Br. J. clin. Pharmac. (1986), **21**, 63–69

Pharmacokinetics of enalapril in normal subjects and patients with renal impairment

J. G. KELLY[1], G. DOYLE, J. DONOHUE, M. LAHER, M. J. VANDENBURG[2], W. J. C. CURRIE[2] & W. D. COOPER[2]

Departments of Nephrology and Pathology, Jervis Street Hospital, Dublin, [1]Institute of Biopharmaceutics, Athlone, Ireland and [2]Medical Department, Merck Sharp and Dohme, Hoddesdon, Hertfordshire

1 The pharmacokinetics of enalaprilat were studied after administration of single and multiple doses of enalapril maleate to people with normal and impaired renal function.

2 Renal impairment was associated with higher serum concentrations of enalaprilat, longer times to peak concentrations, slower decline of serum concentrations and with reduced urinary elimination. Urinary elimination of enalaprilat was closely related to renal function.

3 In patients with severe renal impairment (GFR values below 30 ml min^{-1} 1.73 m^{-2}) significantly smaller doses of enalapril maleate will be required than in patients with normal or less severely impaired renal function.

Keywords enalapril renal impairment pharmacokinetics

Introduction

Enalapril, (*N*-[(s)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline), is approximately 60% absorbed after oral administration (as enalapril maleate) but is not of itself a particularly potent angiotensin converting enzyme inhibitor (Patchett *et al.*, 1980; Gross *et al.*, 1981; Ulm *et al.*, 1982). *In vivo* hydrolysis in the liver, however, results in production of the poorly absorbed but much more potent diacid, enalaprilat (*N*-[(S)-1-carboxy-3-phenylpropyl]-1-alanyl-L-proline), (Gross *et al.*, 1981; Tocco *et al.*, 1982). A significant proportion of the enalaprilat formed (43%) is eliminated in the urine (Ulm *et al.*, 1982).

Angiotensin converting enzyme inhibitor drugs may be considered for use in people with hypertension of renal origin or hypertension in the presence of renal impairment. Therefore it is important to examine the pharmacokinetics of orally administered enalapril after both single and multiple doses, especially in people with severely diminished renal function. This paper reports the results of two studies examining the effects of renal dysfunction on the formation and elimination of enalaprilat after the oral administration of enalapril maleate. In the first study, single doses of enalapril maleate were administered to people with varying degrees of renal function. In the second study, enalapril maleate was administered daily for 7 days to a group of healthy people and to a group with poor renal function.

Methods

Each study was approved by the Hospital Ethics Committee and all participants gave informed consent.

Single dose study

Twenty-four subjects aged 19 to 70 years, with varying degrees of renal function were studied. Six subjects were chosen to fill each of four groups, based on ^{Cr}51-EDTA determined

Correspondence: Dr J. G. Kelly, Institute of Biopharmaceutics, Athlone, Ireland

glomerular filtration rate (GFR). The first group (Group 1) comprised six healthy volunteers with GFR values greater than 100 ml min^{-1} 1.73 m^{-2}. The remaining groups were chosen from patients with various degrees of renal dysfunction as follows:
Group 2: GFR 31–80 ml min^{-1} 1.73 m^{-2}.
Group 3: GFR 10–30 ml min^{-1} 1.73 m^{-2}.
Group 4: GFR less than 10 ml min^{-1} 1.73 m^{-2}.
Individual details are presented in Table 1. Subjects were hospitalised during the study. On the first morning of the study, subjects were fasting. Upon rising, each subject emptied his bladder and consumed 150 ml water. Enalapril maleate 10 mg was administered at 08.00 h, accompanied by 250 ml water. Each subject drank 150 ml water hourly for the next 4 h and freely thereafter. A standard light meal was allowed at 2 h after drug administration and lunch provided 2 h after this. Subjects then resumed their normal diets.

Blood specimens (5–10 ml) were obtained before and at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after drug administration. The serum was separated and stored at −20°C prior to analysis for enalaprilat. Urine specimens for determination of enalaprilat concentrations were collected over the following time periods after dose: 0–2, 2–4, 4–6, 6–8, 8–12, 12–24 and 24–28 h. The volumes were measured and aliquots again stored at −20°C.

Table 1 Details of subjects in the single dose study

Subject	*Age (years)*	*Sex*	*Clinical details*	*GFR (ml min^{-1} 1.73^{-2})*	*Peak enalaprilat concentration (ng ml^{-1})*	*Time to-peak (h)*	*48 h urinary elimination (mg)*
1	21	F	Normal volunteers	103	69	4	3.1
2	22	F		124	65	4	3.7
3	23	F		103	50	5	2.3
4	21	M		120	31	4	2.7
5	23	M		118	50	4	2.3
6	23	M		126	36	4	0.9
7	39	F	Chronic pyelonephritis (CP)	72	23	6	0.5
8	32	M	Focal sclerosing glomerulonephritis	88	30	5	1.4
9	47	F	Primary hyperparathyroidism	54	96	6	2.1
10	36	F	CP	77	88	6	2.1
11	70	F	Cerebral haemorrhage, angina	45	81	5	1.4
12	59	M	Ischaemic heart disease	58	33	6	1.2
13	67	M	Thrombophlebitis	20	61	10	1.6
14	59	M	Angina, DVT	30	12	6	0.7
15	69	M	Ulcerative colitis, ileostomy, intestinal fistula	21	55	10	0.6
16	40	M	Chronic renal failure	29	30	8	1.0
17	45	M	Nephrotic syndrome	29	101	6	3.7
18	46	M	Ulcerative colitis, ileostomy, focal sclerosing GN	20	134	24	1.5
19	37		Diabetes mellitus	5	131	12	0.7
20	26		CP	7	58	10	0.4
21	65	M	Angina, prostatic hypertrophy	8	214	12	0.6
22	47	M	Aortic valve disease, end stage renal disease (ESRD)	9	135	12	0.5
23	19	M	CP, ESRD	10	201	10	1.1
24	42	M	Chronic glomerulonephritis, ESRD	8	152	10	1.2

Multiple dose study

Observations were made in two groups, each composed of six subjects.

Group 1 was a group of healthy volunteers with values of GFR in excess of 100 ml min^{-1} 1.73 m^{-2}. These subjects received enalapril maleate as a single 10 mg dose on each of seven successive mornings. On each morning, blood specimens (5 ml) were obtained before and at 4 h after this dose. The 4 h specimen was chosen to reflect the time of peak concentrations in this group, as determined in the single dose study. After the last dose of enalapril maleate, blood specimens were obtained at 4, 12, 24, 36 and 48 h for estimation of serum enalaprilat concentrations. The serum was again stored at −20°C until required for assay.

Group 2 was a group of people having severely impaired renal function (Table 2) with values of GFR no greater than 28 ml min^{-1} 1.73 m^{-2}. None had a requirement for dialysis. Each person received enalapril maleate as a single 2.5 mg dose every morning for 7 days. Selection of this dose was based on the finding in the single dose study that the mean 48 h urinary recovery of enalapril in group 4 was approximately one quarter of that in group 1 (see **Results**). On each morning, blood specimens were obtained before and at 9 h following administration of enalaprilat maleate. The time of 9 h was chosen as a reflection of the later time-to-peak enalaprilat concentrations in this group (see results of single dose study). Following the last dose of enalapril maleate, blood specimens were obtained at 9, 24, 33, 48, 57, 72, 96, 120, 144 and 168 h. These were processed and stored as before.

Assay of enalaprilat

Concentration of enalaprilat in serum (10 μl aliquots) and in urine (10 μl aliquots following appropriate dilution) were measured by radioimmunoassay (Hichens *et al.*, 1981). This assay is insensitive to enalapril. The useful working range of the assay is from 0.3 ng ml^{-1} to 200 ng ml^{-1} in serum and from 30 ng ml^{-1} to 20 μg ml^{-1} in urine. The inter-assay coefficient of variation was 5.9% and the intra-assay coefficient of variation was 7.2% (at a serum enalaprilat concentration of 10.2 ng ml^{-1}). Where the concentration of enalaprilat in a specimen approached or exceeded the upper limits of sensitivity, it was diluted and reassayed.

Results

Single dose study

No subject experienced any adverse effects during the course of this study or the multiple dose study. Figure 1 shows the mean serum concentrations of enalaprilat observed in the four groups at various times following administration of enalapril. It is apparent from this that progressive renal dysfunction is associated with slower elimination and prolonged high concentrations of enalaprilat. The post-peak serum concentration time profile of enalaprilat in healthy subjects was not log-linear.

Peak serum enalaprilat concentrations increased with decreasing renal function (Table 1). There was a significant inverse relationship between GFR and peak serum concentrations (Spearman's rho = 0.562, $t = 3.19$, $P < 0.02$). In Figure 2, 24 h serum enalaprilat concentrations

Table 2 Details of the patients (group 2) in the multiple dose study.

Subject	*Age (years)*	*Sex*	*Clinical details*	*GFR (ml min^{-1} 1.73 m^{-2})*
1	19	F	Rheumatoid arthritis/renal amlydoidis	8
2	28	M	Glomerulonephritis/ESRD/ chronic rejection of transplant kidney	7
3	40	M	Hypertension/chronic renal failure	14
4	52	F	Polycystic kidneys	15
5	63	M	Hypertension/chronic renal failure	28
6	69	F	Interstitial nephritis	7

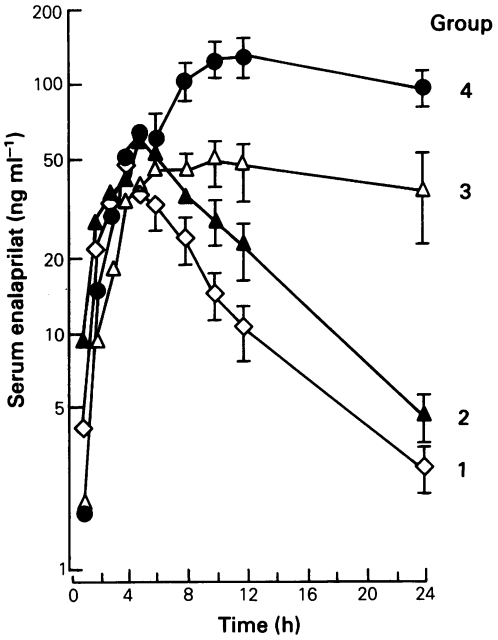

Figure 1 Mean serum concentrations of enalaprilat in the four groups. (Group 1 GFR > 100 ml min^{-1} 1.73 m^{-2}, Group 2 GFR 31–80 ml min^{-1} 1.73 m^{-2}, Group 3 GFR 10–30 ml min^{-1} 1.73 m^{-2} and Group 4 GFR < 10 ml min^{-1} 1.73 m^{-2}).

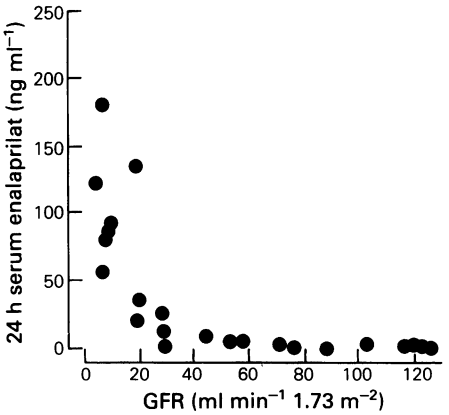

Figure 2 Relationship between 24 h serum enalaprilat concentrations and glomerular filtration rate.

are plotted against GFR. There is an obvious 'threshold' effect where GFR values of less than 20–30 ml min^{-1} 1.73 m^{-2} are associated with markedly increased serum concentrations. At 24 h, all subjects in groups 1 and 2 had serum enalaprilat concentrations of less than 10 ng ml^{-1} whereas in group 4 the lowest 24 h concentration was 55 ng $ml.^{-1}$

The time required to reach peak serum concentrations of enalaprilat was also related to renal function (Table 1). In people with GFR values greater than 40 ml min^{-1} 1.73 m^{-2}, peak concentrations were typically observed at 4–5 h. Below this value the time-to-peak increased and in group 4, times-to-peak were 10 h or greater. Mean cumulative urinary elimination of enalaprilat for the four groups is presented in Figure 3. Decreasing degrees of renal function were associated with decreasing urinary elimination of enalaprilat. Thus the mean 48 h elimination of enalaprilat in group 1 was 2485 μg (approximately 35% of the dose of enalapril base) and this fell to 704 μg in group 4. There was a significant linear relationship between cumulative urinary elimination of enalaprilat and GFR (Figure 4; 48 h cumulative urinary elimination, mg = 0.807 + 0.0135 GFR; $r = 0.58$; $P < 0.01$).

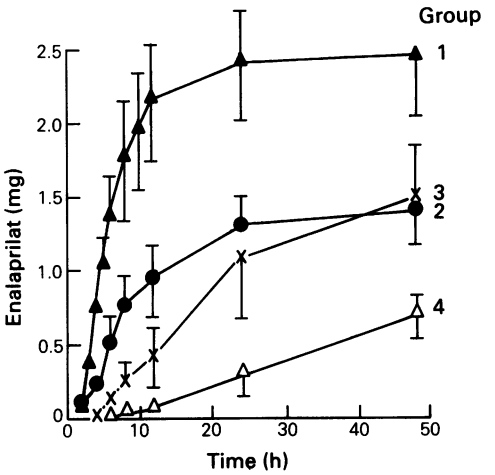

Figure 3 Mean cumulative urinary elimination of enalaprilat in the four groups. (Group 1 GFR > 100 ml min^{-1} 1.73 m^{-2}, Group 2 GFR 31–80 ml min^{-1} 1.73m^{-2}, Group 3 GFR 10–30 ml min^{-1} 1.73 m^{-2} and Group 4 GFR < 10 ml min^{-1} 1.73 m^{-2}).

Multiple dose study

Mean serum concentrations of enalaprilat in groups 1 and 2 after 10 mg and 2.5 mg respectively of enalapril maleate are illustrated in Figure 5. The graph shows mean peak and trough concentrations and concentrations following the final dose of enalapril maleate. There were considerable differences in serum enalaprilat concentrations between the two groups. The mean predose concentrations of enalaprilat prior to the final dose was 8.3 ± 3.2 ng ml^{-1} (s.e. mean) with a range of 1.6–22 ng ml^{-1} in group 1 and was

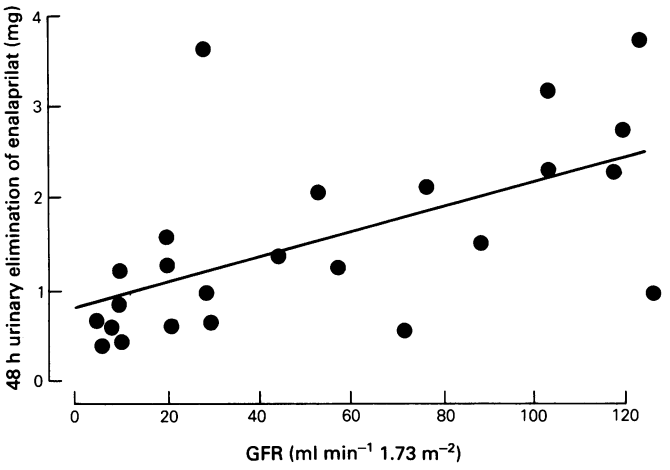

Figure 4 Graph of urinary elimination of enalaprilat *vs* glomerular filtration rate. The line is the line of best fit (see text).

89.5 ± 25.8 ng ml^{-1} with a range of 9.8–160 ng ml^{-1} in group 2. Mean observed peak enalaprilat concentrations following this final dose were 50.5 ± 4.0 ng ml^{-1} (range 35–59 ng ml^{-1}) in group 1 and 120.0 ± 26.3 ng ml^{-1} (range 25–185 ng ml^{-1}) in group 2. Figure 6 shows the individual pre- and post-dose concentrations of enalaprilat for all six subjects in group 2. Three subjects had GFR values less than 10 ml min^{-1} 1.73 m^{-2}. These three subjects had enalaprilat concentrations following the last dose of enalapril maleate of 160 ng ml^{-1} or greater and their serum enalaprilat concentrations were consistently higher than in the other three. The remaining three had concentrations of 115 ng ml^{-1} or less. The subject with highest value of GFR had much the lowest serum enalaprilat concentrations.

In Figure 7, the mean results for serum enalaprilat concentrations following the final dose are plotted (log scale) against time. This shows the substantially slower elimination of enalaprilat in the people with renal impairment. In the subjects with normal renal function, the serum concentration 24 h after the last dose was below 10 ng ml^{-1} while in the people with renal impairment, a mean concentration of close to 10 ng ml^{-1} was reached only at 168 h after the last dose.

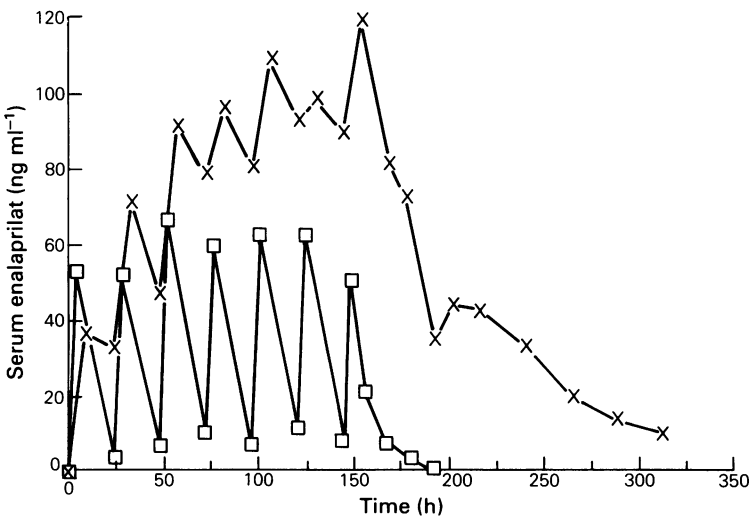

Figure 5 Mean serum concentration of enalaprilat (log-scale) in the two groups (□. Group 1 GFR > 100 ml min^{-1} 1.73 m^{-2}, × Group 2 GFR < 29 ml min^{-1} 1.73 m^{-2}).

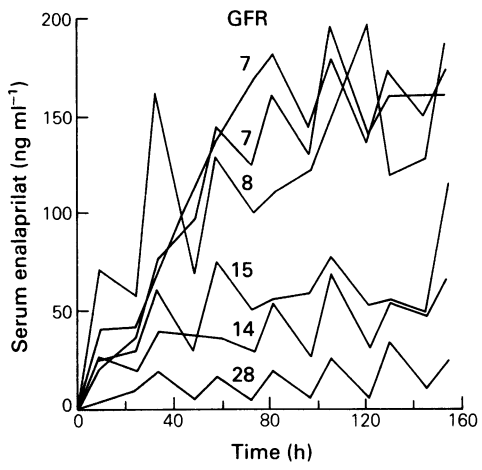

Figure 6 Pre- and post-dose concentrations of enalaprilat in the six renally impaired subjects from the multiple dose study. Values of GFR (in ml min^{-1} 1.73 m^{-2}) are indicated.

Discussion

The majority of enalaprilat formed after the administration of enalapril to man is eliminated unchanged in the urine (Ulm *et al.*, 1982). The pharmacokinetic profile of this enalaprilat correlates with renal function in a reasonably predictable manner. In particular, there is a good relationship between renal function, assessed by measurement of glomerular filtration rate, and cumulative renal elimination of the drug. In the single dose study, the group with the most severe renal impairment (Group 4), demonstrated a reduction in the cumulative 48 h renal elimination of enalapril to a figure approaching one-quarter of that seen in healthy individuals. It was for this reason that a dose of 2.5 mg daily was chosen for the renally impaired people in the multiple dose study. In more moderate renal impairment, such as might be encountered in elderly people, the urinary elimination was approximately halved (Ewy *et al.*, 1969; O'Malley *et al.*, 1980). While these pharmacokinetic characteristics are those which one might expect, based on previous studies on renal elimination of drugs, there is one important difference between drugs previously studied and the present one. Enalaprilat is formed by hepatic esterolysis of enalapril (which is, in effect, a prodrug). Enalapril itself is, however, to some extent (approximately 18%) eliminated unchanged in the urine and a significant fraction of this appears in the urine collected early after the dose (Ulm *et al.*, 1982). All of these factors must be taken into account when interpreting the present results.

Impaired renal elimination of enalapril will result in the presence of larger amounts of this substance for a longer time with a resulting increased amount of enalaprilat formed (assuming no impairment of the relevant metabolic process by disease). Impaired renal elimination of enalaprilat will add to this process, resulting in further elevations in serum enalaprilat concentrations. The net result is seen not only in prolonged high serum concentrations of enalaprilat in severe renal impairment but also in a progressive

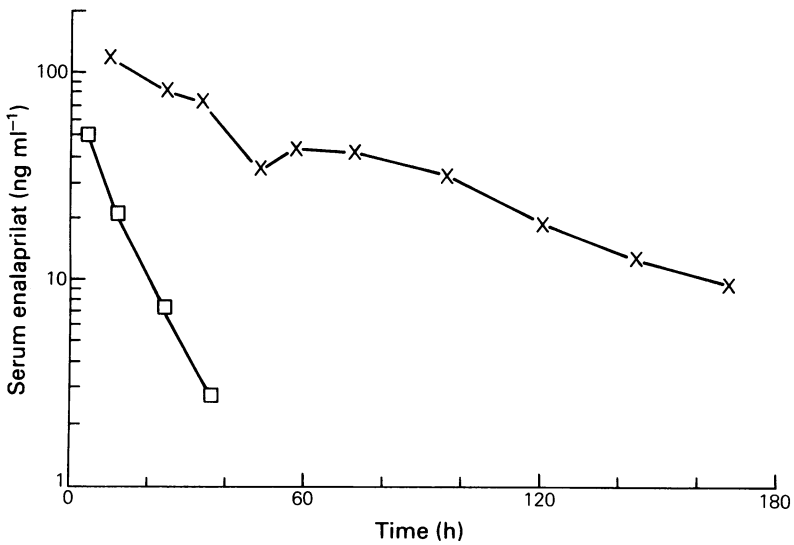

Figure 7 Mean serum concentrations of enalaprilat (log-scale) following the final dose of enalaprilat maleate in the multiple-dose study.

increase in time-to-peak serum concentrations as GFR falls. The role of alterations in other pharmacokinetic parameters, especially in changes in volumes of distribution with renal disease are potentially also important but would require further studies to be performed.

Serum concentrations of enalaprilat were significantly higher after both single and multiple dose administration of enalapril maleate to people with severe renal impairment. In the multiple dose study this was the case even though these people received only 2.5 mg of enalapril maleate daily, one quarter of the dose given to the healthy subjects. The decline in serum concentrations of enalaprilat was also much slower in renal impairment and this is particularly clearly seen in Figure 7 where the average time for serum enalaprilat concentrations to decline to half their estimated peak was approximately 7 h for the healthy group and 35 h for the renally impaired group.

Ulm *et al.* (1982) have suggested the existence of a prolonged terminal phase of elimination resulting from the drug binding to angiotensin converting enzyme in blood. The extent of this would relate to amounts of the enzyme in blood and would not reflect the dose of the drug (Till *et al.*, 1984). The effects of this component on serum enalaprilat concentrations is only readily apparent at low concentrations (less than 1–2 ng ml^{-1}).

The results described here have clear implications in respect of the use of enalaprilat in renal impairment. Decreased renal function is associated with increased serum concentrations of enalaprilat, increased time-to-peak concentrations, slower declines in serum concentrations and with decreased urinary elimination of the drug. This will result in decreased dosage requirements of enalapril maleate. Minimal dosage alteration would appear necessary until GFR values fall below 30–40 ml min^{-1} 1.73 m^{-2}. GFR values of 30 ml min^{-1} 1.73 m^{-2} and less however, represent conditions where handling of enalaprilat changes rapidly. It is for these values and certainly for values below 10 ml min^{-1} 1.73 m^{-2} that dosage reduction should be considered to avoid administration of amounts of drug in excess of that required for therapeutic effects.

We are grateful to Dr Alice Till and Dr. Martin Hichens of Merck Sharp and Dohme Research Laboratories, Westpoint, PA. U.S.A. for helpful discussions.

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(Received 15 July 1985, accepted 10 September 1985)