 10-mg oral dose of fosinopril sodium was administered with 250 ml of tap water shortly after the instillation of the first peritoneal dialysis exchange. The patients were then asked to move around freely to facilitate dialysate mixing and to remain ambulatory for the succeeding 12 h. Venous blood samples were obtained just prior to (0 h) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 48, 72, and 96 h after fosinopril sodium administration. In addition, just prior to fosinopril sodium administration a single dose of inulin (50 $mg \cdot kg^{-1}$) was given intravenously to estimate residual glomerular filtration rate. Urine was collected just prior to (0 h) and at 0–12, 12-24, 24–48, 48–72, and 72–96 h following fosinopril sodium administration in those patients who were not anuric. Complete collections of dialysate fluid coinciding with the end of each exchange were made at 0–6, 6–12, 12–16, 16–24, 24–30, 30–36, 36–40, and 40–48 h. Blood pressure (mm Hg) and pulse rate (beats · min^{-1}) were measured before and at 0.5, 1, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h following drug administration. Mean arterial pressure (MAP) was calculated using the formula: [(2(Diastolic pressure) + Systolic pressure)/3].

Assays

Concentrations of fosinoprilat were determined in serum, urine and dialysate by radioimmunoassay (RIA). Fifty µl of fosinoprilat antisera and 200 µl of ^{125}I-fosinopril-histamine were added to 25 µl of unknown serum samples. After mixing, the tubes were incubated for 2 h at room temperature. Separation of bound and free radioactivity was accomplished by the addition of polyethylene glycol-goat anti-rabbit gamma globulin followed by centrifugation. The resulting supernatants were decanted completely and counted in a standard well-type gamma scintillation counter with a discrimination setting of 20–50 KeV. Each sample was assayed in duplicate. Intraassay variability (C.V.) was 7.6% for a low control (6.7 $ng \cdot ml^{-1}$), and 3.3% for a high control (41 $ng \cdot ml^{-1}$), and interassay variability was 6.0% and 5.8% for the low and high controls, respectively. The limit of detection for this compound is 1 $ng \cdot ml^{-1}$. Since it has previously been determined that conversion of fosinopril sodium to fosinoprilat is virtually complete [2], unchanged fosinopril concentrations were not measured.

Plasma renin activity (PRA) was determined by a RIA that measures the in vitro generation of angiotensin I. The assay used a generation time of 90 min and a system pH of 6.0 (GammaCoat, Clinical Assays, Cambridge, MA.) [3]. Plasma aldosterone levels were determined by a solid-phase RIA (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA.) [3]. Serum angiotensin-converting enzyme (ACE) activity was measured by a radioassay (Ventrex, Portland, ME.) [4]. In brief, the radiolabelled tripeptide ^{3}H-Hip-Gly-Gly was added to serum as substrate for angiotensin-converting enzyme followed by incubation for 30 min and acidification with 0.5 N HCl. The reaction product ^{3}H-Hip was then separated from unreacted substrate by extraction with Ventrex Scintillation Cocktail # 1 and counted. Angiotensin-converting enzyme was reported as the percentage of available substrate hydrolyzed per min.

Plasma and urine inulin concentrations were determined by a colorimetric method employing anthrone, with spectrophotometric determination at an absorbance wavelength of 620 nm [5].

Pharmacokinetic analysis

The results from 5 subjects are reported collectively (mean with SD) with patient L. W. presented separately. Model-independent pharmacokinetic parameters were calculated using standard procedures [6]. Area under the serum concentration vs. time-curve AUC(0–t) was determined from time 0 to time t by the linear trapezoidal method. AUC from time 0 to infinity was determined by summing AUC(0–t) and $C_t/\lambda z$, where C_t = concentration of fosinoprilat at the last sampling time point after drug administration and λz = the absolute value of the slope of a least squares regression of the natural log of serum concentration vs. time in the terminal phase of drug disposition.

The area under the first-moment curve AUMC(0–t) from time 0 to time t was determined using the linear trapezoidal method for the product of time and the concentration of fosinoprilat in serum vs. time. AUMC was calculated by $AUMC(0\text{–}t) + [t(C_t)/\lambda z + C_t/\lambda z^2]$ where t = final time at which a serum concentration data time point was available. Mean residence time (MRT) was calculated by AUMC/AUC. Elimination half-life ($t_{1/2}$) was determined by $\ln 2/\lambda z$.

Although the absolute bioavailability of fosinoprilat was not calculated as part of this study, apparent oral clearance, $CL \cdot f^{-1}$, was also estimated, where f represented the fraction of the administered dose ultimately reaching the systemic circulation. $CL \cdot f^{-1}$ was calculated by Dose/AUC. The total oral clearance represents the sum of nonrenal, renal, and peritoneal clearances as expressed by the following equation: $(CL \cdot f^{-1})_{TOTAL} = CL_R + CL_P + CL_N$. The clearance of fosinoprilat via peritoneal dialysis (CL_P) was determined by CL_P = CDE/AUC(0–48 h) where CDE = cumulative 48 h excretion of fosinoprilat in dialysate (µg). The renal clearance was determined by CL_R = CUE/AUC(0–48 h) where CUE = cumulative 48 h urinary excretion of fosinoprilat (µg).

The following parameters were also determined from visual inspection of the serum concentration vs time curves for individual patients: (1) the time to maximal serum concentration (t_{max}) and (2) the maximal serum concentration (C_{max}). Peritoneal urea nitrogen clearance was also determined using standard clearance methodology.

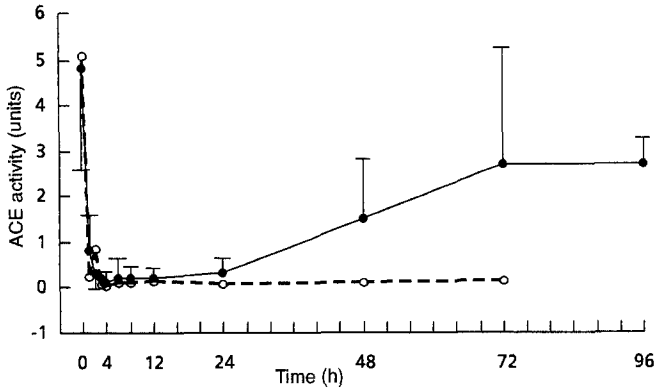

Fig. 2. Serum angiotensin-converting enzyme (ACE) activity (units) following oral administration of fosinopril sodium (10 mg) to 5 CAPD patients (·) and 1 CAPD patient (L. W., o) with concomitant liver dysfunction. Values are expressed as mean with SD.

Pharmacodynamic analysis

The relationship between fosinoprilat concentration and ACE inhibition as a percent of baseline ACE activity (%ACEI) was assessed by means of a nonlinear regression analysis and the E_{max} model [8].

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

where E is the % ACE inhibition from baseline, 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}. Those parameters were estimated by the nonlinear least squares regression program PCNONLIN [9].

Table 2. Model-independent pharmacokinetic parameters for fosinoprilat after oral administration of fosinopril sodium (10 mg) to CAPD patients

Patient	$t_{1/2}$ (h)	C_{max} ($ng \cdot ml^{-1}$)	t_{max} (h)	AUC ($\mu g \cdot h \cdot ml^{-1}$)	MRT (h)	AUMC ($\mu g \cdot h^2 \cdot ml^{-1}$)	$CL \cdot f^{-1}$ ($ml \cdot min^{-1}$)
C.M.	14.4	319	6	6.47	16.2	105	25.8
R.B.	27.6	195	6	4.29	21.3	91.7	33.7
H.J.	25.2	144	6	1.65	15.3	25.3	100.9
J.M.	9.5	148	3	1.53	10.1	15.4	108.9
J.J.	20.8	205	3	1.99	13.3	26.4	83.8
Mean	19.5	202	4.8	3.19	15.2	52.7	70.6
(SD)	(7.5)	(70.8)	(1.6)	(2.15)	(4.1)	(41.9)	(38.5)
L.W.	65.4	182	9	18.06	95.9	1730	9.2

$CL \cdot f^{-1}$ = apparent oral fosinoprilat clearance

Table 3. Fosinoprilat and urea peritoneal dialysis clearance and cumulative fosinoprilat urinary excretion after oral administration of fosinopril sodium (10 mg) to CAPD patients

Patient	CL_{BUN} ($ml \cdot min^{-1}$)	CDE/CUE (μg)	AUC(0–48 h) ($\mu g \cdot h \cdot ml^{-1}$)	CL_P ($ml \cdot min^{-1}$)	CL_R ($ml \cdot min^{-1}$)
C.M.	4.2	26.3/44.7	6.27	0.07	0.12
R.B.	6.9	47.3/0	3.90	0.20	0.0
H.J.	4.6	2.0/14.0	1.53	0.02	0.15
J.M.	4.2	7.3/24.3	1.50	0.08	0.27
J.J.	6.8	11.1/7.1	1.87	0.10	0.63
Mean	5.3	18.8/30.8	3.02	0.09	0.23
(SD)	(1.4)	(18.3/27.8)	(2.07)	(0.07)	(0.24)
L.W.	5.3	96.6/0.0	6.86	0.23	0.0

CL_{BUN} = renal urea nitrogen clearance
CDE/CUE = cumulative dialysate excretion/urinary excretion
CL_P = peritoneal fosinoprilat clearance
CL_R = renal fosinoprilat clearance

Results

Fosinoprilat pharmacokinetics

Mean serum fosinoprilat concentrations ($n = 5$) following a 10 mg oral dose of fosinopril sodium are represented in Fig. 1. One patient (L. W.) is depicted separately because of pharmacokinetic differences which were presumably related to his abnormal hepatic function. In that patient, serum fosinoprilat concentrations beyond 12 h were considerably higher than those values observed in the 5 other patients.

Model-independent pharmacokinetic parameters are reported in Table 2 for the entire patient population ($n = 6$), with the mean (SD) calculated for values obtained from the 5 patients with normal hepatic function. The $t_{1/2}$, C_{max}, t_{max} and AUC values for those 5 patients were 19.5 (7.5) h, 202 (70.8) $ng \cdot ml^{-1}$, 4.8 (1.6) h, and 3.19 (2.15) $\mu g \cdot h \cdot ml^{-1}$, respectively. The pharmacokinetic parameter values are to be contrasted with those of L. W., where the $t_{1/2}$, C_{max}, t_{max}, and $AUC_{0\text{-inf}}$ were 65.4 h, 182 $ng \cdot ml^{-1}$, 9 h, and 18.1 $\mu g \cdot h \cdot ml^{-1}$, respectively.

The calculated apparent oral clearance, $CL \cdot f^{-1}$, was 70.6 (38.5) $ml \cdot min^{-1}$ in the 5 CAPD patients with normal hepatic function and 9.2 $ml \cdot min^{-1}$ in L. W. Mean residence time (MRT) was similarly affected by the presence of dual organ dysfunction, ie, 95.9 h in L. W. versus 15.2 (4.1) h in the other 5 patients.

Table 3 reports both urea and fosinoprilat peritoneal clearance as well as the cumulative fosinoprilat urinary excretion and clearance. Peritoneal clearance, $CL_{PERITONEAL}$, of fosinoprilat over 48 h was negligible, ranging from 0.07 to 0.23 $ml \cdot min^{-1}$. Even though the estimated glomerular filtration rate [3.7 (1) $ml \cdot min^{-1}$], as determined by inulin clearance, was low in the four patients producing urine, in all instances urinary excretion of fosinoprilat still exceeded that by dialysis.

Fosinoprilat pharmacodynamics

The change in ACE activity following fosinopril sodium administration is depicted in Fig. 2. ACE activity remained significantly suppressed at 24 and 48 h with mean (SD) decreases of 94.2 (7.3) % and 70.6 (15.3) %, respectively. ACE activity was suppressed to an even greater degree in patient LW, remaining 97% inhibited even 72 h following the administration of fosinopril sodium.

In the 5 CAPD patients with normal hepatic function, the serum fosinoprilat concentrations were related to the inhibition of serum ACE activity using the E_{max} model. Fig. 3 depicts the profile from a single representative patient. The data sets from each patient were fitted independently and individual parameter estimates reported in Table 4. Mean (SD) E_{max} was 97.8 (3.42) % and IC_{50} was 1.98 (0.87) $ng \cdot ml^{-1}$ for the 5 patients. Due to the prolonged, near maximal inhibition of serum ACE activity in the CAPD patient with hepatic dysfunction, the data from this patient was not able to be analyzed.

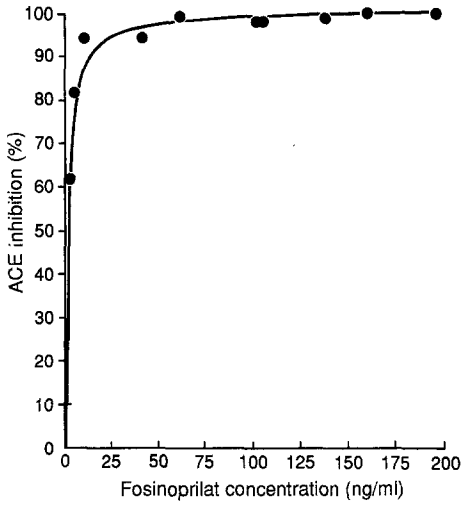

Fig. 3. Relationship between serum % ACE inhibition from baseline and serum fosinoprilat concentration ($ng \cdot ml^{-1}$) for 1 representative CAPD patient. The curve has been generated utilizing the E_{max} model.

Plasma renin activity (PRA) and plasma aldosterone concentrations were determined in 4 of the 6 patients (Table 5). PRA increased [mean maximum % increase, 453 (646) %] and plasma aldosterone concentrations decreased [mean maximum % decrease, 45.1 (5.9) %] following the administration of fosinopril sodium.

Blood pressure did not change appreciably following a single dose of fosinopril sodium even though additional blood pressure medications were not administered during the course of the study. Daily weights remained stable, decreasing from baseline by mean values of 0.1, 0.25, and 0.4 kg at 6, 24, and 48 h, respectively. No adverse reactions were noted during this single-dose study.

Table 4. Individual parameter values for E_{max} model relating serum fosinoprilat concentration and % ACE inhibition in 5 CAPD patients

Patient	E_{max}[a] (%)	IC_{50}[b] ($ng \cdot ml^{-1}$)
C.M.	92.5	2.35
J.M.	101	1.18
H.J.	98.3	1.51
R.B.	101	1.54
J.J.	96.8	3.34
Mean	97.8	1.98
(SD)	(3.43)	(0.87)

[a] E_{max}, Theoretical maximum percent inhibition of ACE activity
[b] IC_{50}, Fosinoprilat serum concentration producing half maximal inhibition of ACE activity

Table 5. Baseline PRA and aldosterone concentrations and maximum response following the administration of fosinopril sodium to CAPD patients

Patient	Baseline PRA ($ng\ AI \cdot ml^{-1} \cdot h^{-1}$)	Baseline Aldosterone ($ng \cdot dl^{-1}$)	Max. % PRA Increase (%)	Max. % Aldo. Decrease (%)
R.B.	0.7	9.3	28.6	36.6
H.J.	2.7	17.3	77.8	49.1
J.M.	7.8	83.9	301.3	45.3
J.J.	1.2[a]	32.7	1405.0	49.2
Mean	3.1	35.8	453.2	45.1
(SD)	(3.2)	(33.5)	645.6	5.9

[a] PRA value done 1 h after fosinopril

Discussion

The pharmacokinetics of fosinoprilat appear to be altered in the CAPD population. Although considerable interpatient variability in C_{max} existed [202 (70.6) $ng \cdot ml^{-1}$], this value was comparable to that obtained in hemodialysis patients [197 (21) $ng \cdot ml^{-1}$] [10] but was substantially higher than the value obtained in healthy subjects [111 (24) $ng \cdot ml^{-1}$] [2]. The higher C_{max} values observed in dialysis patients would be expected based on the reduction in renal clearance and lack of appreciable dialyzability of fosinoprilat in this patient population.

The t_{max} of 4.8 (1.6) h was somewhat longer than that of 2.7 (0.3) h observed in normal volunteers [2]. Time to peak concentration has also been noted to increase in conditions of renal impairment for other orally administered ACE inhibitors such as captopril [11], lisinopril [7, 12], and enalapril [12] even though enalaprilat is formed by esterolytic cleavage of enalapril. This phenomenon currently remains unexplained. The one CAPD patient with liver dysfunction displayed a t_{max} value (9 h) which was markedly prolonged suggesting that fosinopril sodium absorption was delayed and/or the rate of hydrolysis to fosinoprilat slowed.

The disposition of fosinoprilat as described by the parameters of $t_{1/2}$ [19.5 (7.5) h] and MRT [15.2 (4.1) h] was similar to that seen in haemodialysis patients [$t_{1/2}$, 28.3 (12.3) h; MRT, 16.3 (2.5) h] [10]. Compared to values obtained in patients with varying degrees of renal function, where $t_{1/2}$ and MRT values were 15 and 7 h in healthy subjects (mean creatinine clearance, $99\ ml \cdot min^{-1}$), 18 and 12 h in patients with mild renal insufficiency (mean creatinine clearance, $61\ ml \cdot min^{-1}$), 22 and 11 h in patients with moderate renal insufficiency (mean creatinine clearance, $32\ ml \cdot min^{-1}$), and 19 and 13 h in patients with severe renal insufficiency (mean creatinine clearance, $15\ ml \cdot min^{-1}$) [13], $t_{1/2}$ and MRT were similar among all patients with some degree of renal impairment. $t_{1/2}$ was similar, as well, to normal volunteers whereas the MRT values were approximately twice normal in all renally impaired patients.

The elimination of fosinoprilat by peritoneal dialysis was insignificant, averaging 2.0 (1.4) % of simultaneously determined peritoneal urea clearance. This result is not unexpected since the drug is highly protein bound (95–98%) and has a relatively high molecular weight (427 daltons) [2]. Peritoneal dialysis clearances are not available for enalapril or lisinopril but have been shown to be comparably low for captopril [14].

After a single dose of fosinopril sodium, ACE activity fell precipitously and remained low (> 90% inhibition) for at least 24 h. In the case of L. W., ACE activity remained low for at least 72 h, reflective of the diminished clearance of fosinoprilat. The prolonged inhibition of ACE activity in this study is consistent with detectable levels of fosinoprilat in serum up to 96 h post dose.

The relationship between serum ACE inhibitor concentrations and ACE activity has most often been described by a linear model or via %ACEI log transformation [7, 15, 16]. These models have severe shortcomings which have been previously described [17]. A more "physiologic", pharmacokinetic-pharmacodynamic model between fosinoprilat concentration and %ACEI is provided by the E_{max} model [8]. Although there was some variability in individual IC_{50} values for the five evaluable patients, the low values indicate that serum ACE activity is highly sensitive to the actions of the drug. The fact that serum fosinoprilat concentrations are much higher than the IC_{50} for prolonged periods following drug administration indicates that there may be additional factors which are operative in the blood pressure lowering effects of the drug.

Whereas CAPD patients have been reported to have relatively high basal unstimulated PRA and aldosterone concentrations [18, 19], basal levels of PRA and aldosterone concentration were normal in 3 of the 4 patients studied. As would be expected, PRA increased and plasma aldosterone concentrations decreased following the administration of fosinopril sodium. Though mean blood pressure trended downwards in 4 of the patients, mean blood pressure did not significantly decrease during the study. The one patient with a high baseline PRA value (J. M.) demonstrated the most significant drop in his mean blood pressure (113 to 76 mm Hg) which occurred at 8 h post dose. Without a placebo-treated group of patients, it is difficult to assess the single-dose antihypertensive effect of fosinopril sodium.

As with other ACE inhibitors, dose modifications based solely on the single-dose pharmacokinetic profile are difficult to discern since the concentration of drug in serum often does not correlate with the desired effect of blood pressure reduction [15, 20]. The modest pharmacokinetic alterations observed in these patients compared to populations without end stage renal disease, and the lack of adverse effects associated with this drug would suggest that initial dose modifications should not be necessary in most CAPD patients. Particular caution may be indicated in those dialysis patients with concomitant liver dysfunction.

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