

The pharmacokinetics of enalapril in hospitalized patients with congestive heart failure

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1 The pharmacokinetics of the converting enzyme inhibitor, enalapril, were studied in an open, randomized, balanced crossover design in 12 hospitalized patients with stable, chronic congestive heart failure (CHF). Enalapril maleate is a prodrug requiring *in vivo* hepatic esterolysis to yield the active diacid inhibitor enalaprilat.

2 CHF results in changes in regional blood flow that may affect the gastrointestinal absorption, hepatic hydrolysis and renal excretion of enalapril and enalaprilat.

3 In order to evaluate the pharmacokinetics of enalapril in CHF, the following treatments were given: enalapril maleate 10 mg orally, enalapril maleate 5 mg intravenously and enalaprilat 5 mg intravenously. Each dose was followed by a 72 h period with frequent blood sampling and fractionated urine collection for the radioimmunoassay of enalaprilat, before and after sample hydrolysis.

4 Mean absorption for the oral dose was 69%, hydrolysis 55%, bioavailability 38%, urinary recovery 77% and estimated first-pass effect 10%.

5 The results were compared with available data in normal subjects. After oral administration of 10 mg enalapril maleate, the extent of absorption, the degree of hydrolysis and the bioavailability in CHF patients appear to be similar to those in normals with differences less than 10%. The rate of absorption and hydrolysis appear to be slightly slower in CHF. The serum concentrations of enalaprilat were consistently greater in CHF and maximal concentrations were reached at 6 h in CHF as compared to 4 h in normal subjects.

6 We conclude that the presence of CHF does not appreciably alter the pharmacokinetic behaviour of enalapril. The observed differences may be associated with age as well as the disease state.

Keywords pharmacokinetics congestive heart failure converting enzyme inhibitors enalapril enalaprilat

Introduction

Inhibition of the renin–angiotensin–aldosterone system via blockade of angiotensin converting enzyme has been shown to be of value in reducing both left ventricular filling pressure and

impedance to left ventricular ejection in patients suffering from congestive heart failure (CHF) (Abrams, 1985; Dollery, 1985; Editorial, 1985). The angiotensin converting enzyme inhibitor,

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enalapril maleate, has been the subject of extensive clinical study and appears to be both efficacious and well tolerated (Gomez *et al.*, 1985; Moncloa *et al.*, 1985). The orally administered agent is absorbed as prodrug, enalapril, requiring *in vivo* esterolysis to yield the active diacid inhibitor enalaprilat.

Information is available concerning the absorption, metabolism and elimination of this compound as administered to normal healthy volunteers (Ulm *et al.*, 1982, 1983; Till *et al.*, 1984; Irvin *et al.*, 1984). Absorption of drug is approximately 60% of the administered dose; the bioavailability of the active species (enalaprilat) is approximately 40% of the dose administered. Metabolism other than conversion of enalapril to enalaprilat is not observed in man. Excretion of enalapril and enalaprilat is primarily renal. The pathophysiology involved in congestive heart failure may cause changes in regional blood flow and organ function as a result of decreased perfusion and congestion. Specifically, alterations in gastrointestinal, hepatic and renal function might be expected to affect the absorption, hydrolysis and elimination of the prodrug enalapril.

The primary objectives of this study were to provide information in patients with CHF concerning the absorption of enalapril, the extent of hydrolysis to enalaprilat and thereby determine the bioavailability of enalaprilat from enalapril maleate. In addition, serum drug profiles and the rate and degree of urinary recovery of both enalapril and enalaprilat following administration of oral enalapril maleate, intravenous enalapril maleate and intravenous enalaprilat were determined.

Methods

Patient population

Twelve male patients with chronic CHF were included in the study. The mean age was 66 years (range 52 to 74). The aetiology of heart failure was ischaemic heart disease in 10 patients and dilated cardiomyopathy in two patients. All patients had been stabilized for at least 3 months on digitalis and diuretic therapy and no patients with an acute myocardial infarction during the preceding 6 months were included in the study.

Three patients were considered to be in N.Y.H.A. Functional Class II, six patients in Class III and three patients in Class IV. All patients showed cardiomegaly on biplane chest X-ray with a cardiothoracic ratio exceeding 50% together with radiographic evidence of pul-

monary congestion. Two dimensional echocardiographic and Doppler studies were performed for diagnostic purposes and to exclude valvular stenosis. All patients showed left ventricular dilatation with end-diastolic diameters exceeding 60 mm. The study protocol was approved by both the Norwegian State Drug Regulatory Agency and the Hospital Ethics Committee. Informed consent was obtained from all patients prior to entry into the study.

Study design

The study was an open, randomized, balanced crossover design of 9 days duration. Patients were randomly assigned to receive one of the six possible sequences of three treatments: (a) a single, oral dose of enalapril maleate 10 mg, (b) a single, intravenous bolus of enalapril maleate 5 mg and (c) a single intravenous bolus of enalaprilat 5 mg. For clinical reasons, the wash-out period between each drug administration was limited to 72 h. The patients continued their daily digitalis and diuretic therapy unchanged throughout the study. All vasodilator therapy, apart from long-acting nitrates, was stopped at least 1 week prior to entry. Other concurrent therapy not specified in the protocol included warfarin sodium, mexiletine, insulin, amiodarone, trimethoprim and angiotensin II infusion. On the evening prior to the start of the procedure an arterial cannula was placed into the radial artery and connected to a continuous heparin flushing device. An intravenous cannula was inserted in the same arm with a heparin lock. On each treatment day (i.e., Days 1, 4 and 7) a urinary catheter was placed for a period of 12 h which necessitated immobilization. During these three 12 h periods, the electrocardiogram was monitored and intraarterial blood pressure was recorded. Otherwise, patients were ambulant and encouraged to be as active and mobile as possible during their hospitalization.

On Days 1, 4 and 7 at 07.00 h hepatic blood flow measurements were determined via administration of indocyanine green. These assays were performed immediately prior to the administration of active treatment (see *Methodology*). Drug administration took place at 08.00 h on active treatment days in the fasting state and food was withheld for 2 h. Blood pressure measurements were made every 15 min for 6 h postdrug. Methods and results for these measurements are discussed in detail in a separate manuscript (Dickstein *et al.*, 1987).

For each treatment, serum samples were obtained at 0 (predrug), 10 (intravenous only), 20 (intravenous only), 30, 45 min, 1.5, 2, 3, 4, 5,

6, 8, 12, 24, 30, 36, 48 and 72 h postdrug and urine was collected -2 to 0 (first treatment only), 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, 24-36, 36-48 and 48-72 h.

Methodology

The arterial cannula was employed to draw blood for drug assay, indocyanine green determinations and to record intravascular pressure. The intravenous cannula provided access for administration of drug (enalapril maleate and enalaprilat) and indocyanine green. The urinary catheter permitted accurate fractionated urine sampling for drug recovery assay. During the study period of 216 h, 106 blood samples were drawn from each patient resulting in a total blood loss of 710 ml. All samples were immediately centrifuged and stored at -20°C . The blood and urine sampling schedule permitted the following pharmacokinetic parameters to be observed or estimated: serum drug concentration profile, rate and extent of urinary recovery, extent of absorption and hydrolysis, extent of bioavailability and first pass effect.

Drug assay

Serum and urine samples were analyzed for enalaprilat and total drug, where total drug represents the sum of enalapril and enalaprilat expressed in terms of enalaprilat equivalents after hydrolysis of any intact enalapril. All analyses were performed by the Department of Drug Metabolism, Merck Sharp & Dohme Research Laboratories. Enalaprilat was determined in triplicate by radioimmunoassay using 15 μl aliquots of serum or of 1:100 diluted urine (Hichens *et al.*, 1981).

The standards ranged from 0.4 to 160 ng ml^{-1} . Samples were diluted as necessary to fall within this range. Extrapolation was permitted to 90% of the lowest standard so that detection limits were 0.36 ng ml^{-1} for serum and 36 ng ml^{-1} for urine. Samples having less than these concentrations were reported as < less than the lower assay limit. Hydrolysis of intact enalapril to enalaprilat was effected with a rat liver homogenate. Because no intact enalapril persists after 12 h postdrug, hydrolysis was performed only on samples taken up to 12 h.

Liver blood flow measurements

Liver blood flow was approximated via determination of indocyanine green clearance following intravenous injection of 0.5 mg indocyanine green kg^{-1} , with plasma sampling at 0, 5, 8, 11, 14, 17,

20 and 30 min (Grainger *et al.*, 1983). Indocyanine green concentrations were determined using a Hitachi 100-20 spectrophotometer with optical densities read at 805 nm to determine percent absorbance. These values were converted to plasma concentration by the use of an indocyanine green standard. Indocyanine green clearance rate was determined by least squares regression over the log-linear phase from 5 to 30 min. Blood flow was calculated by dividing plasma flow by one minus the haematocrit.

Statistical analysis

The following variables were analyzed for treatment differences using analysis of variance for a three-period crossover design: (1) Urinary recovery of enalaprilat; (2) Urinary recovery of total drug; (3) Indocyanine green clearance at 0 h.

Initially, carryover effects were included in the models, but all such effects were found to be nonsignificant. Thus, the final models only included terms for effects due to subject, period and treatment.

The normality assumption of analysis of variance was tested using the Shapiro-Wilk statistic, and was generally accepted for all models. The assumption of homogeneity of variances was tested and accepted for each model using Hartley's Maximum F statistic.

Oral enalapril maleate and intravenous enalapril maleate were compared using a paired *t*-test for each of the following responses: (1) Urinary recovery of total drug, and (2) Bioavailability of enalaprilat (here the data were first transformed using a log scale). Approximate 95% confidence intervals for the means of the bioavailability of enalaprilat from oral enalapril maleate and intravenous enalapril maleate were obtained from the log-transformed data. The upper and lower limits of the resulting confidence intervals were then exponentiated to obtain approximate 95% confidence intervals for the corresponding geometric means. In a similar manner, approximate 95% confidence intervals were obtained for the geometric means of absorption of drug and extent of hydrolysis of enalapril to enalaprilat. All confidence intervals were calculated assuming a *t*-distribution.

All tests of significance were two-tailed at $\alpha = 0.05$.

Results

All patients completed the study. Data were available from 932 out of the 940 blood samples taken for drug assay. The blood sampling

schedule resulted in small but clinically non-significant reductions in haemoglobin (13.2 vs 12.4 g%) and haematocrit (39.6 vs 36.6 vol%). Routine haematology and biochemistry taken prior to and upon completion of the study remained essentially unchanged. One patient received an angiotensin II infusion due to symptomatic hypotension following the 5 mg dose of intravenous enalaprilat. No other clinical adverse experience occurred.

Figure 1 depicts the mean serum concentration profiles for enalapril and enalaprilat following oral enalapril maleate. Enalapril concentrations were calculated as the difference between enalaprilat before and after hydrolysis multiplied by a molecular weight correction factor of 1.08. The mean maximum serum concentration ($C_{\max}$) for enalapril was $77.6 \text{ ng ml}^{-1} \pm 22.6$ ($n = 12$) and that for enalaprilat was $46.8 \text{ ng ml}^{-1} \pm 25.4$ ($n = 11$). The mean times at which $C_{\max}$ occurred ($t_{\max}$) were $1.4 \text{ h} \pm 0.7$ for enalapril and $6 \text{ h} \pm 1.2$ for enalaprilat.

Seventy-two-hour urinary recoveries of enalaprilat and total drug (enalaprilat measured following hydrolysis of the sample) expressed as a percent of administered enalaprilat equivalents for each subject during each treatment period are shown in Table 1. Urinary recovery of enalaprilat was significantly greater ($P < 0.01$) after intravenous enalaprilat than after oral or intravenous enalapril maleate. The difference in the mean recovery following oral or intravenous enalapril maleate was not significant ($P > 0.1$). Mean recoveries of enalaprilat were $35\% \pm 12$, $41\% \pm 11$ and $88\% \pm 7$ for oral enalapril maleate, intravenous enalapril maleate and intravenous enalaprilat, respectively. Mean recoveries of total drug were $53\% \pm 8$ and $77\% \pm 13$ for oral enalapril maleate and intravenous enalapril

Table 1 Mean urinary recovery of enalaprilat (ET) and total drug (TD)* following oral and intravenous administration of enalapril maleate (EM_{po} or EM_{iv}) and intravenous administration of enalaprilat (ET_{iv})

Patient	Urinary recovery (% of dose**)				ET_{iv} ET
	EM_{po} ET	EM_{po} TD	EM_{iv} ET	EM_{iv} TD	
1	18	58	18	84	91
2	28	44	42	99	87
3	34	52	37	74	(-)
4	(-)	(-)	42	80	84
5	35	56	43	86	77
6	38	45	48	55	84
7	21	41	34	81	99
8	44	56	45	67	83
9	45	56	46	77	97
10	33	54	35	60	89
11	58	67	65	83	87
12	(-)	(-)	(-)	(-)	(-)
Mean	35	53	41	77	88
s.d.	12	8	11	13	7

* Enalaprilat plus enalapril

** As administered enalaprilat equivalents

(-) Indicates incomplete urine collections

maleate, respectively. Recovery of total drug from intravenous enalapril maleate was significantly greater than recovery from oral enalapril maleate ($P < 0.01$).

Table 2 contains the mean incremental urinary recovery ratios of enalaprilat to total drug (through 12 h) and the total recovery ratio (0–72 h) following oral enalaprilat maleate. By 12 h, greater than 90% of the urinary recovery of drug was enalaprilat. Of the total urinary recovery (0–72 h), approximately 65% was as enalaprilat.

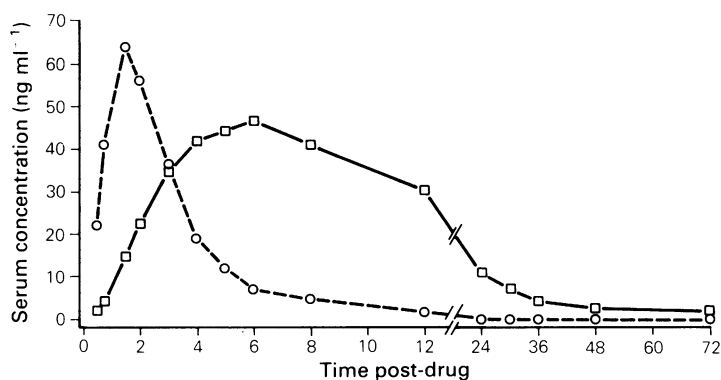


Figure 1 Mean serum concentration of enalapril (○) and enalaprilat (□) following enalapril maleate_{po} in patients with congestive heart failure ($n = 12$).

Table 2 Mean urinary recovery ratios of enalaprilat (ET) to total drug (TD)* following oral administration of enalapril maleate ($n = 9$)

Urine collection interval (h)	ET/TD	
	Mean	s.d.
0-2	0.05	0.06
2-4	0.26	0.16
4-6	0.65	0.18
6-8	0.82	0.08
8-10	0.89	0.05
10-12	0.91	0.05
0-72 (total collection)	0.65	0.18

*Enalaprilat plus enalapril

The bioavailability of enalaprilat from oral and intravenous enalapril maleate is estimated from the ratio of urinary recovery of enalaprilat (in mg) for these preparations to that for intravenous enalaprilat, corrected for dose of enalaprilat equivalents administered. Absorption of enalapril from oral enalapril maleate is estimated from the ratio of total drug recovered in the urine (in mg), oral enalapril maleate to intravenous enalapril maleate, corrected for dose. The results are presented in Table 3. The bioavailability of enalaprilat from intravenous enalapril maleate (0.45) is significantly greater than the bioavailability of enalaprilat from oral enalapril maleate (0.38). Absorption of enalapril from oral enalapril maleate was 69%.

The ratio of the bioavailability of enalaprilat to absorption of enalapril provides an estimate of the extent of hydrolysis of enalapril to enalaprilat. Hydrolysis following oral enalapril maleate is approximately 0.55 (Table 3). Assuming 100% absorption for intravenous administration, the bioavailability of enalaprilat following intravenous enalapril maleate (0.45) is a measure

of the bioconversion of systemically available enalapril to enalaprilat. The hydrolysis or bioconversion of enalapril to enalaprilat following oral enalapril maleate is significantly greater than following intravenous enalapril maleate ($P < 0.01$). The difference between oral and intravenous bioconversion (approximately 10%) in this instance is a rough estimate of the first-pass effect. The validity of this simple estimate of first-pass metabolism is dependent on the pharmacokinetic parameters of the drug in question. The calculation has been shown to be valid for enalapril (unpublished data).

The pretreatment indocyanine green determined liver blood flow showed no statistically significant differences between treatment days. This establishes comparability for the baseline state of this parameter that could affect the pharmacokinetic behaviour of enalapril. No significant differences were detected between treatments at 0 or 6 h. Within treatments, no significant differences were found between 0 and 6 h. These results are displayed in Table 4. Lack of a significant effect on liver blood flow has also been reported for another angiotensin converting enzyme inhibitor, captopril (Shepherd *et al.*, 1985).

Discussion

This study provides extensive data profiling the pharmacokinetic behaviour of single dose enalapril and enalaprilat as administered to hospitalized patients with CHF. Representative bioavailability data for normal subjects following oral administration of enalapril maleate as well as data for intravenous administration of enalapril maleate and enalaprilat are available (Irvin *et al.*, 1984). These data, together with some unpublished

Table 3 Summary of mean absorption, bioavailability and hydrolysis parameters for oral and intravenous administration of enalapril maleate (EM_{po} and EM_{iv})

	Absorption of E^* EM_{po}	Bioavailability of ET		Hydrolysis of E to ET^{**} EM_{po}
		EM_{po}	EM_{iv}	
n	10	9	10	0
Geometric mean	0.69	0.38	0.45‡	0.55‡
95% C.I. for the mean	(0.59, 0.81)	(0.28, 0.52)	(0.35, 0.59)	(0.42, 0.72)

*Assumed to be 100% for intravenous administration

**Equivalent to bioavailability for EM_{iv} , given 100% absorption†Significantly greater than bioavailability for EM_{po} ($P = 0.02$)‡Significantly greater than hydrolysis for EM_{iv} ($P < 0.01$)

Table 4 Indocyanine green (ICG) clearance at baseline (0 h) and 6 h following oral and intravenous administration of enalapril maleate (EM_{po} or EM_{iv}) and intravenous administration of enalaprilat (ET_{iv}), ($n = 12$)

	ICG clearance ($l\ min^{-1}\ m^{-2}$)					
	EM_{po}		EM_{iv}		ET_{iv}	
	0 h	6 h	0 h	6 h	0 h	6 h
Mean	1.25	1.31	1.27	1.36	1.34	1.37
s.d.	0.38	0.39	0.42	0.39	0.42	0.47

Within- and among-treatment changes were not significant, $P > 0.2$.

data from the same study (used with the permission of the investigators, R. K. Ferguson, P. H. Vlasses and M. Rocci: a full manuscript is in preparation) will be used as a basis of comparison for the results obtained in this study in patients with CHF. Statistical comparisons across the two studies are not appropriate.

The mean percentage of the dose recovered in the urine was 88% (CHF) vs 91% (normal subjects) for intravenous enalaprilat and 77% (CHF) vs 86% (normal subjects) for intravenous enalapril maleate. Mean bioavailability, absorption and hydrolysis parameters for patients with CHF, calculated on the basis of these standards, were similar (within 10%) to those obtained for normal subjects. Following oral administration of enalapril maleate, the mean bioavailability of enalaprilat was 38% (CHF) vs 39% (normal subjects). Mean absorption of drug was 69% (CHF) vs 64% (normal subjects) and mean hydrolysis of enalapril to enalaprilat was 55% (CHF) vs 61% (normal subjects). Mean bioavailability of enalaprilat following intravenous administration of enalapril was 45% (CHF) vs 43% (normal subjects). The estimate of first pass effect was 10% (CHF) vs 18% (normal subjects).

Comparison of the incremental urinary recovery ratios of enalaprilat to total drug for both CHF and normal subjects following oral administration of enalapril (Figure 2) shows that during the 0–2 and 2–4 h collection periods the ratios for normal subjects are approximately twice those for CHF patients; in the 8–12 h period, the ratios in both groups are greater than 0.9, but slightly greater in normal subjects than in CHF patients. Ratios are the same in both groups for the total urinary collection. In the serum, peak concentrations of enalapril and enalaprilat occur slightly later in CHF patients than in normal subjects. Mean t_{max} for enalapril is 1.4 h (CHF) vs 0.9 h (normal subjects); mean t_{max} for enalaprilat is 6 h (CHF) vs 4 h (normal subjects). These data

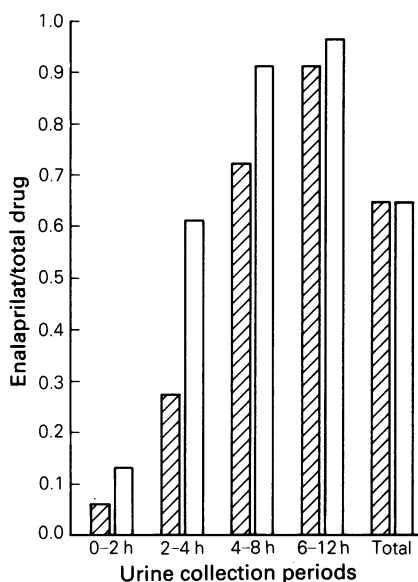


Figure 2 Urinary recovery ratios, congestive heart failure (CHF, ▨) vs normal volunteers (□).

suggest a slightly slower rate of absorption and/or hydrolysis in CHF when compared to normal subjects. Lack of significant effect of CHF on the hydrolysis of enalapril in this study is consistent with the findings of Jackson *et al.* (1984), who concluded from limited serum data that the liver disease associated with cardiac failure does not cause a reduction in the bioactivation of enalapril.

The mean serum profiles for enalapril and enalaprilat following oral administration of 10 mg enalapril maleate in normal subjects (Figure 3) as compared with patients with CHF (Figure 1) provide an interesting observation. Enalapril profiles are similar for the two groups. But, despite comparable bioavailability for enalaprilat, serum enalaprilat concentrations appear to be greater in the CHF patients than in normals. Profiles are of a similar shape. Figures 4 and 5 show that enalaprilat concentrations are consistently higher in CHF patients following intravenous administration of both enalapril maleate and enalaprilat as well. Although less marked, similar relative observations were made for oral administration of enalapril maleate and intravenous administration of enalaprilat in healthy, elderly subjects (age 65 to 76 years) vs healthy, young subjects (20 to 27 years) (Hockings *et al.*, 1985). In the present study in CHF, one patient was 52 years of age and 11 were over 61 years of age, of which eight were over 65 and three were over 71 years. The greater enalaprilat serum

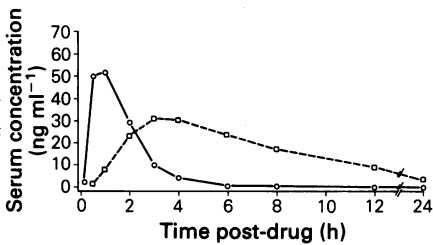


Figure 3 Mean serum concentration profiles of enalapril (○) and enalaprilat (□) following enalapril maleate_{po} in normal subjects ($n = 10$).

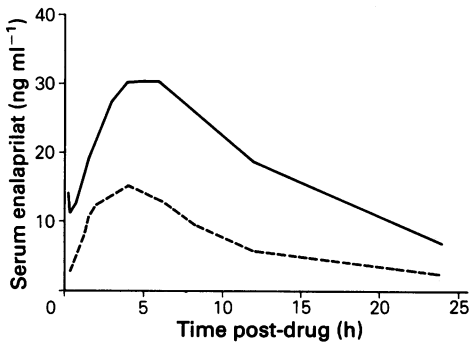


Figure 4 Mean serum concentration profiles of enalaprilat following enalapril maleate_{iv} in patients with congestive heart failure (CHF, —) and in normal volunteers (---).

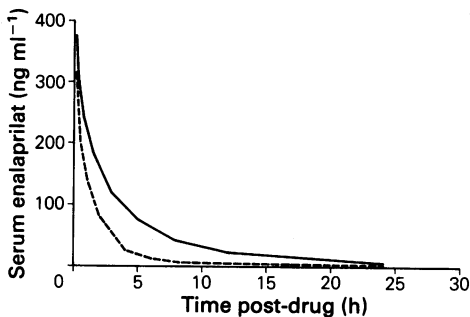


Figure 5 Mean serum concentration profiles of enalaprilat_{iv} in patients with congestive heart failure (—) and in normal volunteers (---).

concentrations observed in this study may be attributable, therefore, to the impact of age, as well as CHF, on the pharmacokinetics of enalaprilat.

Following oral administration of enalapril maleate or intravenous administration of enalaprilat, serum concentrations of enalaprilat in

normal subjects are polyphasic, with a prolonged terminal phase (Till *et al.*, 1982, 1984). Based on observations in humans (Till *et al.*, 1982) and further work in animals (unpublished data), it has been postulated that the terminal phase of the enalaprilat serum profile reflects non-linear binding of enalaprilat to angiotensin converting enzyme (Till *et al.*, 1984). The contribution of a non-linear binding component to enalaprilat serum profiles precludes conventional model-dependent and model-independent (based on the area under the curve measurements) calculations of such parameters as apparent volume of distribution, clearance and half-life serum unless the serum data can be appropriately corrected for this binding. An effective half-life for accumulation (Kwan *et al.*, 1984) of enalaprilat following multiple oral doses of enalapril maleate has been calculated from urine data. As expected, this half-life (approximately 11 h in healthy subjects) was found to be unrelated to the observed terminal phase of the enalaprilat serum profile following single doses of enalapril maleate or enalaprilat.

Although the data from this study in CHF do not permit the calculation of the key pharmacokinetic parameters volume of distribution, clearance and half-life, the observed elevated serum concentrations of enalaprilat are consistent with a hypothesis of a decreased volume of distribution (accompanied by a decrease in plasma clearance) due to CHF and/or age, associated with a decrease in cardiac output and organ perfusion (Wilkinson *et al.*, 1976). If, as found for quinidine (Ueda *et al.*, 1981), a reduction in volume of distribution and clearance is not accompanied by an increase in half-life (effective half-life for accumulation), steady-state concentrations of enalaprilat would be expected to be higher in CHF following multiple dosing of a given dose of enalapril maleate or enalaprilat, but the accumulation ratio would be the same in CHF as found in normals (approximately 1.3) (Till *et al.*, 1984). That is, the concentration of enalaprilat in the body at steady state would be predicted to be approximately 1.3 times that for the first dose of enalapril maleate or enalaprilat. The similarity in the shapes of the enalaprilat serum profiles for CHF patients and normal subjects lends support to this speculation, but only a multiple dose study in CHF can provide information.

Conclusions

The results of this study elucidate the pharmacokinetic profile of single dose enalapril in patients with CHF. Following oral administration, the

extent of absorption of drug and hydrolysis to enalaprilat and the bioavailability in CHF patients appear to be similar to those in normal subjects. The rate of absorption and hydrolysis appears to be slightly slower in CHF patients. Enalaprilat serum concentrations are consistently greater in CHF patients as compared to normals and may

be associated with age as well as the disease state. We conclude that the presence of CHF does not appreciably alter the pharmacokinetic behaviour of enalapril. Lack of significant accumulation of enalaprilat in CHF following multiple doses of enalapril maleate or enalaprilat is suggested, but remains to be confirmed.

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