The pharmacokinetics of quinapril and quinaprilat in patients with congestive heart failure

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The pharmacokinetics of quinapril and its active metabolite quinaprilat were studied in 12 patients with congestive heart failure (CHF) after multiple oral doses of 10 mg quinapril twice daily. Six patients had an ejection fraction of <35% and six had an ejection fraction between 35%–50%. Increases in the apparent elimination half-life and in AUC(0,12h) values of quinaprilat were associated with smaller ejection fractions, decreased creatinine clearance, and increased patient age. Comparison with data from age-matched controls having comparable renal function suggests that creatinine clearance is the major determinant of quinaprilat clearance. CHF *per se* appears to have minimal effect. Dosing of quinapril in patients with CHF should be based on their renal function.

Keywords quinapril quinaprilat pharmacokinetics congestive heart failure

Introduction

Quinapril is a nonsulphydryl angiotensin converting enzyme (ACE) inhibitor which is de-esterified *in vivo* to the active di-acid metabolite quinaprilat. Quinaprilat is largely excreted unchanged by the kidneys and its clearance is directly related to renal function [1]. Quinapril, like other ACE inhibitors, is useful in the treatment of CHF. Pathophysiological changes in patients with CHF include diminished renal and/or hepatic arterial flow, splanchnic blood flow and liver metabolic capacity, and the development of gastrointestinal wall oedema and hepatic venous congestion [2]. These changes may affect pharmacokinetics. Therefore, we have measured steady-state plasma concentrations of quinapril and its active metabolite quinaprilat in patients with chronic CHF.

Methods

Subjects

Twelve outpatients (10 male, 2 female) aged 49 to 77 years (mean 65 years) and weighing 55 to 91 kg (mean 80 kg), with NYHA class II or III CHF participated in this study. Six patients had a cardiac ejection fraction of <35% and six a cardiac ejection fraction of 35–50%. Exclusion criteria included a

history of significant renal or hepatic disease, aortic or mitral valve disease, unstable angina pectoris, ventricular fibrillation, systemic lupus erythematosus, a myocardial infarction within the past 3 months, a history of adverse reactions to quinapril or other ACE inhibitors, a readily treatable cause for CHF, systolic blood pressure of <100 mm Hg or >160 mm Hg, diastolic pressures >95 mm Hg or an ANA titre >1:40. Females of childbearing potential were excluded as were subjects receiving other investigational drugs or any drug known to cause pharmacokinetic interactions. Potassium sparing diuretics, vasodilators, other ACE inhibitors, calcium antagonists, and long acting nitrates were excluded. The study was approved by the Canterbury Area Health Board ethics committee and written informed consent was obtained from each patient.

Drug dosage and administration

The starting dose of quinapril was 5 mg orally and, if tolerated, this was repeated at 12 h intervals until day 5. On day 5 the dose was increased to 10 mg and, if tolerated, this dose was administered at 12 h intervals for 4 weeks. On the 29th day, after an 8 h overnight fast, a final dose was administered along with 100 ml of tap water.

Clinical evaluation

Physical examination was performed at screening and again 24 h after the last dose of quinapril. Recumbent blood pressures and heart rates were measured at screening and again at the end of the study. Serial blood pressures and heart rates were measured with the patient supine and standing on days 1 and 5 at 0.25, 0.5, 1, 1.5, 2 and 6 h after dose. Electrocardiography was performed at screening, at the end of the study, and at other times if clinically indicated. All adverse effects were recorded by each patient in a diary along with the time of ingestion of each dose. Each patient was given a bottle containing excess tablets and a tablet count was made to estimate compliance.

Left ventricular ejection fractions were measured at screening and again on day 28 between 0–2 h after the morning quinapril dose using a radionuclide method. Specifically, following *in vivo* red blood cell labelling with 99-m technetium, patients were imaged in a modified left anterior oblique position using a GE 400 AT gamma camera interfaced to a Star 2 computer system (General Electric Medical Systems, USA). Data were analysed using a fully automatic software option (General Electric P.A.G.E.).

Haematology, biochemical tests and urinalysis were performed at screening and again on days 1, 7, 15, 22 and the day following discontinuation of quinapril.

Blood collections

Blood was collected for analysis of plasma quinapril and quinaprilat concentrations just prior to quinapril dosing on day 1, and immediately before the morning dose on day 22 and day 29. On day 29, samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h after dose.

Blood samples were centrifuged, and plasma samples transferred to plastic tubes and stored frozen at -20°C until assay.

Analytical methods

Quinapril and quinaprilat in plasma were assayed using gas chromatography/electron capture. Details of the method and its precision have been given previously [1].

Pharmacokinetic analyses

Peak drug and metabolite concentrations ($C_{\max}$) and corresponding times to peak concentrations ($t_{\max}$) were obtained directly from the data. Values of AUC(0,12h) were calculated from quinaprilat concentration-time data using the linear trapezoidal rule. An apparent elimination rate constant (λ_z) was estimated from the slope of the least squares linear regression of logarithmic plasma quinaprilat concentrations in the terminal elimination phase. The apparent elimination half-life ($t_{1/2,z}$) was calculated from 0.693 divided by λ_z . The equation of Cockcroft & Gault [3] was used to calculate creatinine clearance from serum creatinine values on day 30.

Statistical analyses

Relationships between pharmacokinetic parameters for quinaprilat, ejection fraction determined on day 28, and creatinine clearance were evaluated using linear regression and multiple linear regression.

Results

Multiple doses of quinapril up to 10 mg twice daily were generally well tolerated by patients with CHF. Four patients (33%) reported a total of six adverse drug reactions during the trial. None required withdrawal from the study. Mild tiredness, nausea, headache and dry cough were reported following 10 mg twice daily of quinapril. One subject experienced syncope on day 8. A pacemaker was inserted. This symptom was thought unlikely to be related to quinapril administration as the patient had experienced similar symptoms prior to the study.

There were no significant changes in physical examinations or electrocardiograms. Blood pressure reductions during the 4 h period following initial 5 and 10 mg dose titrations were generally transient and well-tolerated. Heart rates remained unchanged throughout the study. Ejection fractions decreased in six patients and increased in the other six patients over the 1 month period of treatment. No clinical laboratory abnormalities were considered related to study medication.

Individual and mean pharmacokinetic parameters of quinaprilat and values of ejection fraction on day 28 are shown in order of decreasing creatinine clearance in Table 1. The short half-life and low plasma concentrations of quinapril precluded reliable assessment of its pharmacokinetics.

Increases in $t_{1/2,z}$ and AUC(0,12h) values of quinaprilat were associated with smaller ejection fractions, decreased creatinine clearance, and increased patient age. Regression analyses indicated that there were significant relationships between the $t_{1/2,z}$ of quinaprilat and ejection fraction ($r^2 = 0.57$, $P = 0.005$), and creatinine clearance and age ($r^2 = 0.64$, $P = 0.002$).

Discussion

Values of AUC(0,12h) of quinaprilat in patients with CHF in the present study were similar to those observed previously in elderly subjects without CHF, but substantially different from those in younger subjects [4]. Elderly patients with CHF and elderly subjects without CHF were relatively well-matched with respect to age and creatinine clearance values in these separate studies. Therefore, the results confirm previous findings showing the importance of renal function in the dosing of quinapril.

Similar results have been reported for other ACE inhibitors. Dickstein *et al.* [6] attributed the lower clearance of enalaprilat in patients with CHF to the

Table 1 Individual and mean pharmacokinetic parameters for quinaprilat at steady-state in patients with congestive heart failure shown in order of decreasing creatinine clearance

Subject	CL _{cr} ^a	Ejection fraction (ml min ⁻¹)	C _{max} (%) ^b	t _{max} (h)	AUC(0,12h) (µg l ⁻¹ h)	t _{1/2,z} (h)
12	101	30	235	1.5	1030	2.9
9	98	27	606	2.5	2480	3.1
11	96	55	276	2.5	1090	3.2
10	92	71	287	1.0	1140	1.6
8	85	54	372	2.5	1760	3.3
1	69	17	388	0.5	1750	6.4
2	66	39	307	1.5	1580	3.1
3	65	31	428	2.5	2490	3.8
4	63	21	218	2.5	1250	4.3
5	47	23	425	1.5	1940	3.8
6	40	18	379	2.5	1580	4.3
7	38	30	424	1.5	2380	4.3
Mean	72	35	362	1.88	1706	3.7
s.d.	22	17	197	0.71	533	1.2
Range	38–101	17–71	281–606	0.5–2.5	1030–2490	1.6–6.4

^aCL_{cr} Creatinine clearance determined from a serum creatinine measurement on day 30.^b Determined on day 28.

greater age of the patients. An age-dependent decline in renal function appears to account for a lowered enalaprilat clearance in healthy elderly subjects [7]. Using a population pharmacokinetic approach, Thompson *et al.* [8] reported that the clearance of lisinopril was reduced in patients with CHF in association with a reduction in renal function. Gautam *et al.* [9] reported similar findings and proposed that lisinopril dosage should be adjusted on the basis of renal function in elderly patients with CHF. Differences in ramipril pharmacokinetics between patients with CHF and normal subjects may also be attributable to reduced renal function in elderly patients with CHF [10].

The absolute values of $t_{1/2,z}$ in this study should be

treated with caution. A prolonged terminal phase related to binding to the ACE molecule in plasma has been observed with a variety of ACE inhibitors, but it is evident only if the assay detects very low concentrations [5]. A prolonged terminal phase has been shown for quinapril with a more sensitive assay (sensitivity 0.3 µg l⁻¹) [11] than used in this study (sensitivity 5 µg l⁻¹).

In summary, comparison of our data with those from control subjects of similar age and renal function suggests that the latter is the major determination of quinaprilat clearance, with CHF *per se* having minimal effect. Dosing of quinapril in patients with CHF should be based on renal function.

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