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The pharmacokinetics of lisinopril in hospitalized patients with congestive heart failure

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1 The pharmacokinetics of the angiotensin converting enzyme inhibitor, lisinopril, were studied in an open, randomized, balanced, two-period, crossover design in 12 in-patients with stable, chronic congestive heart failure (CHF).

2 To evaluate the pharmacokinetics of lisinopril in CHF, lisinopril was administered orally (10 mg) and intravenously (5 mg) in each patient. Each dose was followed by a 72 h period with frequent blood sampling and fractional urine collections for radioimmunoassay of lisinopril.

3 Mean urinary recovery of lisinopril was 15 and 88% following oral and intravenous administration, respectively; absorption/bioavailability of lisinopril based on urinary recovery ratios was 16%, less than that found in normal subjects.

4 Serum concentrations of lisinopril following intravenous administration were higher in this study than those previously observed in normal subjects.

5 The results of this study suggest a reduced absorption of lisinopril in CHF and altered disposition, possibly associated with age as well as the disease state.

Keywords lisinopril congestive heart failure pharmacokinetics converting enzyme inhibitors

Introduction

Lisinopril is an angiotensin converting enzyme (ACE) inhibitor structurally related (lysine analogue) to the ACE inhibitor enalaprilat. Successful clinical trials have been conducted with lisinopril in essential hypertension (Bussien *et al.*, 1985), renovascular hypertension (Karlberg *et al.*, 1984), and congestive heart failure (Dickstein *et al.*, 1986). Following administration of lisinopril in normal subjects elimination is primarily renal; there is no evidence of metabolism; absorption of an oral dose is approximately 25 to 29% (Ulm *et al.*, 1982; Beermann *et al.*, 1986). Because congestive heart failure (CHF) results in changes in regional blood flow which could alter the absorption and/or disposition of lisinopril, the present study was undertaken to evaluate the pharmacokinetics of lisinopril in patients with chronic, stable CHF.

Methods

Patient population

Twelve patients with stable, chronic CHF and a mean age of 57 years (range 25 to 69 years) participated in this study. The aetiology of CHF was ischaemic heart disease in nine male patients and dilated cardiomyopathy in one male and two female patients. All patients had been stabilized on digitalis and diuretics and no patients with an acute myocardial infarction during the preceding 6 months were included. All patients

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were considered to be in NYHA Class III or IV and showed cardiomegaly on biplane chest X-ray with radiographic evidence of pulmonary congestion. Two-dimensional echocardiographic and Doppler studies were performed for diagnostic purposes and to exclude valvular stenosis. Informed consent was obtained from all patients and the protocol was approved by the Hospital Ethics Committee and the State Drug Regulatory Agency.

Study design

The study was an open, randomized, balanced, two-period, crossover design of 6 days duration. Patients were randomly assigned to receive each of the following treatments: (1) a single, 10 mg tablet of lisinopril, and; (2) a single, 5 mg intravenous bolus of lisinopril. For clinical reasons the washout period between treatments was limited to 72 h. Patients continued their digitalis (digitoxin) and diuretic (frusemide) therapy unchanged throughout the study. All vasodilator therapy, apart from long-acting nitrates, was stopped at least 1 week before entry. Incidental concurrent therapy included nifedipine, mexiletine, warfarin sodium, amiodarone and verapamil. On the evening before the start of each treatment 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 a urinary catheter was placed for a period of at least 6 h, which required immobilization. During these 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 treatment days drug administration took place at 08.00 h in the fasting state and food was withheld for 2 h. Serum samples were obtained at 0 (predrug), 10, 20, 30 and 45 min, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 30, 36, 48 and 72 h. Urine was collected −2 to 0 (first treatment only), 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 24, 24 to 36, 36 to 48 and 48 to 72 h. All samples were stored at −20° C until assayed.

Drug assay

Lisinopril was measured in serum and urine by a radioimmunoassay specific for lisinopril (Hichens *et al.*, 1981). Samples were assayed in triplicate using 15 μl aliquots of serum or of 1:100 diluted urine.

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' and considered as 'zero' for data analyses. Samples exceeding the upper limit of the assay were diluted appropriately.

Interassay coefficients of variation were as follows for the concentrations indicated in parentheses, based upon a minimum of 23 assays: serum, 7.5% (2 ng ml^{-1}), 6.1% (10 ng ml^{-1}), 6.8% (100 ng ml^{-1}); urine, 10.0% (0.2 μg ml^{-1}), 6.4% (1 μg ml^{-1}), and 5.3% (10 μg ml^{-1}).

Data analysis

The following pharmacokinetic parameters were observed or estimated: lisinopril serum concentration-time profiles; percent-dose urinary recovery of lisinopril; ratio urinary recovery of lisinopril (oral *vs* intravenous administration, dose-adjusted) and 72 h area under the lisinopril serum concentration-time curves (AUC). Percent-dose urinary recovery was not calculated for Patient 1 following administration of lisinopril i.v. due to incomplete urine collection. This patient was thus excluded from the analysis of urinary recovery.

Analysis of variance for a two-period, crossover design (Grizzle, 1965, 1974) was used to analyze % dose urinary recovery and 72 h AUC. The test for carryover effects was not significant for AUC, but was significant for % dose urinary recovery. Comparison of treatment sequences using the Wilcoxon Rank-Sum test with respect to ranks of the ratio % dose urinary recovery, oral to intravenous administration, implied, however, that the urinary recovery carryover effect was negligibly small relative to the treatment differences. Approximate 95% confidence intervals were constructed for mean % dose urinary recoveries and mean AUC. Approximate 95% confidence intervals for the mean ratio % dose urinary recovery were constructed from log-transformed data. The upper and lower limits of the resulting confidence intervals were then exponentiated to obtain an approximate 95% confidence interval for the geometric mean. All confidence intervals were calculated assuming a *t*-distribution.

Results

All patients completed the study as per protocol. Both the oral and intravenous treatments were well tolerated (Dickstein *et al.*, 1987a). No adverse effects were observed. Mean intra-arterial blood pressure at hour 0 was 94 ± 13 mm Hg before oral administration of lisinopril and 93 ± 13 mm Hg before intravenous administration of lisinopril and fell markedly following both oral and intravenous administration of lisinopril. The maximum hypotensive effect for intravenous lisinopril was −25 ± 9 mm Hg and occurred at 105 min after dosing; that for oral lisinopril was −19 ± 9 mm Hg and occurred at 210 min after dosing. Symptoms of hypotension were absent. There was no significant difference in serum creatinine before (95 ± 18 μmol l^{-1}) and after (96 ± 16 μmol l^{-1}) dosing.

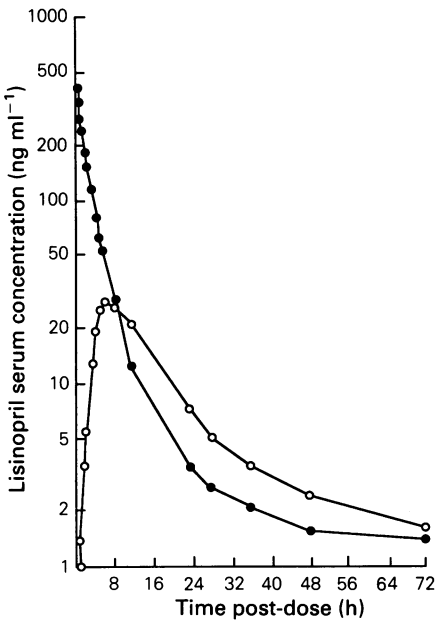

Figure 1 Mean serum concentrations of lisinopril following oral (10 mg) (○) and intravenous (5 mg) (●) administration in patients with congestive heart failure (n = 12).

Figure 1 shows the mean lisinopril serum concentrations after oral and intravenous administration. Both profiles are polyphasic with a prolonged terminal phase. The mean profile for oral administration peaks at approximately 6 h after dosing.

Summary results for urinary recoveries of lisinopril and AUC are presented in Table 1. Mean urinary recoveries ± s.d. were 15 ± 6 and 88 ± 7% for oral and intravenous administration of lisinopril, respectively. The geometric mean ratio of urinary recoveries, oral to intravenous administration, of 16% (range 8 to 29%) is an estimate of absorption and bioavailability of lisinopril from the oral dosage form.

Discussion

The results of a study in which a single 10 mg oral dose of lisinopril was given to normal subjects (Ulm *et al.*, 1982) and a study in which a 5 mg dose of lisinopril was given as an intravenous bolus in normal subjects (Beermann *et al.*, 1986, 1988) serve as a basis of comparison for the results obtained in this study in patients with congestive heart failure (CHF), although statistical comparisons across studies are not appropriate.

Table 1 Summary results* for urinary recoveries and 72 h area under the serum concentration-time curve (AUC) for lisinopril following oral and intravenous administration of lisinopril in patients with congestive heart failure

	n	*Mean*	*s.d.*	*Range*	*95% C.I.*
Urinary recovery†					
Oral (10 mg) (% dose)	11	15	6	(7.0, 26.0)	(11.0, 19.0)
Intravenous (5 mg) (%dose)	11	88	7	(74.0, 100.0)	(83.0, 92.0)
Oral/intravenous (dose-adjusted)	11	0.16**	—	(0.08, 0.29)	(0.12, 0.21)
72 h AUC (ng ml^{-1} h)					
Oral (10 mg)	12	530	377	(213, 1530)	(290, 769)
Intravenous (5 mg)	12	1203	334	(748, 1798)	(990, 1415)

* Number of subjects included in analyses (*n*); mean; standard deviation (s.d.); range; 95% confidence intervals (C.I.)

** Geometric mean

† Patient 1 excluded due to incomplete urinary recovery for lisinopril i.v. treatment

Essentially all of the dose is recovered in the urine when lisinopril is administered intravenously to normal subjects and patients with congestive heart failure. The small difference in mean calculated percent-dose urinary recovery (~ 88% (CHF) *vs* ~ 100% (normal subjects)) probably reflects the difficulties encountered in determining the exact volume of solution administered and, hence, the exact dose and/or incomplete urine collections. Given complete recovery of lisinopril in the urine following intravenous administration, urinary recovery following oral administration *per se* as well as urinary recovery ratios, oral to intravenous administration, provides an estimate of both bioavailability and absorption (i.e., for this drug, bioavailability equals absorption). Absorption (bioavailability) of an oral dose of lisinopril appears to be reduced in congestive heart failure when compared with normal subjects (~ 16% *vs* ~ 29%).

The mean serum profiles for lisinopril for intravenous and oral administration in patients with congestive heart failure compared with normal subjects are presented in Figures 2 and 3, respectively. Both the oral and intravenous profiles are similar in shape for normal subjects and CHF patients. Mean oral profiles peak at the same time (approximately 6 h after the dose) for normal subjects and patients. Serum concentrations, however, are greater in CHF patients than in normal subjects for intravenous administration of lisinopril and generally less in CHF patients than in normal subjects for oral administration of lisinopril. Corresponding AUCs are 1203 ng ml^{-1} h (CHF) *vs* ~ 980 ng ml^{-1} h (normal subjects) for intravenous dosing and 530 ng ml^{-1} h (CHF) *vs* ~ 680 ng ml^{-1} h (normal subjects) for oral dosing.

The intravenous results are similar to those reported for the converting enzyme inhibitor enalaprilat (Dickstein *et al.*, 1987b) and are consistent with a hypothesis of a decreased plasma clearance for lisinopril in CHF patients, which could be a function of age (associated with, for example, a reduction in renal function) as well as the disease state. Five of the CHF patients were > 60 years of age, four were 55 to 59 years of age. The maximum age of the normal subjects was 34 years in the intravenous study and 27 years in the oral study. Renal function, however, was not assessed in any of the three studies.

Although there appears to be an approximate 45% reduction in absorption (bioavailability) for oral administration of lisinopril in CHF patients compared with normal subjects based on urinary recoveries, the corresponding reduction in AUC is only approximately 22%. Given the observed increase in AUC for intravenously

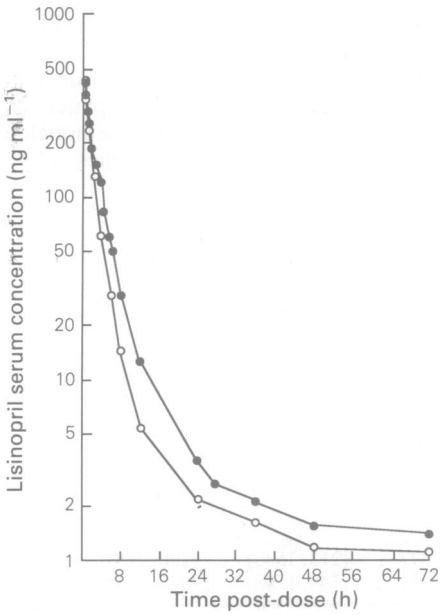

Figure 2 Mean serum concentrations of lisinopril following a 5 mg intravenous dose in normal subjects (Beerman *et al.*, 1988) (○) and in patients with congestive heart failure (●) (n = 12).

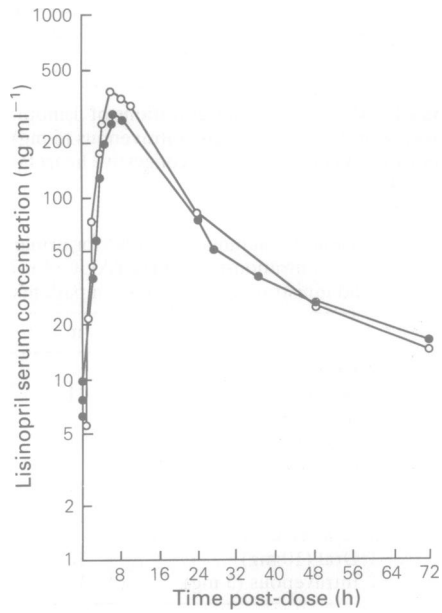

Figure 3 Mean serum concentrations of lisinopril following a 10 mg oral dose in normal subjects (Ulm *et al.*, 1982) (○) and in patients with congestive heart failure (●) (n = 12).

administered lisinopril (approximately 23%) for CHF patients *vs* normal subjects, it is likely that in the case of orally administered lisinopril, serum concentrations in CHF patients compared with normal subjects represent the net effect of reduced absorption of lisinopril and a reduced plasma clearance.

As with enalaprilat (Till *et al.*, 1982, 1984) it has been postulated that the terminal phase of the lisinopril serum concentration profile reflects nonlinear binding of lisinopril to angiotensin converting enzyme (Beermann *et al.*, 1986). The contribution of a nonlinear binding component to lisinopril serum profiles precludes conventional model-dependent and model-independent calculations of such parameters as apparent volume of distribution, clearance and serum half-life unless the serum data can be appropriately corrected for this binding. As previously noted, however, serum concentration data in this study are consistent with a hypothesis of a decreased plasma clearance and a decrease in absorption associated with the decreased cardiac output and organ perfusion of CHF (Wilkinson, 1976) and/or ageing. In addition, similarity in the shapes of the lisinopril serum profiles for CHF patients and normal subjects and in the effective half-lives for accumulation of lisinopril (approximately 12 h in CHF patients, estimated in this single-dose study from the ratio of urinary recovery of lisinopril extrapolated to infinity to urinary recovery for a dosing interval (0 to 24 h) following oral administration (Kwan *et al.*, 1984) *vs* 12.6 h in normal subjects (Beerman *et al.*, 1985)) supports speculation that the apparent reduction in plasma clearance for lisinopril in CHF is accompanied by a corresponding reduction in volume of distribution, as was found by Ueda & Dzindzio (1981) for quinidine. Steady-state concentrations of lisinopril would be expected to be higher in CHF following intravenous multiple dosing of a given dose of lisinopril and lower following oral multiple dosing of a given dose of lisinopril, therefore, but the time to reach steady state and the accumulation of lisinopril at steady state should be the same in CHF patients as found in normal subjects (achievement of steady state by the third daily oral dose with an accumulation ratio at steady state of 1.38 (Beermann *et al.*, 1985)). The predicted accumulation ratio for once-daily dosing of lisinopril in CHF patients at steady state is approximately 1.35.

Conclusions

Intravenous lisinopril data suggest a reduced plasma clearance with a corresponding reduced volume of distribution in congestive heart failure patients when compared with normal subjects, which may be associated with age as well as the disease state; absorption of orally administered lisinopril appears to be reduced as well. As a result, intravenous administration of lisinopril in congestive heart failure patients could result in slightly elevated serum concentrations of drug while oral administration could result in reduced serum concentrations.

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