COMMUNICATIONS

Pharmacokinetics of lisinopril (MK521) in healthy young and elderly subjects and in elderly patients with cardiac failure

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The pharmacokinetics of lisinopril were determined in 6 healthy young, 6 healthy elderly and 6 elderly patients with cardiac failure. Lisinopril (5 mg day^{-1}) was administered for 7 days. Plasma lisinopril concentration was measured at 1, 2, 4, 6, 8 and 24 h on days 1 and 7 of the study. The two elderly groups had higher serum lisinopril concentrations than the healthy young subjects ($P < 0.05$). There were no significant differences in any of the areas under the curve (AUC) for lisinopril plasma concentration (over time) between the healthy young and healthy elderly groups. The healthy young patients had AUC values on day 7 lower than elderly patients with cardiac failure ($P < 0.01$). Creatinine clearance was correlated with lisinopril clearance ($r = 0.63$; $P = 0.006$) and with AUC on day 7 ($r = -0.67$; $P = 0.004$). Lisinopril clearance was different in the three groups ($P < 0.05$): healthy young patients had the highest and elderly patients with cardiac failure the lowest values. Thus, in the elderly a reduced renal clearance of lisinopril leads to higher and more sustained blood levels. In elderly patients with cardiac failure, renal function should be estimated before lisinopril is prescribed as a reduction in dose may be appropriate.

Lisinopril (MK-521-MSD), a lysine analogue of enalaprilat, the active metabolite of enalapril, is a new long acting angiotensin converting enzyme (ACE) inhibitor. It is absorbed unchanged from the gastrointestinal tract, though the precise site of absorption is unknown (Ajayi et al 1984). Its pharmacological effects are attributed to the absorbed fraction of between 20 and 30%, all of which is excreted (unchanged) through the kidneys (Ulm et al 1982).

Renal blood flow and creatinine clearance are progressively reduced with increasing age (Rowe et al 1976). There are also changes in tubular function impairing Na/K exchange in the distal tubule (Macias Nunez et al 1978; McLachlan 1978). Renal function may be further reduced by conditions such as chronic cardiac failure where there is a reduction in renal perfusion (Schlant & Sonnenblick 1982). Therefore, in the elderly with cardiac failure, drugs that depend primarily on renal excretion will accumulate, increasing the possibility of toxic or untoward effects (James 1981).

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The aims of this study were to determine the effects of ageing and of cardiac failure on the pharmacokinetics of lisinopril.

Methods

Subjects. Eighteen volunteers were studied — 6 healthy young subjects (mean age ($\pm$s.d.): 28.7 ± 6.7 years), 6 healthy elderly subjects (mean age: 76.3 ± 6.4 years) and 6 elderly patients with chronic cardiac failure (CCF) (mean age: 77.8 ± 9.5 years). Subjects and patients with mental impairment, significant intrinsic renal or hepatic disease were excluded along with women taking the oral contraceptive pill, pregnant or nursing, or in whom pregnancy was a possibility.

Chronic cardiac failure patients were stabilized on diuretics alone with an upper limit of 80 mg of frusemide daily. They were not taking spironolactone or cardiac glycosides. None of the subjects or patients had blood pressures over 160/90 mmHg. All volunteers gave their informed consent and the protocol was approved by the Hospital Ethical Committee.

Trial design. Each volunteer received 5 mg of lisinopril (1 tablet) daily for 7 days. On the first day of the study (day 1), blood samples for drug assays were collected before the drug was taken (time 0) and at 1, 2, 4, 6, 8 and 24 h thereafter. Urine was collected over 0–8 and 8–24 h. Blood samples were taken on day 7 as on day 1, but further samples were taken at 48, 72 and 96 h post-drug. Urine samples on day 7 were collected as on day 1 and for a further 24 h. Between day 2 and 6, pre-drug and 4 h post-drug blood samples were taken to ensure drug compliance. 24 h urinary creatinine clearance (Ccr) and electrolyte excretions were measured before beginning and immediately after completion of the study.

All blood specimens for drug assay were centrifuged at 2000 rev min^{-1} for 20 min and the serum stored at -20 °C. All urine volumes were measured and stored at -20 °C.

Lisinopril concentration was measured (at the Institute of Bio-Pharmaceutics, Monksland, Athlone, Ireland) by a specific radioimmunoassay in which the

technique of double antibody was used (Hitchens et 1981). A logit-log transformation was used to calculate the standard curve. The sensitivity of the assay was to 0.4 ng mL^{-1} of lisinopril in serum and 40 ng mL^{-1} in urine. The intra-assay coefficients of variation were (n = 7) 7.2 and 8.5% at standard prepared concentrations of 9.6 and 101.1 ng mL^{-1} respectively. The areas under the curve (AUC) for plasma lisinopril concentration with time were calculated using the trapezoidal rule. Steady state lisinopril clearance for each patient was calculated using day 7 data:

Lisinopril clearance
= (lisinopril eliminated)/(AUC(0–24 h) × mL min^{-1}.

Statistical analysis. Differences between the groups were analysed using Student's *t*-test. The relationships between Ccr and AUC, and between Ccr and lisinopril clearance were tested by Pearson correlation and multiple regression analysis. The SPSS-X package (SPSS-X 1982) on the IBM computer at Liverpool University was used for the analyses.

Results
Complete data were obtained in 17 subjects (one of the elderly patients with cardiac failure asked to be withdrawn from the study on day 7).

Serum lisinopril concentration varied in all the volunteers, particularly in the elderly patients with cardiac failure who also had higher serum levels at all times (Fig. 1). The values after 24 h (day 1) and on day 7 predose (0 h) were significantly higher in the healthy elderly and in the elderly patients with cardiac failure than in the healthy young subjects (all $P < 0.05$). There

were no significant differences in any of the AUC values between nealthy young and healthy elderly nor between healthy elderly and elderly patients with cardiac failure (Table 1). The healthy young had significantly lower AUC values on day 7 when compared with elderly patients with cardiac failure ($P < 0.01$).

Urinary excretion of lisinopril varied widely between groups (Table 1). Combining all 3 groups, there was a significant correlation between Ccr and lisinopril clearance (r = 0.63; $P = 0.006$) and between Ccr and AUC (0–96 h) (r = -0.67; $P = 0.004$).

Ccr before and after lisinopril administration was significantly higher in the healthy young compared with the healthy elderly or with the elderly patients with cardiac failure (all $P < 0.05$). Ccr following the administration of lisinopril did not change in the healthy young, though their urinary sodium excretion decreased significantly ($P < 0.05$). Healthy elderly subjects showed a significant reduction in Ccr at the end of the lisinopril administration ($P < 0.05$). There was no difference in sodium excretion in this group before and after lisinopril (Table 1). In the elderly patients with cardiac failure, Ccr and urinary sodium excretion increased following lisinopril administration, but the changes were not statistically significant ($P = 0.504$ and 0.227 respectively; Table 1). Urinary sodium excretion was correlated with Ccr (r = 0.81; $P = 0.025$).

Lisinopril clearance was significantly different in the three groups (all $P < 0.05$). Elderly patients with cardiac failure had the lowest lisinopril clearance rates. As a result their AUC (0–96) was the highest of the three groups (Table 1). Even healthy elderly without any apparent renal dysfunction had a relatively low lisinopril clearance rate when compared with the
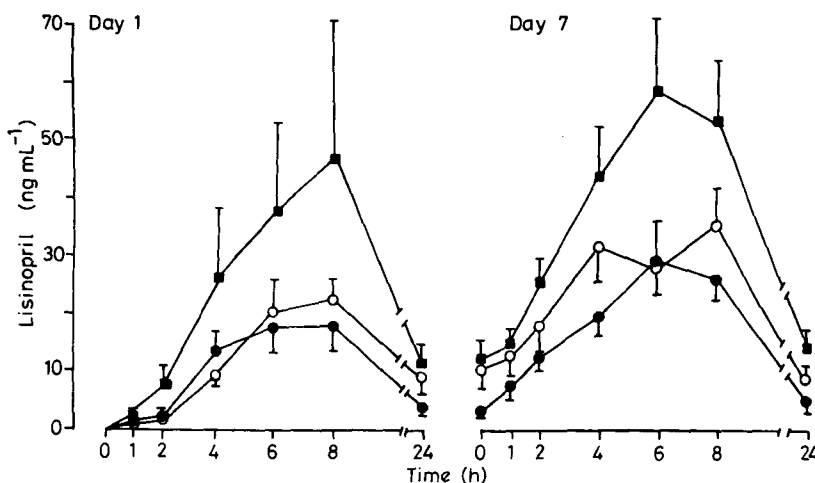

FIG. 1. Serum lisinopril concentrations (mean ± s.e.m.) in (●) healthy young, (○) healthy elderly and (■) elderly patients with cardiac failure.

Table 1. Mean (±s.e.m.) AUC and lisinopril, creatinine and sodium excretion in the urine.

Group	AUC 0–96 h (ng mL^{-1}h^{-1})	Lisinopril clearance (mL min^{-1})	Creatinine clearance		Urine sodium excretion	
			Pre-drug	Post-drug	Pre-drug	Post-drug
			(mL min^{-1})		(mmol/24 h)	
HY*	526·2 ± 77·8	47·5 ± 8·3	110·6 ± 11·4	110·5 ± 9·8	171·0 ± 19·1	134·8 ± 20·2
HE*	870·4 ± 139·2	20·8 ± 5·0	67·2 ± 8·1	58·0 ± 7·2	106·5 ± 14·0	105·2 ± 15·2
CF*	1195·9 ± 145·8	12·2 ± 3·7	31·2 ± 12·0	38·8 ± 10·7	88·3 ± 11·4	107·8 ± 19·1

* HY = healthy young. HE = healthy elderly. CF = elderly with cardiac failure.

healthy young subjects ($P = 0.20$; Table 1). A multiple regression analysis, however, did not show an *independent* effect for age or for cardiac failure on lisinopril clearance or AUC (0–96).

Discussion

This study confirms previous observations (Hansen et al 1970; James 1981) that renal elimination of drugs is impaired with increasing age. It is known that lisinopril is excreted exclusively by the kidneys (Ulm et al 1982) and in our study renal excretion of lisinopril followed Ccr and thus, renal clearance of lisinopril was impaired in the elderly groups. The reduced clearance resulted in higher and more sustained lisinopril levels in the blood, though no side effects were reported with the dose (5 mg day^{-1}) used.

The combined effects of ageing and cardiac failure further reduced lisinopril clearance. In elderly patients with cardiac failure, AUC (0–96 h) and lisinopril clearance did not change significantly in spite of the improvement in renal function seen at day 7 (Table 1). A larger study may clarify the possible independent effect of age and cardiac failure on lisinopril clearance. Nevertheless, our results suggest that renal function should be estimated before administration of lisinopril in patients with cardiac failure.

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