The effects of age on the pharmacokinetics and pharmacodynamics of single oral doses of benazepril and enalapril

N.-J. MACDONALD, A. SIOUFI¹, C. A. HOWIE, J. R. WADE & H. L. ELLIOTT

University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, G11 6NT and ¹Laboratories Ciba-Geigy, Biopharmaceutical Research Centre, BP 308, Rueil-Malmaison Cedex, France

- 1 Eighteen healthy, normotensive subjects (nine young and nine elderly) participated in a double-blind, 3-way, crossover study to compare aspects of the pharmacokinetics and pharmacodynamics of single oral doses of 10 mg benazepril, 10 mg enalapril and placebo.
- 2 The hypotensive effect was similar after both drugs but the absolute reductions were greater in the elderly who had higher initial levels of blood pressure.
- 3 The AUCs for both benazeprilat and enalaprilat were higher in the elderly but by a significantly greater amount for enalaprilat (+113% vs 40%; $P < 0.01$).
- 4 The AUCs for both drugs tended to be highest in subjects with the lowest creatinine clearance.
- 5 The changes in kinetics and dynamics observed in the elderly after benazepril are qualitatively similar to those with other ACE inhibitors. The clinical significance of the quantitative differences requires further investigation.

Keywords age benazepril enalapril pharmacokinetics pharmacodynamics

Introduction

Initially, it was suggested that the magnitude of the antihypertensive response to angiotensin converting enzyme (ACE) inhibitor drugs was directly dependent upon the level of plasma renin activity [1]. Thus, the reduced pharmacodynamic response reported in elderly patients treated with the ACE inhibitor, captopril [2] might simply reflect the age-related decline in plasma renin activity [3]. It has now become apparent that the blood pressure response to ACE inhibitors is not consistently related to the pretreatment plasma renin activity [4], irrespective of age, and ACE inhibitors have been used successfully to control blood pressure in the elderly in several large clinical trials over relatively long periods of time [5, 6, 7]. However, the age-related decline in renal function and the dependency of many ACE inhibitors (e.g. captopril and enalaprilat) on renal elimination has led to recommendations for dose reduction of the currently available ACE inhibitors in the elderly [8]. In contrast, preliminary studies with benazepril hydrochloride (CGS 14824A), a new non-sulphydryl-containing ACE inhibitor, suggest that it undergoes significant extra-renal (hepato-biliary) elimination such that dose reduction in the elderly might not be required [9]. To investigate further the safety, efficacy and

appropriate dose of benazepril in the elderly we have undertaken a comparative study in healthy young and healthy elderly subjects. The principal aims were to assess and compare the pharmacokinetics, hypotensive activity and extent of ACE inhibition after the administration of single doses of benazepril and enalapril to young and elderly subjects.

Methods

Subjects

A total of 18 healthy, normotensive subjects gave written, informed consent for their participation in the study which was approved by the local Ethics Committee. The young group (nine males, 21–39 years) and the elderly group (six males, three females, 66–76 years) were recruited after screening by history, physical examination, urinalysis, electrocardiogram and routine tests of haematology and serum biochemistry to exclude any significant illness. The elderly group had a significantly higher mean pre-study supine blood pressure of $147/80 \pm 18/9$ mm Hg, compared with $127/72 \pm 13/7$ mm Hg in

the young group. Creatinine clearance, based on a timed 24 h urine collection, was significantly lower in the elderly group (78 ± 25 , range 44–110 ml min⁻¹ vs 112 ± 31 , range 89–147 ml min⁻¹) but considered within normal limits according to age.

Design

Subjects undertook 3 study days, at intervals of not less than 1 week, in a double-blind, placebo-controlled, randomised, crossover manner with treatments allocated according to a balanced (3×3) Latin Square design. Treatments were single oral doses of 10 mg benazepril hydrochloride, 10 mg enalapril maleate and placebo. Following an overnight fast, subjects reported to the Clinical Pharmacology Research Unit at 08.00 h on each study day. After insertion of an indwelling intravenous cannula into a forearm vein, baseline measurements were obtained and the appropriate treatment was administered. Thereafter, at frequent intervals until 12 h post dosing, venous blood was withdrawn for measurement of plasma drug concentrations and plasma ACE activity. Further blood samples were obtained at 24, 48 and 72 h post-dose. At corresponding times blood pressure and heart rate, supine and erect, were measured in duplicate by semiautomated sphygmomanometer (Sentron-Bard Biomedical). These sphygmomanometers are serviced each month by the hospital Medical Physics Department and calibrated against a mercury column.

Laboratory methods

Plasma ACE activity was assayed by an enzyme kinetic assay utilising Hip-His-Leu as substrate and the released hippuric acid was measured by high pressure liquid chromatography [10, 11].

Enalapril and benazepril were measured as their respective active metabolites, enalaprilat and benazeprilat. Plasma concentrations of benazeprilat were determined by gas chromatography-mass spectrometry [12] and of enalaprilat by specific radioimmunoassay [13]. In addition, the extent of protein binding was investigated using an equilibrium dialysis technique using blood samples obtained at 2 and 6 h post-dose.

Statistical methods

Heart rates were compared by repeated measures analysis of variance. All results are expressed as mean $\pm$ s.d. Despite the Latin Square design a significant period effect was detected and, for the blood pressure measurements, the proposed repeated measures analysis of variance was modified to an analysis of covariance using the baseline value as covariate. This approach took account of the recognised fact that Δ BP is a function of the pre-dose BP and the assumptions of linearity, equal slopes and normality were validated beforehand.

Drug concentration-time data were analysed using standard model independent methods; AUCs 0– ∞ were calculated using the linear and log linear trapezoidal rule regression of the last two concentration-time points for each subject. The relationship between plasma drug concentrations and inhibition of plasma ACE activity was described in individuals by the Hill equation.

Results

Blood pressure and heart rate

In both young and elderly subjects there were significant reductions in supine and erect blood pressure after administration of each ACE inhibitor, without any significant changes in heart rate.

There were no significant differences between enalapril and benazepril in the magnitude of their hypotensive effects in either young or elderly subjects.

The reductions in blood pressure, both supine and erect, were generally greater in the elderly group. For example, the mean maximum placebo corrected reduction in supine blood pressure for the elderly was $17/11 \pm 11/9$ on enalapril and $15/9 \pm 9/8$ mm Hg on benazepril. The corresponding reductions in the young group were $9/9 \pm 4/8$ and $2/6 \pm 5/9$ mm Hg.

Although the absolute reductions in systolic blood pressure were significantly greater in the elderly group (ANOVA), to take account not only of the baseline differences between the groups but also of a period effect (with baseline blood pressure tending to fall over the 3 study days) an analysis of covariance (with baseline BP as covariate) was also undertaken. By ANCOVA, there was no statistically significant difference between the groups for the magnitude of the blood pressure fall.

Plasma ACE activity

For benazepril, the time to reach maximum inhibition of plasma ACE activity ($t_{\max}$) had a median value of 1.5 h in the young and 2.0 h in the elderly (see Figure 1). This was significantly quicker than with enalapril with median $t_{\max}$ values of 4 and 5 h in young and elderly respectively. Maximal ACE inhibition, 98% for benazepril and 89% for enalapril, was not significantly different for the two drugs and was sustained for several hours after dosing. At 24 h post-dose there remained significant ACE inhibition with both drugs: 47% (young) and 59% (elderly) for benazepril and respectively 44% and 55% for enalapril. For ACE inhibition there were no significant differences between the young and elderly groups.

Plasma drug concentrations

The results are shown in Figure 2 and Table 1.

Peak plasma levels ($C_{\max}$) of benazeprilat were attained within 3 h in all subjects, young and elderly. The $C_{\max}$ for enalaprilat was slightly but significantly later at 4–5 h and additionally was more variable, across a range of 2–10 h. Additionally, peak plasma concentrations of enalaprilat tended to be higher in the elderly but this was not apparent with benazeprilat. At 72 h post-dose similar mean plasma levels were measured for both drugs: for benazeprilat, 3.0 and 5.0 nmol l⁻¹ for the young and elderly respectively and for enalaprilat, 1.7 and 4.4 nmol l⁻¹ for the young and elderly respectively.

The AUC (0– ∞) (and 0–72 h, not shown) was significantly increased in the elderly for both enalaprilat and benazeprilat. The magnitude of the increase was +40% for benazeprilat but was proportionately significantly greater with enalaprilat at +113% ($P < 0.01$). For both

Figure 1 Time profiles of plasma ACE inhibition in young (□) and elderly (■) subjects. a) benazepril, b) enalapril.

drugs the highest AUCs occurred in the subjects with the lowest creatinine clearance but across this limited range of clearance values there was no significant correlation between AUC and creatinine clearance.

The relationship between plasma drug concentrations and the inhibition of plasma ACE activity in individual subjects was described by the Hill equation (Table 2). There were no significant differences with each drug in the parameters $I_{\max}$ (maximum inhibition), IC_{50} (the

drug concentration producing half maximal inhibition) and γ (describing the sigmoidicity of the relationship) between the two age groups. Thus, no age-related difference was detected in the sensitivity of plasma ACE activity to inhibition by either drug.

Protein binding

The extent of protein binding was significantly different for the two drugs at 91.7% for benazeprilat and 25.4% for enalaprilat in the young subjects. Binding was significantly lower in the elderly at 89.4% ($P < 0.025$) for benazeprilat and 13.6% ($P < 0.007$) for enalaprilat. This represents a significantly greater relative increase in the free drug fraction for benazeprilat in the elderly (+28%), compared with enalaprilat (+16%).

Symptomatic effects

Enalapril and benazepril were generally well tolerated. One subject (elderly female, aged 74 years, weight 50 kg) had symptomatic orthostatic hypotension at 4–8 h after the administration of enalapril and also at 6–9 h after benazepril. On each occasion she was nursed supine with relief of symptoms. She had recovered by 12 h after the administration of each drug.

No other adverse events were reported.

Discussion

There were no significant differences between benazepril and enalapril in the magnitude of the blood pressure reductions. Although the absolute maximum falls in systolic blood pressure were greater in the elderly, after adjustment for the variations in starting blood pressure, there was no significant age-related difference in the blood pressure response. Generally, both benazepril and enalapril were well tolerated although a 'first dose' effect (symptomatic orthostatic hypotension), as has previously been described with ACE inhibitor drugs [14, 15], was observed in a single elderly subject after both drugs. Although small in stature this patient had none

Figure 2 Plasma drug concentration-time profiles in young (□) and elderly (■) subjects. a) benazepril, b) enalapril.

Table 1 Pharmacokinetic parameters for young and elderly subjects after enalapril and benazepril

	$C_{\max}$ (nmol l ⁻¹)	AUC (nmol l ⁻¹ h)	$t_{1/2}$ (terminal phase) (h)	$t_{\max}$ (h)	Protein bound (%)
<i>Benazeprilat</i>					
Young	476 ± 152	2765 ± 775	43 ± 13	1.5	91.7 ± 1.4
Elderly	444 ± 114	3867 ± 1340	34 ± 13	1.5	89.4 ± 4.3
<i>Enalaprilat</i>					
Young	128 ± 63	1272 ± 215	37 ± 20	4.0+	25.4 ± 11.7
Elderly	199 ± 105	2709 ± 1459	30 ± 14	5.0	13.6 ± 9.4**

* Significant difference between age groups: * $P < 0.05$ ** $P < 0.01$

+ Significant difference between drugs.

Table 2 The relationship between plasma enalaprilat or benazeprilat and percentage of plasma ACE inhibition

	$I_{\max}$ (%)		IC_{50} (nmol l ⁻¹)		Slope (gamma)	
	Enalaprilat	Benazeprilat	Enalaprilat	Benazeprilat	Enalaprilat	Benazeprilat
<i>Young subjects</i> ($n = 9$)	114.0	99.9	29.1	7.0	0.80	1.01
	127.0	99.2	30.5	7.8	0.64	1.14
	71.8	102.0	12.4	8.6	2.45	1.14
	—	—	—	—	—	—
	123.0	103.0	23.0	9.2	0.57	0.97
	101.0	90.9	20.2	16.3	0.74	1.44
	116.0	104.0	28.1	16.6	0.74	0.99
	110.0	89.6	25.9	21.8	0.90	1.96
	90.7	94.5	13.8	12.1	1.25	2.10
Mean ± s.d.	106.7 ± 17.1	97.9 ± 5.2	22.9 ± 6.5	12.4 ± 4.9	1.01 ± 0.58	1.34 ± 0.42
<i>Elderly subjects</i> ($n = 9$)	94.7	99.9	21.3	12.9	1.19	1.25
	—	—	—	—	—	—
	86.4	96.8	25.4	13.1	1.17	2.15
	86.6	103.0	20.1	19.0	0.92	0.92
	72.2	95.1	19.9	11.6	1.86	2.10
	127.0	100.0	23.5	11.0	0.79	1.12
	94.2	94.5	7.6	20.1	0.93	1.70
	106.0	101.0	20.3	12.6	0.77	0.90
	93.0	101.0	17.0	11.8	1.19	1.05
Mean ± s.d.	95.6 ± 14.2	98.9 ± 3.1	19.4 ± 5.0	14.0 ± 3.5	1.10 ± 0.33	1.40 ± 0.51

Footnote: Due to lack of fit, i.e. $F^2 < 0.8$ the data from one subject in each group have been omitted.

of the recognised predisposing factors such as sodium or volume depletion or pretreatment with diuretics and in a subsequent study was able to tolerate repeated administration of benazepril for 7 days.

The pharmacokinetic parameters derived in this study were in general agreement with those reported in the literature for both enalaprilat [16, 17] and for benazeprilat [9, 18]. There were significant age-related differences, with the AUCs for both benazeprilat and enalaprilat tending to be greater in the elderly subjects and with plasma protein binding tending to be reduced. However, there were also significant differences between the two drugs: as assessed by the appearance of their active metabolites, the conversion of benazepril to benazeprilat was more rapid than the conversion of enalapril (reduced $t_{\max}$ and increased $C_{\max}$) and the extent of the age-related changes was significantly less with benazeprilat. In particular, the AUC (0–∞) for enalaprilat was significantly greater in the elderly compared with the young subjects ($P < 0.01$) and the increment of 113% was significantly greater than that of 40% with benazeprilat. With both drugs the highest plasma concentrations and

the largest AUCs tended to occur in the elderly subjects who had the lowest creatinine clearances.

Maximal ACE inhibition was achieved more rapidly with benazepril but there were no significant age-related differences in the extent of ACE inhibition, although the duration of inhibition tended to be prolonged in the elderly. Such an age-related prolongation of plasma ACE inhibition has been reported previously after enalapril [16], although it has not been an invariable finding [17]. There was evidence to suggest that benazeprilat had greater relative potency as an ACE inhibitor since for 8/9 elderly subjects and 7/9 young subjects the concentration of benazeprilat calculated to produce half maximal inhibition of plasma ACE activity (IC_{50}) was lower than the corresponding value for enalaprilat.

Although there were some differences between enalaprilat and benazeprilat in pharmacokinetics and ACE inhibition these were not reflected in the measured hypotensive responses which were comparable. One possible explanation in the elderly subjects is that although the age-related increment in total benazeprilat concentration was less than with enalaprilat there was

comparatively more free benazeprilat (37% vs 15%) available to have pharmacological effects. Overall, the reductions in blood pressure were small in these normotensives so that differences between the drugs in the extent of blood pressure reduction might have been difficult to detect. Such differences might more readily be distinguishable in a hypertensive population.

In conclusion, benazepril demonstrates some age-related pharmacokinetic differences which are similar in

nature though not in extent to other ACE inhibitors. These differences are likely to reflect a reduction in drug clearance, whether renal or hepatic, although changes in volume of distribution cannot be excluded. Further studies, particularly with multiple doses in hypertensive patients, are required to establish the clinical relevance of the observed differences between benazepril and enalapril.

References

- Case DB, Wallace JM, Kein HJ, Sealey OE, Laragh JH. Possible role of renin in hypertension as suggested by renin sodium profiling and inhibition of converting enzyme. *New Engl J Med* 1977; **296**: 64–66.
- Lijnen P, Fagard R, Groeseneken D, M'Buyambo JR, Staessen J, Amery A. The hypotensive effect of captopril in hypertensive patients is age related. *Methods Find exp clin Pharmac* 1983; **5**: 655–660.
- Weidman P, De Myttenaere-Bursztein S, Maxwell MH, De Lima J. The effect of ageing on plasma renin and aldosterone in normal man. *Kidney Int* 1975; **8**: 325.
- Man in't Veld AJ, Schicht IM, Derkx FHM, de Bruyn JH, Schalekamp MADH. Effects of an angiotensin converting enzyme inhibitor (captopril) on blood pressure in anephric subjects. *Br med J* 1980; **280**: 288–290.
- Jenkins AC, Knill JR, Dieslinski GR. Captopril in the treatment of the elderly hypertensive patient. *Arch Int Med* 1985; **145**: 2029–2031.
- Cooper WD, Sheldon D, Brown P, Kimber GR, Isit VL, Currie WJE. Post marketing surveillance of enalapril: experience in 11,710 hypertensive patients in general practice. *J Roy Coll Gen Pract* 1987; **37**: 346–349.
- Corea L, Bentiroglio M, Verdecchio P, Provviderza M. Converting enzyme inhibition versus diuretic therapy as a first therapeutic approach to the elderly hypertensive patient. *Curr Ther Res* 1987; **36**: 347–351.
- Reid JL, Macdonald N-J, Lees KR, Elliott HL. Angiotensin converting enzyme inhibitors in the elderly. *Am Heart J* 1989; **117**: 751.
- Kaiser G, Ackermann R, Sioufi A. Pharmacokinetics of a new angiotensin-converting enzyme inhibitor, benazepril hydrochloride, in special populations. *Am Heart J* 1989; **117**: 746–751.
- Cushman DW, Cheung HS. Spectrophotometric assay and properties of the angiotensin converting enzyme of rabbit lung. *Biochem Pharmac* 1971; **20**: 1637–1648.
- Chiknas, SG. A liquid chromatography assisted assay for converting enzyme (peptidyl dipeptidase) in serum. *Clin Chem* 1979; **25**: 1259–1262.
- Sioufi A, Pommier F, Kaiser G, Dubois JP. Determination of benazepril, a new angiotensin-converting enzyme inhibitor, and its active metabolite, benazeprilat, in plasma and urine by capillary gas chromatography-mass-selective detection. *J Chromatogr* 1988; **434**: 239–246.
- Hichens M, Hand EL, Mulcahy WS. Radioimmunoassay for angiotensin converting enzyme inhibitors. *Ligand Quarterly* 1981; **4**: 43.
- Hodsman GP, Isle CG, Muvigy GD, Usherwood TP, Webb DJ, Robertson JIS. Factors related to first dose hypotensive effect of captopril: prediction and treatment. *Br med J* 1983; **286**: 832–834.
- Webster J, Newnham DM, Petrie JC. Initial dose of enalapril in hypertension. *Br med J* 1985; **290**: 1623–1624.
- Hockings N, Ajayi AA, Reid JL. Age and the pharmacokinetics of angiotensin converting enzyme inhibitors enalapril and enalaprilat. *Br J clin Pharmac* 1986; **21**: 341–348.
- Lees KR, Reid JL. Age and the pharmacokinetics and pharmacodynamics of chronic enalapril treatment. *Clin Pharmac Ther* 1987; **41**: 597–602.
- Kaiser G, Ackermann R, Dieterle W, Durnin CJ, McEwen J, Ghose K, Richens A, Holmes IB. Pharmacokinetics and pharmacodynamics of the ACE inhibitor benazepril hydrochloride in the elderly. *Eur J clin Pharmac* 1990; **38**: 379–385.

(Received 17 January 1992,
accepted 23 April, 1993)