A comparison in young and elderly subjects of the pharmacokinetics and pharmacodynamics of single and multiple doses of benazepril

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- 1 The pharmacokinetics and pharmacodynamics of single and multiple oral doses of the ACE inhibitor benazepril were investigated in young and elderly normotensive subjects.
- 2 Following multiple doses the trough concentrations were significantly higher in the elderly and the areas under the plasma concentration-time curves (AUC_{0–24}) were significantly greater, by approximately 23%.
- 3 The fall in blood pressure tended to be greater in the elderly subjects but this is likely to be attributable to their higher initial blood pressures, although it may reflect the small differences in pharmacokinetics.
- 4 The age related differences in kinetics and dynamics following multiple dosing are quantitatively similar to those obtained with single doses. However, there appears to be a quantitative difference between benazepril and other ACE inhibitors in that the age related increases were of a relatively smaller magnitude.

Keywords pharmacokinetics pharmacodynamics benazepril age

Introduction

Benazepril hydrochloride (CGS 14824A) is a non-thiol angiotensin-converting enzyme inhibitor which, after oral administration, is hydrolysed *in vivo* to the active metabolite benazeprilat (CGS 14831) [1, 2].

The effects of age on the single dose pharmacokinetics and pharmacodynamics of oral benazepril have been reported previously in a comparative study with enalapril [3]. In brief, there were pharmacokinetic differences between young and elderly subjects for both enalapril and benazepril. Overall, these differences were qualitatively similar to those reported for other ACE inhibitors [4, 5], but, with benazepril, the magnitude of the differences was significantly less than with enalapril. For example, the AUC_{0–∞} of benazeprilat in elderly subjects was 40% greater than in young subjects but this was significantly less than the corresponding 113% increment for enalaprilat. Furthermore, peak plasma concentrations of benazeprilat, unlike enalaprilat, were not significantly increased in the elderly. Despite these kinetic differences the blood pressure reductions were similar after the administration of each ACE inhibitor. This study in young and elderly subjects extends the previous observations by investigating the effects of multiple oral doses of benazepril on the plasma levels of benazeprilat, on angiotensin-converting enzyme activity and on blood pressure responses.

Methods

Subjects

The same group of nine young subjects, aged 21–39 years (all male), and nine elderly subjects, aged 66–76 years (six male), who had participated in the single dose study took part in this subsequent study. They were judged healthy on the basis of history, physical examination and routine laboratory tests including urinalysis, ECG, haematology and serum biochemistry. The principal differences between the two groups were that the elderly subjects had significantly higher initial blood pressures $147/80 \pm 18/9$ compared with $127/72 \pm 13/7$ mm Hg ($P < 0.02$) and significantly lower creatinine clearances (based on timed 24 h urine collection) 78 ± 25 ml min⁻¹ compared with 112 ± 31 ml min⁻¹ ($P < 0.05$). All subjects gave written informed consent and the study was approved by the local Ethics Committee.

Study design

In an open study, each subject received 10 mg benazepril daily for 8 consecutive days and on the eighth day reported to the Clinical Pharmacology Research Unit after an overnight fast to undertake a study identical to that after the first dose. Venous blood was collected prior to the final dose of benazepril, frequently over the

12 h following drug administration and again at 24, 48 and 72 h post-dose. Supine and erect blood pressure were measured in duplicate by Sentron semiautomated sphygmomanometer (Sentron, Bard Bimedical) at the same times as the plasma concentration measurements.

Laboratory methods

Plasma angiotensin-converting enzyme (ACE) activity was assayed by measuring the rate of generation of hippuric acid in an incubation mixture containing plasma and the peptide hippuryl-histidyl-leucine [6]. Hippuric acid was measured by h.p.l.c. as described by Chiknas [7].

Benazepril and benazeprilat were assayed by gas chromatography-mass spectrometry [8]. The extent of protein binding was investigated by means of an equilibrium dialysis technique using blood samples obtained at 2 and 6 h post dose.

Pharmacokinetic and statistical analysis

The areas under the plasma concentration-time curves were calculated by the linear trapezoidal rule. The apparent elimination half-lives ($t_{1/2}$) of benazeprilat in each individual were calculated by weighted non-linear regression of the plasma concentration-time curves from $t_{\max}$ to 72 h using a biexponential equation. The weighting factor was $1/(\text{concentration})^2$.

Plasma ACE activity inhibition and plasma benazeprilat concentrations were fitted to a sigmoid $I_{\max}$ model in individual subjects, where $I_{\max}$ is the maximum inhibition, C_{50} the metabolite concentration producing half maximum inhibition and gamma (γ) describes the sigmoidicity of the relationship.

The blood pressure data were subjected to repeated measures ANCOVA with pretreatment blood pressure as the covariate. Results throughout are presented as mean $\pm$ s.d.

Results

In general, benazepril was well tolerated by both young and elderly subjects, although one elderly female subject experienced symptomatic orthostatic hypotension after the initial 10 mg dose of benazepril. For the first day of repeated dosing she was given 5 mg benazepril without adverse event and thereafter she continued with benazepril 10 mg for the subsequent 7 days. There were no other adverse events reported.

Blood pressure and heart rate

In both groups the baseline (pre-dose) supine blood pressures were significantly lower after 1 week's dosing— $115/67 \pm 12/7$ mm Hg compared with $127/73 \pm 14/7$ mm Hg in the young and correspondingly $129/75 \pm 10/6$ mm Hg compared with $136/76 \pm 13/4$ mm Hg in the elderly. There were no overall differences between single and multiple dosing in the magnitude of the blood pressure reduction throughout the two study days. As observed in the single dose study [1], the placebo corrected absolute maximal blood pressure reductions— $24/14$ mm Hg supine and $19/10$ mm Hg erect in the elderly compared with $7/8$ mm Hg supine and $13/10$ mm Hg erect in the young—tended to be greater in the elderly group but, as baseline blood pressures also tended to be higher, there was no significant age-related difference in the hypotensive effect, for either systolic or diastolic pressure.

There were no significant differences in the heart rate response to single or multiple doses of benazepril and no significant age-related differences.

Plasma ACE activity

Plasma ACE activity is shown in Figure 1. There were no significant differences between young and elderly subjects in the steady state profiles of inhibition up to 12 h after dosing. At 24 h (and beyond) the elderly

Figure 1 Percentage inhibition of plasma angiotensin converting enzyme in young ($\square$) and elderly ($\blacksquare$) subjects after a) acute and b) chronic dosing with benazepril.

showed more prolonged ACE inhibition, $31 \pm 16\%$ in the elderly compared with $16 \pm 9\%$ in the young ($P < 0.005$).

Pharmacokinetics

As expected, after repeated administration, benazeprilat was detected in the plasma of all subjects immediately before the last dose of benazepril. Mean values were $15.3 \pm 4.5 \text{ nmol l}^{-1}$ for the young and significantly greater at $36.5 \pm 16.6 \text{ nmol l}^{-1}$ for the elderly ($P < 0.05$). These are in agreement with the corresponding values 24 h later ($17.4 \pm 7.2 \text{ nmol l}^{-1}$ in the young and $28.9 \pm 9.5 \text{ nmol l}^{-1}$ in the elderly) consistent with achieved steady state. The time to peak concentration ($t_{\max}$) was the same at 1.5 h after both acute and chronic administration in both young and elderly subjects. The parameters characterising the disposition of benazeprilat at steady state were not significantly different from those following the first dose but the AUC for benazeprilat was significantly greater in the elderly group compared with the young group ($P < 0.01$). There was no significant change in $t_{1/2\alpha}$ during chronic administration but there were non-significant trends for both $t_{1/2\alpha}$ and $t_{1/2z}$ to be

longer in the elderly after both single and multiple dosing (Table 1).

No difference was detected between young and elderly in the sensitivity of plasma angiotensin converting enzyme to inhibition by benazeprilat (Table 2). However, after repeated administration, the IC_{50} , the plasma concentration of benazeprilat required to produce 50% inhibition of plasma ACE activity, showed a non-significant overall increase from 12.8 ± 3.7 to $17.2 \pm 8.7 \text{ nmol l}^{-1}$. The trend was the same in both groups.

Protein binding of benazeprilat was consistent in both groups following single and multiple dosing: and so the small but significant difference between the groups was sustained: 91.7 ± 1.4 and 92.0 ± 1.6 in the young, 89.4 ± 4.3 and $89.3 \pm 1.3\%$ in the elderly.

Discussion

As with the single dose study [3], there were significant differences between the two age groups in the steady state disposition of benazeprilat. The trough concentrations were significantly higher in the elderly, 37 nmol l^{-1}

Table 1 Pharmacokinetic parameters for benazeprilat in young and elderly subjects

Trough	Young		Elderly	
	Acute	Chronic	Acute	Chronic
$C_{\max}$ (nmol l ⁻¹)	476 ± 152	518 ± 100	444 ± 114	497 ± 94
AUC (nmol l ⁻¹ h)	2784 ± 804	2764 ± 637	3745* ± 1336	3391* ± 1026
$t_{1/2\alpha}$ (h)	2.5 ± 0.4	2.5 ± 0.5	3.4 ± 1.0	3.3 ± 0.9
$t_{1/2z}$ (h)	24.4 ± 2.9	26.9 ± 9.1	29.6 ± 7.6	28.4 ± 9.3

Group mean ± s.d

AUC acute = 0–72 h

AUC chronic = 0–24 h

* $P < 0.01$ elderly vs young

Table 2 Inhibition of ACE activity (I) vs benazeprilat concentration (C)—derived parameters from the sigmoid $\text{I}_{\max}$ model

	$\text{I}_{\max}$		IC_{50}		Gamma	
	Acute	Chronic	Acute	Chronic	Acute	Chronic
Young						
1	99.9	101.0	7.0	28.9	1.01	1.55
2	99.2	100.0	7.8	16.2	1.14	1.17
3	102.0	96.6	8.6	28.5	1.14	1.92
4	104.0	107.0	17.0	27.0	1.14	0.96
5	103.0	112.0	9.2	31.1	0.97	0.87
6	90.9	94.8	16.3	12.3	1.44	1.61
7	104.0	97.7	16.6	10.8	0.99	1.27
8	89.6	99.0	21.8	8.8	1.96	1.50
9	94.5	92.7	12.1	16.1	2.10	1.75
Mean ± s.d.	98.6 ± 5.2	100.1 ± 5.7	12.9 ± 4.9	20.0 ± 8.3	1.32 ± 0.40	1.40 ± 0.34
Elderly						
10	99.9	98.2	12.9	13.0	1.25	1.35
11	89.9	101.0	16.2	6.8	2.16	0.68
12	96.8	94.9	13.1	20.4	2.15	2.52
13	103.0	102.0	19.0	7.6	0.92	0.87
14	95.1	96.8	11.6	15.0	2.10	1.82
15	100.0	101.0	11.0	23.1	1.12	1.13
16	94.5	101.0	20.1	8.6	1.70	1.13
17	101.0	99.7	12.6	16.1	0.90	0.98
18	101.0	99.6	11.8	23.9	1.05	1.69
Mean ± s.d.	97.9 ± 4.2	99.4 ± 2.3	14.3 ± 3.4	14.9 ± 6.5	1.48 ± 0.54	1.35 ± 0.57

vs 15 nmol l^{-1} , and the area under the plasma concentration-time curve (AUC₀₋₂₄) was significantly greater, by approximately 23%. The age-related difference in AUC was of similar magnitude to that of the single dose. These results are consistent with those obtained with other predominantly renally eliminated ACE inhibitors in elderly subjects and are indicative of a reduction in clearance with increasing age [9]. However, with benazeprilat the increase in AUC in the elderly is of lesser magnitude than that seen with other ACE inhibitors [4, 5]. This is consistent with the suggestion that both renal and extra-renal (hepato-biliary) mechanisms are implicated in the elimination of benazeprilat [10].

There was a non-significant decrease in the sensitivity of plasma ACE to inhibition by steady state benazeprilat: IC_{50} of 13.6 ± 4.3 after acute dosing, compared with 17.5 ± 8.0 at steady state. This decrease, which was more apparent in the young group, is thought to reflect induction of synthesis of angiotensin converting enzyme. There were no significant differences between young and elderly subjects in the IC_{50} for plasma ACE inhibition at steady state. This finding is at variance with the results reported for enalaprilat and perindoprilat under similar conditions where there was a reduction in the sensitivity

of plasma ACE to inhibition after multiple doses [11, 12].

Whether or not there is any clinical significance in the age-related differences in the disposition of benazeprilat remains unclear. The fall in blood pressure did appear to be greater in the elderly, and this may reflect the pharmacokinetic differences, but it may also be attributable to their higher initial pressures. Nevertheless, since the blood pressure reduction in the elderly was as great as in the young and since drug concentrations were significantly higher in the elderly any adjustment of dosage in elderly patients should be in a downward direction and this accords with the recommendations made for the currently available ACE inhibitor drugs. However, since the age-related increase in the AUC of benazeprilat was not as much as that seen with other ACE inhibitors under similar study conditions it suggests that benazeprilat has other routes of elimination which are less affected by age and this may be an important determinant of whether or not such a reduction is necessary in clinical practice.

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