Br. J. clin. Pharmac. (1988), **26**, 781–786

Pharmacokinetics of lisinopril, enalapril and enalaprilat in renal failure: effects of haemodialysis

J. G. KELLY[2], G. D. DOYLE[1], M. CARMODY[1], D. R. GLOVER[3] & W. D. COOPER[3]
[1]Department of Nephrology and Pathology, Beaumont Hospital, Dublin 9, [2]Institute of Biopharmaceutics, Athlone, Ireland and [3]Medical Department, Merck Sharp and Dohme, Hoddesdon, Hertfordshire

1 Lisinopril and enalapril were administered as 2.5 mg single doses and as eight single daily 2.5 mg doses to separate groups of six patients with chronic renal failure. Patients were receiving regular haemodialysis.
2 In the absence of haemodialysis, the decline in plasma concentrations of lisinopril and enalaprilat was extremely slow and plasma concentrations were generally high.
3 Haemodialysis had large effects on plasma concentrations of lisinopril and enalaprilat. A 4 h period reduced plasma concentrations of both drugs by around one-half and often by significantly more than this. Even 1 or 2 h of haemodialysis had significant effects.
4 Haemodialysis plasma clearance was similar for both drugs with mean values of the order of 40 ml min^{-1}. Clearance did not markedly differ when measured after 1, 2 or 4 h of haemodialysis or after single or multiple doses of lisinopril or enalapril.
5 The design of dosage regimens of both lisinopril and enalapril for patients with severe renal impairment or chronic renal failure should take into consideration the use and effects of haemodialysis.

Keywords haemodialysis renal failure lisinopril enalapril enalaprilat

Introduction

The angiotensin converting inhibitors, lisinopril and enalaprilat (the pharmacologically active diacid of enalapril) are primarily eliminated in the urine (Ulm *et al.*, 1982). We and others have previously reported their elimination to be reduced in renal impairment and particularly so in severe renal impairment, associated with glomerular filtration rates less than 30 ml min^{-1} (Kelly *et al.*, 1986, 1987; Sennesael & Verbeelen, 1986; Van Schaik *et al.*, 1987).

The pharmacokinetics of these agents in renal failure are also of interest since the absence of renal function would be expected to result in extremely slow clearances of the drugs. Such information would be necessary for the design of appropriate dosage regimens in people with severely impaired renal function. Since such patients may be receiving haemodialysis, it is also of importance to know the effects of haemodialysis upon concentrations of lisinopril and enalaprilat in blood.

The present study was performed to examine the plasma concentrations of lisinopril, enalapril and enalaprilat after administration of lisinopril or enalapril to patients with chronic renal failure who were receiving regular maintenance haemodialysis.

Methods

Subjects

Observations were made in two separate groups each comprising six patients with end-stage chronic renal failure, who were receiving regular maintenance haemodialysis. All gave informed consent and the study was approved by the Hospital Ethics Committee. Table 1 contains details of the patients studied.

Study procedures

The studies were divided into four periods; baseline, acute pharmacokinetics, chronic treatment, chronic pharmacokinetics.

Table 1 Details of subjects

Subject	Sex	Age (years)	Weight (kg)	Height (cm)	Creatinine clearance (ml min^{-1})
			Lisinopril		
TCu	M	57	64	168	4.5
JC	M	36	61	165	6.0
P DOY	F	30	58	155	2.8
TCa	F	43	63	158	4.0
LO'B	F	47	64	158	2.5
PR	M	59	69	165	1.7
			Enalapril		
JL	M	54	63	170	5.4
TW	M	19	65	167	0
P DON	M	50	70	169	3.6
LB	F	38	67	168	2.0
TB	M	21	64	167	5.2
TMF	F	43	48.5	163	3.8

Period 1 (Washout) Any antihypertensive medication was discontinued. This period lasted for 7 days and patients were monitored for any consequences of treatment withdrawal. Haemodialysis (4 h) was carried out on days 1, 3 and 5 as part of a routine schedule.

Period 2 (Acute pharmacokinetics) On period 2, day 1, patients received a light breakfast and haemodialysis was performed from 08.00–12.00 h. At 12.00 h, the lisinopril group received lisinopril 2.5 mg orally. Venous blood specimens were obtained before and at 2, 4, 6, 8,20, 24, 44, 45, 46, 48, 50, 72 and 92 h afterwards. At 12.00 h the enalapril group received enalapril 2.5 mg orally. Blood specimens were obtained before and at 2, 4, 6, 8, 20, 24, 44, 45, 46, 48, 50, 72 and 92 h afterwards. For both groups, the period 44–48 h was a haemodialysis period and 'arterial' blood (blood entering the machine) was sampled as well as 'venous' blood (blood leaving the machine). Haemodialysis was performed using a Gambro system (model AK10, Gambro AB, Lund, Sweden) operated at a flow rate of approximately 230 ml min^{-1}.

Period 3 (Chronic treatment) Patients were studied over an eight day period. On each day, the lisinopril group received lisinopril 2.5 mg at 12.00 h and the enalapril group received enalapril 2.5 mg at 12.00 h. Haemodialysis was performed in both groups, as part of a routine schedule on day 1, 3, 5 and 8.

Period 4 (Chronic pharmacokinetics) Following the last dose of lisinopril at 12.00 h on day 8 of period 3, venous blood specimens were obtained at 2, 4, 6, 8, 20, 24, 44, 45, 46, 52, 72, 92, 164 and 168 h. Times of sampling in the enalapril group were 2, 4, 6, 8, 20, 24, 44, 45, 46, 48, 52, 72, 92 and 164 h. Haemodialysis was performed in each group at 44–48 h, 92–96 h and at 164–168 h. In the 44–48 h period both pre- and post-dialyser specimens were obtained as before.

Blood specimens

Blood specimens (3 ml) were placed in heparinized bottles, the plasma separated by centrifugation and stored at −20°C until required for assay.

Assay procedures

Concentrations of lisinopril, enalapril and enalaprilat were measured by radioimmunoassay as described by Hichens *et al.* (1981). Enalapril was assayed as enalaprilat after conversion by enzymic hydrolysis using a crude rat liver homogenate preparation. The limit of assay was 0.4 ng ml^{-1} for lisinopril and enalaprilat and 0.8 ng ml^{-1} for enalapril. Typical values for inter-assay variability (coefficient of variation) were 7% at 10 ng ml^{-1} and 6% at 100 ng ml^{-1} of enalaprilat or lisinopril.

Calculations

Results are expressed as mean values ± s.e. mean. Comparative statistical tests are as des-

cribed in Results. Haemodialysis plasma clearance (CL_D) of lisinopril and enalaprilat was calculated from the formula:

$$CL_D = Q_P \quad \frac{C_A - C_V}{C_A}$$

where C_A and C_V are temporarily corresponding values of pre- and post- dialyser concentrations respectively and Qp is the pumping rate for plasma, calculated as the product of whole blood flow rate and fractional plasma volumes (1 – fractional haematocrit).

Results

Lisinopril group

Venous plasma concentrations of lisinopril following the first and final doses are shown in Figure 1. Following the first dose, plasma concentrations increased steadily to reach a maximum observed mean concentration at 24 h of 25.9 ± 5.5 ng ml^{-1}. The mean peak concentration was 29.7 ± 6.9 ng ml^{-1}, observed at between 8 and 44 h. The mean lisinopril concentration changed little between 24 and 44 h, falling to 23.5 ± 5.5 ng ml^{-1} (not significant, Student's *t*-test for paired data). The effects of haemodialysis were dramatic. This began at 44 h and after 1 h of dialysis the mean plasma concentration fell by 44% with an average fall of 35.4 ± 10.5%. At the end of the 4 h period of haemodialysis, the mean decrease in venous lisinopril concentrations was 50.5 ± 8.7%. A small 'rebound' in plasma concentrations was a common feature and this is evident in Figure 1. Pre- and post- dialyser concentrations were similar at the start of haemodialysis (25.2 ± 5.9 and 23.5 ± 5.5 ng ml^{-1} respectively, (no significant difference) but as dialysis progressed predialyser concentrations were consistently higher than post-dialyser concentrations and 4 h these values were 14.2 ± 2.8 and 10.2 ± 2.1 ng ml^{-1} respectively ($P < 0.01$).

Pre-dose lisinopril plasma concentrations during chronic administration are shown in Table 2. The last column in Table 2 represents predialysis values before the final dose. The final dose was administered after this haemodialysis period and concentrations had fallen to 52.8 ±

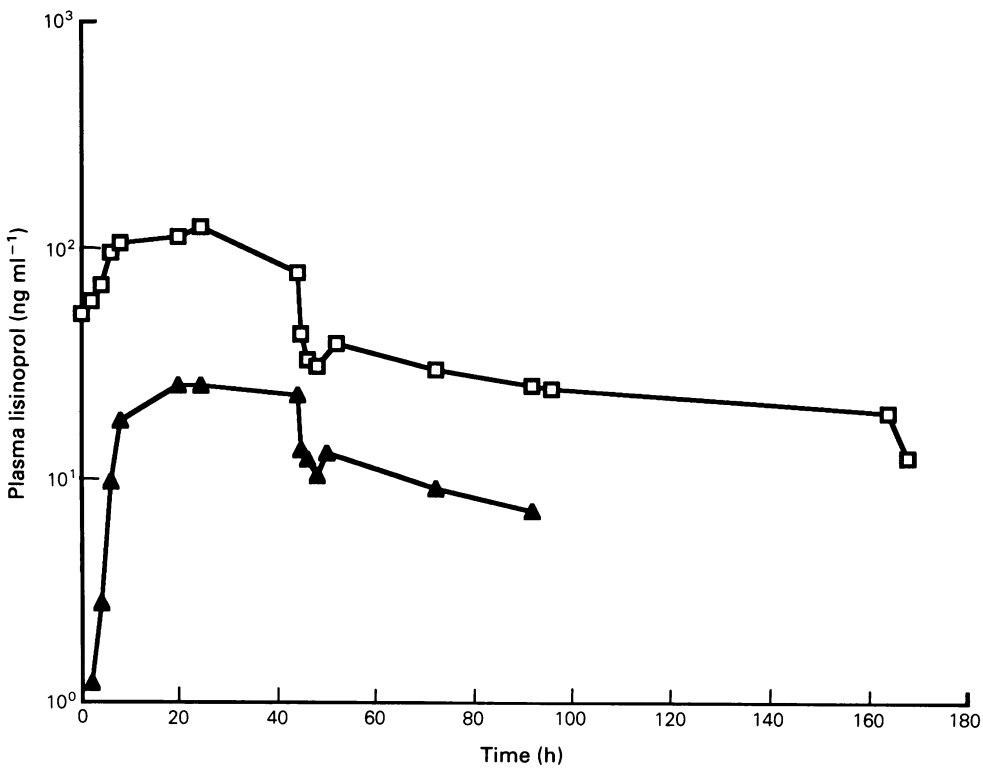

Figure 1 Plasma concentrations of lisinopril (ng ml^{-1}) following the first (▲) and final (□) doses. Note the effects of haemodialysis at 44–48 h.

Table 2 Pre-dose concentrations of lisinopril (ng ml^{-1}). Specimens were obtained at 08.00 h and were followed by 4 h haemodialysis. Lisinopril was administered at 12.00 h immediately following haemodialysis

	Time (days)			
Subject	*1*	*3*	*5*	*8*
TCu	12	250	300	120
JC	3.9	26	60	76
PD	4.0	52	63	63
TCa	6.2	85	173	195
LO'R	1.9	56	135	130
PR	1.5	28	30	41
Mean	4.9	82.8	126.8	104.2
s.d.	3.9	84.7	100.1	55.9
s.e. mean	4.9	34.6	40.9	22.8

Table 3 Lisinopril, mean haemodialysis plasma clearance (ml min^{-1})

	Time (h)		
	1	*2*	*4*
First dose	39.9 ± 7.5	46.6 ± 6.0	47.7 ± 5.6
Last dose	55.4 ± 11.7	40.2 ± 11.6	34.4 ± 3.7

10.6 ng ml^{-1}. Following the final dose, the maximum mean concentration of lisinopril was 126 ± 26.1 ng ml^{-1} at 24 h. The mean peak concentration was 144.7 ± 32.1 ng ml^{-1} observed as for the first dose at between 8 and 44 h. A 4 h period of haemodialysis at 44–48 h was associated with a mean fall of 60.8 ± 5.8% in venous lisinopril concentrations. Pre- and post- dialyser concentrations of lisinopril were respectively 80.5 ± 20.1 and 80.0 ± 20.1 ng ml^{-1} (NS) at the start of haemodialysis and respectively 39.3 ± 9.5 and 30.7 ± 7.0 ng ml^{-1} ($P < 0.05$) at the end of haemodialysis.

Table 3 shows the mean values of haemodialysis plasma clearance for lisinopril at 1, 2 and 4 h after both single and multiple administration of lisinopril. Clearance showed no relationship to the duration of dialysis or to the initial plasma lisinopril concentrations. Values of clearance were not significantly different between single and multiple lisinopril administration.

Enalapril group

Figure 2 shows mean venous plasma concentrations of enalaprilat following the first and final doses of enalapril. Concentrations of enalaprilat

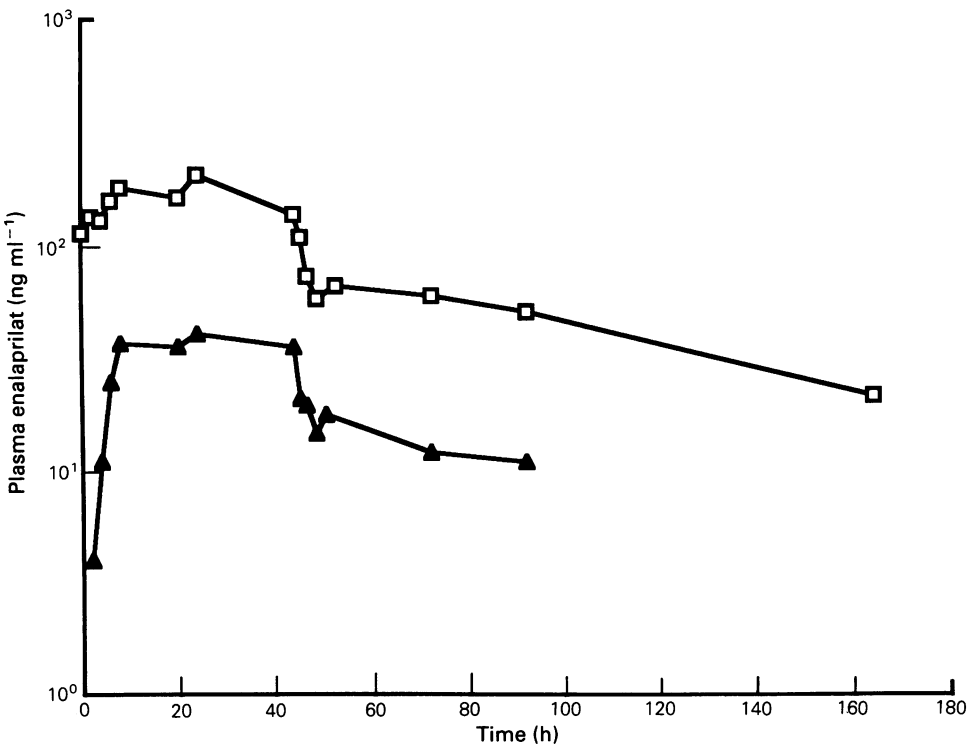

Figure 2 Plasma concentrations of enalaprilat (ng ml^{-1}) following the first (▲) and final (□) doses of enalapril. Note the effects of haemodialysis at 44–48 h.

following administration of 2.5 mg enalapril tended to be greater than concentrations of lisinopril following the same dose. Following the first dose, plasma concentrations of enalaprilat increased slowly with a maximum mean concentration of 41.3 ± 8.6 ng ml^{-1} observed at 24 h. The mean peak concentration was 48.2 ± 7.7 ng ml^{-1} observed, as with lisinopril, at between 8 and 44 h. Haemodialysis also had prompt and significant effects on plasma enalaprilat concentrations. After 1 h the mean enalaprilat concentration fell by 39% with an average fall of 38.0 ± 4.8%. At the end of haemodialysis the mean decrease was 57.0 ± 7.2%. A small 'rebound' after haemodialysis was also a feature of enalaprilat. Mean pre- and post- dialyser concentrations of enalaprilat just before haemodialysis were 35.0 ± 6.9 ng ml^{-1} and 35.0 ± 6.5 ng ml^{-1} respectively (NS), falling to 19.3 ± 2.9 and 15.0 ± 3.0 ng ml^{-1} respectively ($P < 0.05$).

Table 4 shows pre-dose plasma enalaprilat concentrations during chronic administration. As before, the last column is the pre-dialysis value on the morning of the last dose. After 4 h dialysis, this had fallen to 113 ± 27 ng ml^{-1}. Figure 2 shows mean plasma enalaprilat concentrations following the final dose of enalapril. The maximum mean concentration was observed at 24 h was 208.0 ± 63.9 ng ml^{-1} with a mean peak concentration of 223.7 ± 62.1 ng ml^{-1} observed at 6–44 h. Plasma concentrations of enalaprilat fell by an average of 45.7 ± 11.5% over the 4 h haemodialysis period carried out at 44–48 h. Pre- and post- dialyser concentrations were 146.8 ± 36.1 and 135.5 ± 36.2 ng ml^{-1} at the start of haemodialysis (NS) and were 89.2 ± 20.3 and 64.3 ± 11.8 ng ml^{-1} respectively at the end of haemodialysis ($P < 0.05$).

In Table 5 are shown the mean values of haemodialysis plasma clearance for enalaprilat following single and multiple doses of enalapril. While values of clearance tended to be a little lower than for lisinopril, there were no significant differences at any time. As for lisinopril there was no suggestion of variations in clearance with haemodialysis time or with single or multiple drug administration.

Mean plasma concentrations of enalapril reached a peak of 24.7 ± 8.3 ng ml^{-1} following the first dose and initially declined rapidly to 8.2 ± 3.3 ng ml^{-1} at 8 h. In one subject, enalapril was still measurable at 44 h, in a further two it was measurable at 20 h and in the remainder was not measurable after 8 h. Following the final dose, the maximum mean enalapril concentration was 51.2 ng ml^{-1} at 6 h but was not present in measurable quantities at 20 h. It was not possible to draw any conclusions about haemodialysis plasma clearance of enalapril.

Table 4 Pre-dose concentrations of enalaprilat (ng ml^{-1}) Conditions as in Table 2

	Time (days)			
Subject	*1*	*3*	*5*	*8*
JL	6.2	84.0	144.0	170.0
TW	2.7	100.0	134.0	161.0
P DON	2.1	49.0	47.0	77.0
LB	23.0	20.0	184.0	171.0
TB	4.2	72.0	158.0	252.0
TMF	5.1	78.0	96.0	101.0
Mean	7.2	67.2	127.2	155.3
s.d.	7.9	28.5	48.8	61.5
s.e. mean	7.2	11.6	19.9	25.1

Table 5 Enalaprilat, mean haemodialysis plasma clearance (ml min^{-1})

	Time (h)		
	1	*2*	*4*
First dose	49.4 ± 6.1	35.7 ± 5.4	42.0 ± 13.0
Last dose	28.9 ± 7.5	38.8 ± 6.7	38.8 ± 12.4

Discussion

The elimination rate of both lisinopril and enalaprilat is markedly reduced in renal failure. Also, times-to-peak of both substances appear to be long, often observed at 24 h. This is consistent with our earlier findings (Kelly *et al.*, 1986, 1987) of times-to-peak which increase with progressive renal impairment. It is of interest that times-to-peak appear to be similarly influenced by renal failure for both lisinopril and enalaprilat, even though enalaprilat is formed by esterolytic cleavage of enalapril. There is no obvious explanation for this finding at present.

In the absence of haemodialysis, it is apparent that the elimination rate of both lisinopril and enalaprilat would be extremely slow. Inspection of Figures 1 and 2 suggests that without haemodialysis, it would require several days for plasma concentrations of either drug to fall by one-half.

However haemodialysis had dramatic effects on plasma concentrations of both lisinopril and enalaprilat. A 1 h period of haemodialysis is capable of reducing significantly plasma concentrations of either drug. At the end of a 4 h period of haemodialysis, administered following a single 2.5 mg dose of either lisinopril or enalaprilat, venous plasma concentrations of lisinopril and enalaprilat were on average, only 49.7%

and 43.0% respectively of the pre-dialysis values.

Our findings with enalaprilat confirm and add to those of Lowenthal and colleagues (1985) who showed substantially smaller values of areas under the plasma concentration-time curves (AUC 0–6 h) when patients received haemodialysis from 1 to 5 h after a dose of enalapril. In the 2 h following cessation of haemodialysis, there was characteristically a small 'rebound' in plasma concentrations of both drugs, but the mechanism of this is unclear.

Values of haemodialysis plasma clearance were calculated from a knowledge of haematocrit, dialyser flow rate and pre- and post- dialyser concentrations of the drugs. Values tended to be a little lower for enalaprilat but differences were not significant. Values of clearance were quite consistent over the 4 h periods of haemodialysis and did not differ between single and multiple dosing.

Plasma concentrations of enalaprilat tended to be higher than those of lisinopril although doses of lisinopril and enalapril were the same, in agreement with previous findings of lower absorption of lisinopril than enalapril in normal volunteers (Ulm *et al.*, 1982). However it should be remembered that these were different groups and the numbers in each group (6) were quite small. Plasma concentrations of enalapril, the prodrug of enalaprilat, did not show any tendency to accumulate, suggesting that the metabolic conversion process to the diacid was unimpaired in these patients. As a rule, there was no measurable enalapril present at the start of haemodialysis, so that its haemodialysis plasma clearance could not be established.

In conclusion, administration of 2.5 mg daily of lisinopril or enalapril, produces high concentrations of lisinopril or enalaprilat in renal failure. These high concentrations are markedly reduced by haemodialysis. The design of dosage regimens for patients with severe renal impairment or chronic renal failure should take into consideration the use and effects of haemodialysis.

References

Hitchens, M., Hand, E. L. & Mulcahy, W. S. (1981). Radio-immunoassay for angiotensin converting enzyme inhibitors. *Ligand Quarterly*, **4**, 43.

Kelly, J. G., Doyle, G., Donohue, J., Laher, M., Vandenburg, M. J., Currie, W. J. C. & Cooper, W. D. (1986). Pharmacokinetics of enalapril in normal subjects and patients with renal impairment. *Br. J. clin. Pharmac.*, **21**, 63–69.

Kelly, J. G., Doyle, G., Donohue, J., Laher, M., Long, C., Glover, D. G. & Cooper, W. D. (1987). Acute and chronic dose pharmacokinetics of lisinopril: effects of renal impairment. *Br. J. clin. Pharmac.*, **23**, 629–630.

Lowenthal, D. T., Irvin, J. D., Merrill, D., Saris, S., Ulm, E., Goldstein, S., Hichens, M. M., Klein, L., Till, A. & Harris, K. (1985). The effect of renal function on enalapril kinetics. *Clin. Pharmac. Ther.*, **38**, 661–666.

Sennesael, J. & Verbeelen, D. (1986). Intra-individual comparison of captopril and enalapril in patients undergoing regular haemodialysis. *Eur. J. clin. Pharmac.*, **30**, 257–262.

Ulm, E. H. J., Hichens, M., Gomez, H. J., Till, A. E., Hand, E., Vassil, T. C., Biollaz, J., Brunner, H. R. & Schelling, J. L. (1982). Enalapril maleate and a lysine analogue (MK-521); disposition in man. *Br. J. clin. Pharmac.*, **14**, 357–362.

Van Schaik, B. A. M., Geyskes, G. G. & Boer, P. (1987). Lisinopril in hypertensive patients with and without renal failure. *Eur. J. clin. Pharmac.*, **32**, 11–16.

(Received 26 January 1988, accepted 26 July 1988)