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Age and the pharmacokinetics of angiotensin converting enzyme inhibitors enalapril and enalaprilat

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1 The pharmacokinetics of angiotension converting enzyme (ACE) inhibitors enalapril (10 mg orally) and its active metabolite, enalaprilat (10 mg intravenously) were studied in nine young healthy volunteers aged 22–30 years and nine sex matched elderly subjects aged 65–73 years.

2 After both drugs, a biexponential curve was fitted to the decline in plasma enalaprilat concentration. Area under the plasma concentration–time curve (AUC) was greater in the elderly for both drugs.

3 Clearance (CL) and clearance/bioavailability (CL/*F*) were less in the elderly for enalaprilat and enalapril, respectively. There was no difference in *F* between young (0.62 ± 0.16) and elderly subjects (0.61 ± 0.15).

4 Enalaprilat CL and enalapril CL/*F* were significantly and positively correlated to endogenous creatinine clearance.

5 There was a significant difference in the weight corrected volume of distribution at steady state after enalaprilat between the young and elderly ($P < 0.02$).

6 The relationship between plasma enalaprilat concentrations and percentage ACE inhibition, using the Hill equation, showed no difference in the sensitivity to ACE inhibition between the young and the elderly group.

7 The pharmacokinetic differences observed are likely to be related to an age dependent decline in renal function as well as changes in body composition. Kinetic differences partly explain the greater pharmacodynamic response in the elderly.

Keywords enalapril enalaprilat age pharmacokinetics converting enzyme inhibitors

Introduction

The non-thiol angiotension converting enzyme inhibitor, enalapril, is of value in the management of hypertension (Brunner *et al.*, 1981; Hodsman *et al.*, 1982) and congestive heart failure (Kjekhus *et al.*, 1983). Enalapril is itself inactive following oral administration, but is rapidly metabolised by esterolysis in the liver (Toco *et al.*, 1982) to its active diacid metabolite, enalaprilat. Enalaprilat is excreted via the kidney without further metabolism.

Until the recent advent of more appropriate methods of plasma captopril determination (Kawahara *et al.*, 1981; Jarrot *et al.*, 1981), an adequate characterisation of its pharmacokinetics has been limited. Captopril may accumulate in patients with renal impairment leading to concentration-related adverse effects (Hoorntje *et al.*, 1980; Staenssen *et al.*, 1980). Owing to the availability of sensitive assays (Hichens *et al.*, 1981; Ulm *et al.*, 1982; Till *et al.*,

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1984; Toco *et al.*, 1982) the disposition of enalapril can be studied (Ulm *et al.*, 1982). There is, however, no information about kinetics in the elderly population in which the drug is likely to be widely used.

Ageing causes physiological and structural changes which may alter drug disposition. These include changes in body composition (Vestal, 1978), regional blood flow and tissue permeability (Bender, 1969), hepatic metabolism and renal excretion (O'Malley *et al.*, 1971; Triggs & Nation, 1975). However, not all drugs are uniformly affected and thus no generalisations on the effect of age on drug disposition can be made (Greenblatt *et al.*, 1982; Ramsay & Tucker, 1981). Each drug requires separate consideration.

This study examines the effect of age on the bioavailability and disposition of oral enalapril and intravenous enalaprilat, following single doses to young and elderly healthy volunteers. The relationship between enalaprilat concentration and plasma converting enzyme inhibition has also been investigated in order to examine the influence of age on the sensitivity to plasma converting enzyme inhibition. This work was presented previously as a communication to the British Pharmacological Society (Hockings *et al.*, 1985). The effects of enalapril and enalaprilat on blood pressure and autonomic and endocrine function in these subjects are described separately (Ajayi *et al.*, 1986).

Methods

Nine young subjects aged 22–30 years and nine elderly subjects aged 65–73 years, and weighing 64 ± 10 kg and 70 ± 13 kg, respectively, gave informed written consent to participate in the study. Subjects were examined and judged healthy by clinical examination and laboratory investigations including haematology, biochemistry, ECGs and urinalysis prior to entry to the study. The two groups were matched for sex; six males and three females. The study was reviewed and approved by the local research and ethics committee. The demographic and clinical data of the subjects are summarized in Table 1.

Study design

In random order according to a balanced Latin square design subjects received a single intra-

Table 1 Clinical demographic data of subjects

	Age (years)	*Sex*	*Weight (kg)*	CL_{cr} *(ml min^{-1})*	*Est.* CL_{cr} *(ml min^{-1})*
Young subjects					
Y1	22	M	60	69	72
Y2	24	M	58	98	78
Y3	24	M	75	96	111
Y4	27	F	56	109	68
Y5	24	F	54	71	75
Y6	23	F	58	—	97
Y7	22	M	79	97	99
Y8	28	M	62	94	79
Y9	30	M	78	105	94
Mean	25		64	92	86
s.d.	3		10	15	15
Elderly subjects					
E1	73	M	67	64	58
E2	73	F	66	40	64
E3	66	F	64	80	61
E4	72	M	84	–	56
E5	72	F	52	45	41
E6	65	M	73	97	61
E7	65	M	84	78	63
E8	65	M	84	—	67
E9	66	M	53	63	51
Mean	69		70	66	58
s.d.	4		13	19	8
P value	< 0.001		NS	< 0.01	< 0.001

venous bolus dose of enalaprilat 10 mg, or oral enalapril maleate 10 mg, or matching placebo tablet, with 200 ml of water. Study days were at least 1 week apart. Subjects reported at the Clinical Pharmacology Research Unit at 08.30 h after an overnight fast. They abstained from all medicines 2 weeks before study, and avoided alcohol, tea, coffee or cigarettes from the night prior to the study day. On arrival volunteers lay supine and blood samples were collected via an indwelling cannula at 0, 1, 2, 4, 6, 8, 24, 48, 72 and 96 h post dosing. On the intravenous study days additional samples were collected at 5, 10, 20 and 40 min. Blood samples were placed in ice until centrifuged and the plasma stored at −40°C until assayed. A light lunch was served at 4 h after dosing on each study day. Subjects went home after the 8 h blood samples on each study day and reported every morning until the fifth day.

Drug assay

Drug measurements in plasma and urine were made at the Merck Sharp & Dohme Research Laboratories, Westpoint, U.S.A. by a specific radioimmunoassay (Hichens *et al.*, 1981). Oral enalapril was measured as its active metabolite enalaprilat. The limit of sensitivity is 0.4 ng ml^{-1} and within and between assay coefficients of variation were 6.0 and 7.5%, respectively.

Assessment of renal function

Twenty-four hour urine sodium and creatinine clearance were measured on the placebo study day. An estimate of the creatinine clearance was also made using serum creatinine, age and sex (Jelliffe & Jelliffe, 1972).

Pharmacokinetic and statistical analysis

Drug concentration–time data were analysed using standard kinetic models (Gibaldi & Perrier, 1982) and a curve fitting computer program based on the Maximum Likelihood principle (Ross, 1980). Areas under the concentration–time curve (AUC) were calculated by the trapezoidal rule, with concentrations extrapolated to infinity. Dose *(D)* was used to calculate clearance (CL) as CL = *D*/AUC after enalaprilat and after oral enalapril the ratio of clearance (CL) over bioavailability (*F*) (CL/*F*) was calculated as CL/*F* = *D*/AUC. The absolute bioavailability *F* of enalapril was calcualted as

$$\frac{AUC_{po} \times D_{iv} \times 1.4}{AUC_{iv} \times D_{po}}$$

(Since 10 mg of enalapril maleate is the molar equivalent of 7.14 mg enalaprilat and 10/7.14 = 1.4). The apparent volume of the central compartment (V_c) was calculated as $V_c = D/C_{(0)}$ and $V_{ss} = D\ (AUMC/(AUC)^2$. $C_{(0)}$ is the predicted concentration at time zero after bolus dosing, and AUMC (area under the first moment curve is the area under the curve of the product of serum concentration and time plotted against time (Gibaldi & Perrier, 1982). Comparisons were made by Student's *t*-test for unpaired data where appropriate.

The relationship between plasma enalaprilat and percentage (%) inhibition of plasma ACE activity in individuals was described by the Hill equation (Hill, 1910) using the method described by Kelman *et al.* (1983). Inhibition, I, is related to plasma concentration, *C*, by the equation

$$I = \frac{I_{max} \cdot [C]^{\gamma}}{[C_{50}]^{\gamma} + [C]^{\gamma}}$$

where I_{max} is the maximum inhibition, C_{50} is the drug concentration producing half maximal inhibition, and γ describes the sigmoidicity of the relationship.

Results

Intravenous enalaprilat

After intravenous bolus administration of enalaprilat (10 mg) plasma concentrations appeared to decline in a tri-exponential manner in both age groups. The first exponential was, however, ill defined and so the drug levels up to 20 min were excluded from the analysis and the data fitted to a two compartment model. The concen-

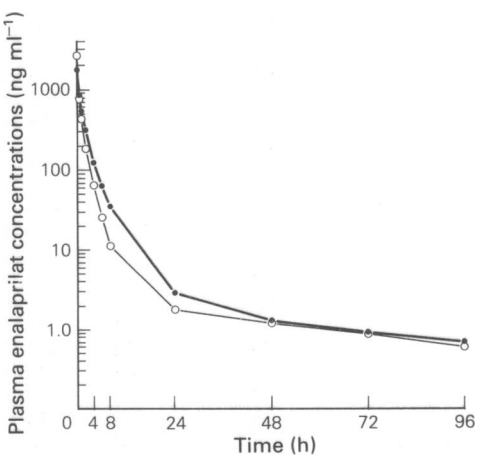

Figure 1 Mean concentration–time profile of enalaprilat following intravenous dosing in young (○) and elderly (●) volunteers (n = 9 in each group).

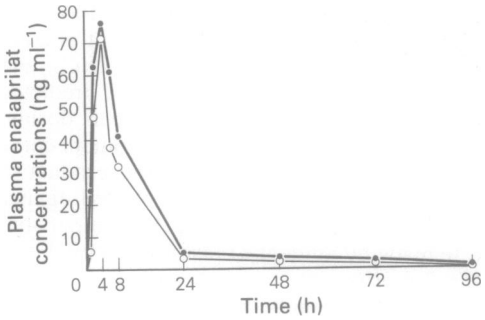

Figure 2 Mean concentration–time profile of enalaprilat following oral dosing of enalapril in young (○) and elderly (●) volunteers ($n = 9$ in each group).

tration–time profile after enalaprilat is shown in Figure 1. A comparison of the kinetic parameters following enalaprilat is shown in Table 2. The AUC was significantly greater in the elderly. The values were 1694 ± 314 in the young, and 2294 ± 475 ng ml^{-1} h in the elderly ($P < 0.01$). There was also a significant difference in the volume of distribution at steady state, V_{ss}, adjusted for weight. The values were 0.278 ± 0.83 l kg^{-1} in the elderly and 0.375 ± 0.059 l kg^{-1} in the young ($P < 0.02$) (Table 2). The clearance of enalaprilat was significantly less in the elderly being 4.46 ± 0.88 l h^{-1} compared with 6.10 ± 1.23 l h^{-1} in the young ($P < 0.01$).

Oral enalapril

These results are shown in Figure 2 and Table 3. Enalapril was measured as its active metabolite, enalaprilat, following oral administration. The kinetics of the absorption phase were not well defined (up to peak concentration) and were thus excluded from the curve fitting. There was no difference in bioavailability, F, between young, 0.62 ± 0.16 and elderly, 0.61 ± 0.15. The AUC was again greater in the elderly (722 ± 188 young *vs* 997 ± 332 ng ml^{-1} h elderly ($P < 0.05$). The CL/F was significantly less in the elderly (10.79 ± 2.72 l h^{-1}) compared to the young 14.65 ± 3.62 l h^{-1} ($P < 0.05$).

The relationship between plasma enalaprilat and percentage inhibition of plasma ACE activity

These results are summarised in Table 4 and Figure 3. The relationship between plasma enalaprilat and the inhibition of plasma ACE activity expressed as a percentage was described by the Hill equation in individuals. There were no differences in the parameters I_{max}, γ, or C_{50},

Table 2 Individual kinetic parameters after enalaprilat in young and elderly subjects

	AUC (ng ml^{-1} h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	V_c(l)	V_{ss}/*weight* (l kg^{-1})	*CL* (l h^{-1})
*Young subjects**						
Y1	1883	1.10	43.3	10.0	0.435	5.31
Y3	2088	1.59	34.7	17.7	0.339	4.79
Y4	1955	1.08	40.8	9.0	0.349	5.12
Y5	1687	1.13	31.5	13.1	0.457	5.93
Y6	1384	0.83	30.1	9.5	0.341	7.23
Y7	1213	0.94	28.9	12.4	0.283	8.24
Y8	1898	1.29	86.6	11.1	0.427	5.27
Y9	1445	1.16	40.8	13.2	0.365	6.92
Mean ± s.d.	1694 ± 314	1.14 ± 0.2	38.5 ± 10.7	12.0 ± 2.8	0.375 ± 0.059	6.10 ± 1.23
Elderly subjects						
E1	1415	1.25	38.5	14.4	0.434	6.92
E2	2698	1.50	27.9	9.4	0.191	3.71
E3	2239	1.43	31.5	10.6	0.257	4.47
E4	2543	1.99	40.8	13.6	0.244	3.93
E5	2904	1.43	77.0	8.3	0.325	3.44
E6	1902	1.94	27.4	16.1	0.351	5.26
E7	2735	1.55	27.4	9.7	0.179	3.66
E8	2165	1.43	46.2	10.8	0.216	4.62
E9	2041	1.14	27.4	8.9	0.305	4.90
Mean ± s.d.	2294 ± 475	1.5 ± 0.3	38.5 ± 8.6	11.3 ± 2.7	0.278 ± 0.083	4.46 ± 0.88
P	< 0.01	< 0.05	NS	NS	< 0.02	< 0.01

* Sample for Subject Y2 were missing.

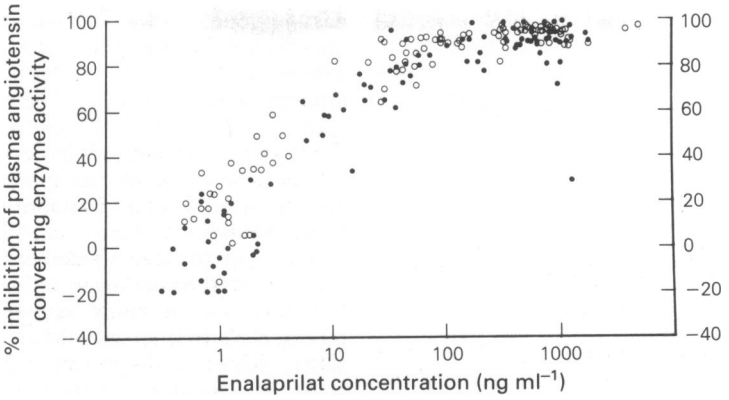

Figure 3 The relationship between plasma enalaprilat concentration and percentage inhibition of plasma angiotensin converting enzyme activity in young (○) and elderly subjects (●).

thus no age related differences in sensitivity of the plasma enzyme to ACE inhibition were detected.

Renal function and pharmacokinetics

The measured creatinine clearance was significantly less in the elderly (Table 1) but because of technical difficulties in three subjects the estimated creatinine clearance, (est. CL_{cr}), was used to correlate renal function and drug clearance. Enalaprilat CL and enalapril CL/*F* were significantly and positively correlated to estimated creatinine clearance ($P < 0.001$) (see Figure 4a and b).

Discussion

Our findings show marked differences in the disposition of the converting enzyme inhibitor enalapril and its metabolite enalaprilat between

Table 3 Individual oral enalapril kinetic parameters in young and elderly subjects.

	AUC (ng ml^{-1} h)	t_{max} (h)	C_{max} (ng ml^{-1})	*CL*/F	F*
Young subjects					
Y1	1097	2	129	9.12	0.81
Y2	591	4	48	16.92	—
Y3	554	2	40	18.05	.36
Y4	768	8	64	13.02	0.55
Y5	707	4	64	14.14	0.59
Y6	763	4	105	13.11	0.77
Y7	476	6	50	21.01	0.55
Y8	657	4	54	15.22	0.48
Y9	889	4	60	11.25	0.82
Mean ± s.d.	722 ± 188	3 ± 1	68 ± 29	14.65 ± 3.62	0.62 ± 0.16
Elderly subjects					
E1	820	2	197	12.20	0.82
E2	1253	4	83	7.98	0.65
E3	1046	2	120	9.56	0.65
E4	710	8	142	14.08	0.39
E5	1746	4	36	5.73	0.84
E6	714	4	149	14.01	0.53
E7	867	6	59	11.53	0.44
E8	938	4	47	10.66	0.61
E9	877	4	77	11.40	0.60
Mean ± s.d.	997 ± 332	4 ± 2	101 ± 54	10.79 ± 2.72	0.61 ± 0.15
P	< 0.05	NS	NS	< 0.05	NS

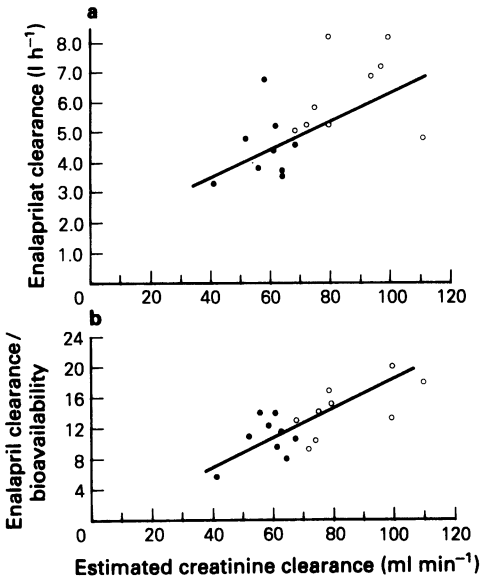

Figure 4 (a) The relationship between endogenous creatinine clearance and enalaprilat clearance (CL) following intravenous administration in young (○) and elderly subjects (●) ($P < 0.001$).
(b) The relationship between creatinine clearance and enalapril clearance/bioavailability (CL/*F*) in young (○) and elderly (●) subjects ($P < 0.001$).

healthy young and elderly subjects. Although the kinetics of the absorption phase were ill defined, there was no evidence of age related differences in t_{max} or C_{max}. The values obtained in this study are similar to those reported by Ulm *et al.*, (1982) in young volunteers. The absolute bioavailability, *F*, of enalaprilat incorporates both the absorption of enalapril and its conversion to enalaprilat (Toco *et al.*, 1982). The value of about 0.6 (60%) obtained in this study indicates good systemic penetration of enalapril. This value is, however, higher than the 0.4 reported by Irvin *et al.* (1984). Unlike Irvin's study, however, the *F* value reported in our study incorporates a correction factor of 1.4: although enalapril was administered, enalaprilat, its active metabolite, was measured and 10 mg of enalapril is metabolised to 7.14 mg of enalaprilat. In keeping with findings of most studies in the elderly, we found no age related effect on the bioavailability of enalaprilat.

The CL and CL/*F* following enalaprilat and enalapril respectively were significantly less in the elderly subjects compared to the young. This age related diminution of total body clearance was reflected in the significantly larger AUCs for both oral enalapril and enalaprilat in the elderly. As enalaprilat excretion depends mainly on renal clearance (Ulm *et al.*, 1982; Till *et al.*,

Table 4 The relationship between plasma enalaprilat and percentage inhibition of plasma ACE activity

	E_{max} (%)	γ	C_{50} (ng ml^{-1})	r^2
Young subjects				
Y1	89.8	2.10	1.83	0.99
Y2	92.6	0.94	5.8	0.99
Y4	90.6	0.93	4.2	0.99
Y5	81.3	0.90	3.9	0.96
Y6	93.0	1.61	4.7	0.97
Y7	94.1	0.99	6.9	0.96
Y8	95.2	0.91	6.0	0.98
Y9	108.4	0.64	12.8	0.90
Mean ± s.d.	93.1 ± 7.5	1.14 ± 0.50	5.8 ± 3.2	
Elderly subjects				
E1	94.9	0.94	3.3	0.98
E2	96.7	1.07	3.9	0.98
E3	96.9	0.69	2.4	0.99
E4	99.0	1.02	10.0	0.97
E5	88.9	1.05	6.2	0.98
E6	95.6	0.84	5.0	0.99
E7	90.8	1.61	2.1	0.99
E8	118.8	0.36	1.7	0.72
E9	93.8	0.75	5.0	0.99
Mean ± s.d.	97.2 ± 8.4	0.93 ± 0.34	4.4 ± 2.6	
Significance	NS	NS	NS	

1984), which declines with age (Vestal, 1978), we related clearance ot the estimated endogenous creatinine clearance. The clearance of enalaprilat and CL/*F* for enalapril were positively and significantly correlated to creatinine clearance as shown by the regression equations. Differences in creatinine clearance accounted for 33% and 41% of the variance in the clearance data for intravenous and oral doses, respectively. Thus, creatinine clearance may be a guide to enalaprilat clearance. This observation is consistent with findings of diminished urinary elimination of enalaprilat in patients with renal impairment (Kelly *et al.*, 1984). Our finding of a significantly smaller weight adjusted V_{ss} in the elderly suggests that enalaprilat distribution may be altered by ageing. The weight corrected V_{ss} is a model independent parameter (Gibaldi & Perrier, 1982) and is suitable for comparison between different groups of subjects or patients (Klotz, 1976). Drug distribution is a physicochemical interaction between drugs and tissues. It is affected by plasma protein binding (Dayton *et al.*, 1973) which may fall in the elderly (Greenblatt *et al.*, 1982), by aqueous and lipid solubility, by body weight and surface area, and by the lean/fat body mass ratio (Klotz, 1976). Enalaprilat is not extensively protein bound (< 80%) (Gomez *et al.*, 1983). Any binding differences are therefore unlikely to alter its pharmacokinetics. It is more likely that the altered distribution results from age related changes in body composition (Bruce *et al.*, 1980; Forbes & Reina, 1970) or tissue blood flow. The unchanged $t_{1/2}$, despite a reduced V_{ss} in the elderly is to be expected because of the parallel reduction in clearance. The $t_{1/2}$ value of 38.5 h is similar to the 35 h previously reported by Ulm *et al.* (1982). This relatively long half-life, however, does not appear to exert the usual influence on the attainment of steady state during repeated dosing (Till *et al.*, 1984). Theoretically, steady state should not be achieved until a period of 3–5 half-lives has elapsed (115–193 h) but Till *et al.*, (1984) have shown that steady state is achieved within a relatively short time, 30–60 h, indicating that the 'effective accumulation half-life' is of the order of 10 h. The apparent terminal phase of the enalaprilat serum profile may be due to binding of enalaprilat to angiotensin converting enzyme (Till *et al.*, 1984) so that it creates an anomalous prolonged terminal phase.

The findings of reduced clearance, greater AUC and reduced distribution volume may partly explain the greater hypotensive effect and prolonged converting enzyme inhibition we have observed in elderly subjects (Ajayi *et al.*, 1986). We detected no age related alteration in the sensitivity of plasma ACE to inhibition. Thus, sensitivity of ACE is unlikely to underlie the pharmacodynamic differences observed between the two groups (Ajayi *et al.*, 1986). The full therapeutic implication of the findings from this single dose study must await further multiple dose studies in the elderly. Whereas the time taken to achieve steady state in elderly subjects may not differ from that in younger subjects, steady state concentrations will be relatively higher because of the reduced clearance. It appears, therefore, that some dosage adjustment may be necessary in the elderly, based on estimates of creatinine clearance.

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