Br. J. clin. Pharmac. (1990), **30**, 213–220

The pharmacokinetics and pharmacodynamics of quinapril and quinaprilat in renal impairment

E. J. BEGG[1], R. A. ROBSON[1], R. R. BAILEY[2], K. L. LYNN[2], G. J. FRANK[3] & S. C. OLSON[3]
[1]Department of Clinical Pharmacology, Christchurch School of Medicine, Christchurch, New Zealand, [2]Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand and [3]Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan, USA

1 The pharmacokinetics and pharmacodynamics of quinapril and its active metabolite quinaprilat were studied in 20 subjects with renal function varying from normal to severe renal failure, during the approach to and at steady-state, and for 72 h after cessation of quinapril 20 mg orally for 7 days.
2 The apparent oral plasma clearance of quinaprilat (dose of quinapril equivalent/AUC of quinaprilat) was directly related to creatinine clearance (CL_{Cr}). The predicted apparent oral clearance of quinaprilat was zero when CL_{Cr} was zero, suggesting minimal extrarenal elimination.
3 Peak and trough concentrations of quinaprilat, and its apparent elimination half-life, varied inversely with CL_{Cr}.
4 Trough concentrations of quinaprilat showed no accumulation between 2 and 7 days, even in severe renal impairment.
5 There was a weak relationship between the oral plasma clearance of quinapril and CL_{Cr}.
6 ACE inhibition was marked and prolonged in all subjects, with 50% inhibition at 2.7 ± 1.9 ng ml^{-1} of quinaprilat. The time for which ACE inhibition was >90% was related inversely to CL_{Cr}.
7 Aldosterone concentrations and plasma renin activity responded in a predictable way, but with no clear relationship to CL_{Cr}.
8 Atrial natriuretic peptide concentrations were not affected by quinapril administration.
9 Glomerular filtration rate, as measured by Tc^{99m}DTPA clearance, was not affected by quinapril administration.
10 Blood pressure at steady-state decreased significantly in the subjects with hypertension. The changes in blood pressure were not related to renal function.
11 These results suggest that the dosage rate of quinapril may have to be altered in renal impairment. Reducing the dose, rather than prolonging the dose interval, may be more convenient in view of the normal dose interval of 24 h.

Keywords quinapril quinaprilat pharmacokinetics pharmacodynamics renal impairment

Correspondence: Dr E. J. Begg, Department of Clinical Pharmacology, Christchurch School of Medicine, Christchurch, New Zealand

Introduction

Quinapril is a non-sulphhydryl angiotensin converting enzyme (ACE) inhibitor which is deesterified to the active diacid metabolite quinaprilat. Quinaprilat is largely excreted unchanged through the kidneys, and its clearance is likely to be affected by renal functional impairment. Renal impairment may also influence metabolic drug clearance (Reidenberg, 1977). It is therefore important to determine how renal impairment influences both the metabolic clearance of quinapril and the renal clearance of quinaprilat. This study was designed to investigate the pharmacokinetics and pharmacodynamics of quinapril and quinaprilat during the approach to steady-state, at steady-state, and after cessation of dosing, in subjects with renal function varying from normal to severe failure.

Methods

Subjects

Twenty volunteers were allocated into four groups of five according to an estimate of their creatinine clearance (CL_{Cr}) using the formula of Cockcroft & Gault (1976), i.e. CL_{Cr} (ml s^{-1}) = [(140 − age).wt (kg)]/48869.[C_{Cr}] (mmol l^{-1}) (×0.85 for females).

Group 1: $CL_{Cr} > 1.5$ ml s^{-1} (>90 ml min^{-1}).
Group 2: $CL_{Cr} > 1.0$ and $< = 1.5$ ml s^{-1} (60–90 ml min^{-1}).
Group 3: $CL_{Cr} > 0.5$ and $< = 1.0$ ml s^{-1} (30–60 ml min^{-1}).
Group 4: $CL_{Cr} < = 0.5$ ml min^{-1} and not on dialysis (<30 ml min^{-1}).

Stability of renal function was established by the measurement of at least two baseline serum creatinine concentrations (C_{Cr}).

Fifteen male and five female subjects aged between 18 and 65 years (mean 39.4 ± 15.9 (s.d.) years) with normal hepatic, cardiac and gastrointestinal function, and (except for two) within 20% of ideal body weight (mean 75.3 ± 12.9 (s.d.) kg) participated in the study. Eleven subjects were hypertensive as defined by a diastolic blood pressure of ≥95 mm Hg. Three were from each of groups 2 and 4, and five from group 3, with prestudy diastolic blood pressures ranging from 95 to 130 mm Hg. Antihypertensive medications were discontinued at least 2 weeks before the study, except in two cases where this proved impossible. Subject 15 was taking labetalol which was stopped but reinstituted when diastolic blood pressures rose to >140 mm Hg. Subject 9 had the nephrotic syndrome and was treated with 160 mg frusemide. This treatment had been critical in his/her management and was not discontinued. Concomitant therapy with any drug known to affect drug disposition was discontinued at least 2 weeks before the study. Patients with secondary hypertension, known allergy or significant adverse reactions to other ACE inhibitors were excluded as were females at risk of pregnancy.

Drug dosage and administration

Each subject received a 20 mg capsule of quinapril orally along with 150 ml of water every morning at 09.00 h for a total of seven doses.

Laboratory evaluation

During the day before the first dose of quinapril, blood (10 ml) was sampled at 09.00 h and 1, 2, 4, 6, 8, 12 and 24 h later, for measurement of ACE activity, aldosterone concentration, plasma renin activity (PRA) and concentration of atrial natriuretic peptide (ANP). Immediately before drug administration each day at 09.00 h, blood (15 ml) was again sampled for measurement of these indices, and also for quinapril and quinaprilat concentrations. After the last dose, blood (5 ml) was sampled at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 24, 48 and 72 h for measurement of quinapril and quinaprilat concentrations. Additional 10 ml samples were taken for measurement of ACE activity, aldosterone concentration, PRA and ANP concentration at 1, 2, 4, 6, 8, 12, 24, 48 and 72 h.

Blood was collected in heparinised tubes for measurement of quinapril and quinaprilat concentrations and ACE activity; in EDTA tubes for PRA and aldosterone concentrations, and EDTA.trasylol tubes for ANP (Yandle *et al.*, 1986).

All urine passed during the 24 h period after the last dose was collected, the volume was measured and a 50 ml aliquot taken for assay of quinapril and quinaprilat.

All samples were stored at −20° C prior to assay except those for measurement of ACE inhibition and ANP which were stored at −80° C.

Blood pressure and heart rate were monitored daily at 08.45 h. Blood pressures were recorded as the mean of four measurements using a standard mercury sphygmomanometer.

Glomerular filtration rate

A formal assessment of glomerular filtration rate (GFR) was made before quinapril was

administered, and again immediately after the last dose using Tc^{99m}DTPA (Technetium labelled diethylenetriamine pentaacetic acid). Three blood samples (5 ml) were taken at the following intervals for each group.

Group 1: 2, 4 and 6 h.
Group 2: 2, 4 and 8 h.
Group 3: 2, 6 and 12 h.
Group 4; 2, 6 and 24 h.

A monoexponential function was fitted to the plasma elimination curve of Tc^{99m}DTPA by linear regression of the log-linear concentration-time data and clearance (i.e. GFR) was calculated from kV, where k is the elimination rate constant and V is the volume of distribution.

Pharmacokinetic analysis

Peak drug and metabolite concentrations (C_{max}) and the corresponding times to peak concentration (t_{max}) were noted directly from the data. The areas under the curves (AUC) of plasma drug and metabolite concentrations from time zero to the time of the last detectable concentrations were calculated using the linear trapezoidal rule. The total AUC of quinapril was calculated by summing the AUC to the last detectable concentration with the last detectable concentration divided by the elimination rate constant (k). The value of AUC(0,24) rather than the AUC to infinity was calculated and used in analysis of the quinaprilat concentration-time curves which exhibited measurable 24 h post-dose concentrations. The oral clearances (CL_{po}) of quinapril and quinaprilat were calculated by dividing the dose by the respective AUCs over the steady-state dosing interval of 24 h. The value for quinaprilat assumed complete conversion of quinapril to this metabolite.

The renal clearances (CL_R) of quinapril and quinaprilat at steady-state were calculated from the amounts excreted in urine over 24 h divided by the corresponding plasma AUC(0,24) values.

Pharmacodynamic analysis

ACE inhibition ACE activity was expressed as percentage inhibition (I%) and plotted against plasma quinaprilat concentration (C) to derive, by non-linear regression, values for maximum inhibition (I_{max}) and the concentration at which 50% inhibition occurs (IC_{50}), using the logistic function, $I\% = I_{max}.C^n/(IC_{50}{}^n + C^n)$, where 'n' is a fitted parameter relating to the slope (Kelman *et al.*, 1983). The concentration at which 90% ACE inhibition occurs was calculated using the fitted parameters. The AUCs of ACE inhibition over 24 and 72 h were measured using the trapezoidal rule, and regressed against CL_{Cr}. In addition, the time for which ACE inhibition was greater than 90% (corresponding to quinaprilat concentrations $>IC_{90}$) was read directly from the individual concentration-time curves with extrapolation using k where necessary.

Aldosterone and PRA Aldosterone concentrations and PRA for each individual were regressed against CL_{Cr}. Aldosterone concentrations and PRA at steady-state during quinapril administration were compared with baseline values.

ANP and GFR Mean ANP and GFR values before and after quinapril were compared.

Blood pressure and heart rate Blood pressure and heart rate were compared before and during drug administration.

Statistical analysis

The effect of renal impairment on the pharmacokinetics of quinapril and quinaprilat was evaluated using linear regression and Pearson's product-moment correlation, with CL_{Cr} as the independent variable. Where the examination of residuals indicated a nonlinear relationship, an inverse function was fitted, if such a relationship was appropriate theoretically, and the residual mean squares were compared with those from linear regression (the number of fitted parameters being equal). The effect of renal impairment on the AUC of ACE inhibition was also evaluated in this manner.

The effect of quinapril administration on ACE inhibition, aldosterone concentrations and PRA, over the 24 h steady-state interdose interval was analysed using ANOVA with comparisons between groups, between predrug and steady-state measurements, and between different time points, with *post-hoc* analysis using Tukey's test. The effect of quinapril administration on daily predose values of ACE inhibition, aldosterone concentration and PRA, and on the values at 24, 48 and 72 h after cessation of drug was analysed by ANOVA, with comparisons between groups and between time points, as was the blood pressure and heart-rate data.

ANP and GFR values before and after quinapril were compared using the paired t-test.

Significance was assumed at a probability level of $P < 0.05$, and for the repeated measures ANOVA analyses the Greenhouse-Geisser correction for possible non-homogeneity of variances and covariances was used (Geisser & Greenhouse, 1958).

Assay methods

Quinapril and quinaprilat Quinapril and quinaprilat were assayed in plasma and urine using a gas-chromatography/electron capture detection method. Plasma or urine were passed through a Bond-Elut® C18 column, the eluate methylated with diazomethane, and the methylated products extracted into hexane and derivatised with trifluoroacetic anhydride. Concentrations of the compounds were measured by relating peak areas to those of an internal standard (CI-907, Warner-Lambert Company). There were no interfering peaks for quinapril, quinaprilat or the internal standard. The standard curve was linear from 5–1000 ng ml^{-1} for plasma, and from 50–2000 ng ml^{-1} for urine. The lower limit was 5 ng ml^{-1} in plasma and 50 ng ml^{-1} in urine for both quinapril and quinaprilat.

For the plasma assay the mean interassay coefficient of variation was 8.3% (2.1–34.6%) and 8.0% (2.3–27.3%) for quinapril and quinaprilat, respectively. The intra-assay coefficient of variation ranged from 6.6–14.4% for quinapril and 8.3–16.9% for quinaprilat.

For the urine assay the mean interassay coefficient of variation was 6.1% (1.8–11.0%) and 6.2% (2.0–16.4%) for quinapril and quinaprilat, respectively. The intraassay coefficient of variation ranged from 6.3–11.6% for quinapril and 4.3–17.3% for quinaprilat.

ACE activity, aldosterone, PRA and ANP ACE activity was measured using synthetic hippuryl-histidyl-leucine substrate (Lieberman, 1984). Aldosterone (Lun *et al.*, 1983), PRA (Dunn *et al.*, 1976) and ANP (Yandle *et al.*, 1986) were all measured by radioimmunoassay.

All subjects gave written, informed consent. The study was approved by the Canterbury Hospital Board Ethics Committee, and conducted in accordance with the Declaration of Helsinki guidelines on medical experimentation.

Results

Pharmacokinetics

The pharmacokinetic parameters of quinapril and quinaprilat are shown in Tables 1 and 2. The mean plasma concentration-time profiles of quinaprilat for each group after the last dose at steady state are shown in Figure 1.

The oral plasma clearance of quinapril decreased slightly as CL_{Cr} decreased ($y = 1084 + 9.3x$, $r^2 = 0.31$, $P = 0.01$, Figure 2). The intercept on the y-axis (i.e. clearance when renal function is zero) suggests predominantly extrarenal elimination.

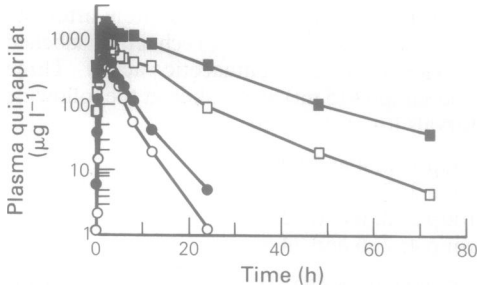

Figure 1 Mean plasma concentrations of quinaprilat after the last dose of quinapril (○ Group 1, CL_{Cr} >90 ml min^{-1}, ● Group 2, 60–90 ml min^{-1}, □ Group 3, 30–60 ml min^{-1}, ■ Group 4, <30 ml min^{-1}).

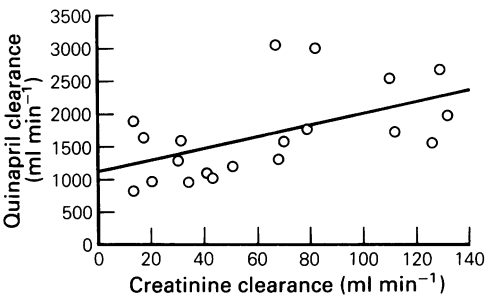

Figure 2 Plasma clearance of quinapril *vs* creatinine clearance. $y = 1084 + 9.3x$, $r^2 = 0.31$, $P = 0.01$.

The mean renal clearance of unchanged quinapril was a small percentage (mean 1.8%) of the plasma clearance (Table 1), confirming that the elimination of quinapril is predominantly by metabolism. The renal clearance of quinapril had a strong direct relationship with CL_{Cr} ($y = 0.48x - 6.32$, $r^2 = 0.6$, $P < 0.001$). Metabolic clearance, derived by subtracting the measured renal clearance from the plasma clearance, was weakly related to CL_{Cr} ($y = 1098 + 8.8x$, $r^2 = 0.28$, $P = 0.01$). The values of C_{max}, t_{max} and $t_{½}$ showed no relationship with CL_{Cr}.

The apparent oral clearance of quinaprilat showed a strong direct relationship with CL_{Cr} ($y = 1.65x - 11.1$, $r^2 = 0.85$, $P < 0.001$, Figure 3). The intercept on the y-axis (i.e. clearance of quinaprilat when CL_{Cr} is zero) was not significantly different from zero suggesting that the elimination of quinaprilat is entirely renal. The measured renal clearance of quinaprilat was only 30% of its total clearance, suggesting that the oral availability of quinaprilat from quinapril

Table 1 Individual CL_{Cr} values and pharmacokinetic parameters for quinapril at steady state

Group	*Subject*	CL_{Cr} (*ml min*$^{-1}$)	CL_{po} (*ml min*$^{-1}$)	CL_R (*ml min*$^{-1}$)	C_{max} (*ng ml*$^{-1}$)	t_{max} (*h*)	$t_{½}$ (*h*)
1	1	132	1984	118	65	2.5	0.9
	2	129	2667	53	123	0.73	0.4
	3	126	1550	35	108	1.7	0.9
	4	112	1727	20	110	1.5	0.7
	5	110	2545	75	64	1.8	0.9
2	6	82	3003	25	97	0.75	0.6
	7	79	1773	25	107	1.4	0.9
	8	70	1580	15	129	0.75	0.8
	9	68	1307	41	234	0.58	1.7
	10	67	3058	ND	93	0.92	0.9
3	11	51	1195	17	230	0.83	0.6
	12	43	1022	25	209	1.5	0.8
	13	41	1096	7	211	0.47	0.9
	14	34	952	ND	350	1.7	0.6
	15	31	1603	ND	107	1.1	1.0
4	16	30	1287	5	183	1.5	0.7
	17	20	972	5	229	0.81	0.8
	18	17	1642	ND	84	0.75	1.4
	19	13	1894	ND	98	1.0	1.0
	20	13	813	ND	234	1.0	1.0

CL_{Cr} = Calculated creatinine clearance
CL_{po} = Oral plasma clearance
CL_R = 24 h renal clearance at steady-state
C_{max} = Maximum plasma concentration
t_{max} = Time to C_{max}
$t_{½}$ = Apparent half-life of elimination
ND = None detected

may be incomplete, or that there may be other routes of metabolism of quinapril. The renal clearance was also related directly to CL_{Cr} ($y = 0.41x - 5.89$, $r^2 = 0.51$, $P < 0.001$). C_{max}, C_{min} and $t_{½}$ showed hyperbolic relationships with CL_{Cr}, each of which fitted well to an inverse function. Plotting the values of each of these parameters against the inverse of CL_{Cr} gave r^2 values of 0.63 for C_{max}, 0.83 for C_{min} and 0.77 for $t_{½}$ (all $P < 0.001$). There was no relationship between t_{max} and CL_{Cr}. Trough concentrations with repeated dosing showed no evidence of accumulation of quinaprilat between day 2 and day 7 even in patients with renal impairment.

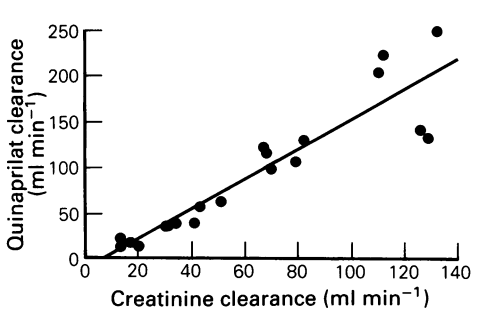

Figure 3 Plasma clearance of quinaprilat *vs* creatinine clearance. $y = 1.65x - 11.1$, $r^2 = 0.85$, $P = 0.001$.

Pharmacodynamics

ACE inhibition The (mean ± s.d.) IC_{50} for quinaprilat was 2.9 ± 1.94 ng ml^{-1}, the I_{max} was 94 ± 4.3%, and the Hill coefficient was 1.36 ± 1.05. The calculated IC_{90} was 14.7 ng ml^{-1}. There were no significant differences in any of these indices between the groups.

A marked and prolonged ACE inhibition was observed in all groups. There was a significant decrease in ACE inhibition towards the end of the dose interval at steady-state in groups 1 and 2 (normal, and mild renal impairment) compared with groups 3 and 4 ($P < 0.05$). The degree of ACE inhibition at 24 h was around 75% in

Table 2 Individual CL_{Cr} values and pharmacokinetic parameters for quinaprilat at steady state

Group	*Subject*	CL_{Cr} (*ml min*$^{-1}$)	CL_{po} (*ml min*$^{-1}$)	CL_R (*ml min*$^{-1}$)	C_{max} (*ng ml*$^{-1}$)	t_{max} (*h*)	$t_{½}$ (*h*)
1	1	132	250	86	235	4.0	1.9
	2	129	134	22	866	1.5	1.8
	3	126	143	34	529	2.0	3.4
	4	112	224	17	407	2.0	2.0
	5	110	205	94	369	2.5	2.2
2	6	82	131	32	604	1.5	2.8
	7	79	107	32	555	6.4	3.0
	8	70	99	19	538	2.0	4.0
	9	68	117	44	768	1.1	2.5
	10	67	123	16	658	2.9	2.0
3	11	51	64	16	791	1.6	4.2
	12	43	57	20	829	2.8	3.8
	13	41	39	7.5	997	1.2	7.3
	14	34	39	6.2	1063	2.4	6.2
	15	31	35	4.7	856	1.6	12.5
4	16	30	35	7.3	874	2.5	9.0
	17	20	14	3.9	1837	3.1	10.6
	18	17	18	2.5	2313	2.1	14.7
	19	13	22	3.2	1054	2.5	11.6
	20	13	12	1.2	1814	5.0	14.8

CL_{Cr} = Calculated creatinine clearance
CL_{po} = Oral plasma clearance at steady-state (i.e. CL_{po} = Dose/AUC(0,24).
CL_R = 24 h renal clearance at steady-state
C_{max} = Maximum plasma concentration
t_{max} = Time to C_{max}
$t_{½}$ = Apparent half-life of elimination (h)

groups 1 and 2 compared with around 88% in groups 3 and 4. Recovery of ACE activity after stopping the drug was significantly prolonged in relation to renal impairment in group 4 compared with the other groups ($P < 0.01$). When the total ACE inhibition for the 24 h period (i.e. AUC ACE inhibition 0–24 h) was plotted against the AUC(0,24) of quinaprilat no relationship was evident. Total ACE inhibition over the period of drug withdrawal (i.e. AUC ACE inhibition 0–72 h after the last dose of quinapril) was significantly greater in group 4 than group 3 which in turn was greater than groups 2 and 1. When the duration of ACE inhibition of >90% (i.e. the time for which concentrations of quinaprilat were above the IC_{90}) was plotted against the inverse of CL_{Cr}, a strong direct relationship was evident (Figure 4).

Pre-dose ACE inhibition values during multiple dosing showed no evidence of a cumulative effect between day 2 and day 7 in any group.

Plasma renin activity (PRA) At steady-state there was a significant elevation of PRA up to 8 h after dosing ($P < 0.01$) but no difference between the groups. There was no significant relationship between PRA and CL_{Cr} ($r^2 = 0.05$, $P = 0.33$).

Aldosterone At steady-state there was a significant decrease in aldosterone concentrations in all groups up to 12 h after dosing ($P < 0.01$), but

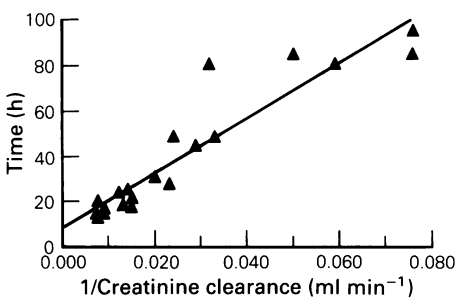

Figure 4 The duration of ACE inhibition of >90% *vs* the inverse of creatinine clearance (ml min^{-1}). y = 7.7 + 1220x, $r^2 = 0.87$, $P < 0.001$.

no difference between the groups. There was no relationship with CL_{Cr}.

ANP There was no change in ANP concentrations from baseline to steady-state (mean difference = 4, 95% C.I. −9.5 to 17.5) or during withdrawal. There were no differences between the groups.

GFR There was no change in Tc^{99m}DTPA GFR or in calculated CL_{Cr} from before to during quinapril therapy (mean difference in GFR = 0.73 ml min^{-1}, 95% C.I. −3.3 to 10.2). The calculated CL_{Cr} was highly correlated with measured GFR ($y = 11.8 + 0.84x$, $r^2 = 0.96$, $P < 0.001$).

Blood pressure and heart rate Quinapril caused a (mean ± s.e. mean) decrease in both systolic blood pressure (13.2 ± 6.3 mm Hg, $P < 0.05$) and diastolic blood pressures (10.9 ± 4.2 mm Hg, $P < 0.05$) in the 11 hypertensive subjects after 6 days of therapy, while there was no change in the nine normotensive subjects. The changes in blood pressure were not related to renal function. There was no change in heart rate.

Discussion

This study confirms that the measured oral clearance of quinaprilat, the active metabolite of quinapril, is directly related to CL_{Cr}. These results are similar to studies of other ACE inhibitors such as cilazapril (Fillastre *et al.*, 1989). Because the steady-state plasma drug concentration is dependent on the dose-rate and drug clearance (C = Dose rate/CL), it follows that the maintenance dose-rate may have to be decreased in direct proportion to any decrease in drug clearance, and hence CL_{Cr}.

For drugs which are partially eliminated unchanged by the kidneys, the dose-rate should usually need to be adjusted only for the fraction which is eliminated unchanged, unless the metabolic clearance is itself significantly affected by renal impairment.

Quinapril is a prodrug which is rapidly converted by ester hydrolysis to the active product quinaprilat, which is largely eliminated unchanged by the kidneys. The pharmacokinetics of quinaprilat are more important in determining possible dose adjustments, although the pharmacokinetics of quinapril itself are of interest because ester hydrolysis has been shown to be slowed in states of renal impairment (Reidenberg, 1977). This study has demonstrated that 30% of the variance in the metabolism of quinapril is explained by CL_{Cr}, providing further indirect evidence of possible impairment of ester hydrolysis in renal impairment. The degree of impairment of quinapril clearance was small, and did not alter the time to peak concentration of quinaprilat, nor the $t_{½}$ of quinapril. The discrepancy between renal and plasma quinaprilat clearances suggests that the assumption of total availability of quinaprilat from quinapril, which was made to calculate the oral clearance, is not valid. However, for the purpose of dose adjustment in renal impairment it is the relationship between apparent oral clearance and creatinine clearance which is important.

If dosage is to be adjusted conveniently in the clinic, it is necessary to have a readily available index of renal function. Because of the logistic problems associated with formal measurements of CL_{Cr} or GFR, there have been attempts to predict CL_{Cr} from serum creatinine concentrations, making allowance for age, weight and sex, such as the approach of Cockcroft & Gault (1976). The high correlation we have observed between the predicted CL_{Cr} and measured GFR ($r^2 = 0.96$, $P < 0.0001$) validates the use of the Cockcroft and Gault formula.

To adjust the dose-rate of quinapril in renal impairment, the dose should be reduced, or the dose interval prolonged. Prolonging the dose interval from the recommended 24 h would lead to dosing on alternate days or less frequently, which might impair compliance. Reducing the dose would therefore be preferable and can also be justified on pharmacodynamic grounds. There is evidence that > 90% ACE inhibition is necessary for substantial antihypertensive effect (Nilsen *et al.*, 1989). Because the duration of ACE inhibition of > 90% is prolonged in renal impairment after the same dose of quinapril (Figure 4), reducing the dose in proportion to the impairment in renal function would result in a similar duration of > 90% ACE inhibition within a 24 h dose interval.

The other findings of this study follow from the decreased clearance of quinaprilat in relation to CL_{Cr}, and the low IC_{90} value for quinaprilat. The $t_{½}$ is related inversely to CL_{Cr} consistent with the inverse relationship between $t_{½}$ and CL. The inverse relationships between both the C_{max} and C_{min} and the CL_{Cr} follow also, since C_{min} will rise in proportion to the increase in $t_{½}$ (given the same dose and dose interval), and, assuming a relatively unchanging V, C_{max} will rise in proportion to the C_{min}.

The lack of relationship between either PRA or aldosterone and CL_{Cr} is consistent with the

high degree of ACE inhibition (i.e. flat portion of dose-response curve) seen in all groups throughout the dosing interval. We do not have enough information to comment on the lack of change in ANP.

In summary, the dose rate of quinapril may have to be decreased in direct proportion to the degree of renal functional impairment. This is achieved most conveniently by reducing the dose rather than prolonging the dose interval.

References

Cockcroft, D. W. & Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31–41.

Dunn, P. J. & Espiner, E. A. (1976). Outpatient screening tests for primary aldosteronism. *Aus. N.Z. J. Med.*, **6**, 131–135.

Fillastre, J. P., Moulin, B., Godin, M., Williams, P. E. O., Brown, A. N., Francis, R. J., Pinta, P. & Manfredi, R. (1989). Pharmacokinetics of cilazapril in patients with renal failure. *Br. J. clin. Pharmac.*, **27**, 275S–282S.

Geisser, S. & Greenhouse, S. W. (1958). An extension of Box's results on the use of the F-distribution in multivariate analysis. *Annals of Mathematical Statistics*, **29**, 885–891.

Kelman, A. W., Reid, J. L. & Millar, J. A. (1983). Concentration effect modelling with converting enzyme inhibitors in man. *Br. J. clin. Pharmac.*, **15**, 506–507.

Lieberman, J. (1984). Elevation of serum angiotensin-converting-enzyme (ACE) level on sarcoidosis. *Am. J. Med.*, **51**, 421–426.

Lun, S., Espiner, E. A., Nicholls, M. G. & Yandle, T. G. (1983). A direct radioimmunoassay for aldosterone in plasma. *Clin. Chem.*, **29**, 268–271.

Nilsen, O. G., Sellevold, O. F. M., Romfo, O. S., Smedsrud, A., Grynne, B., Williams, P. E. O. & Kleinbloesem, C. H. (1989). Pharmacokinetics and effects on renal function following cilazapril and hydrochlorothiazide alone and in their combination in healthy subjects and hypertensive patients. *Br. J. clin. Pharmac.*, **27**, 323S–328S.

Reidenberg, M. M. (1977). The biotransformation of drugs in renal failure. *Am. J. Med.*, **62**, 482–485.

Yandle, T. G., Espiner, E. A., Nicholls, M. G. & Duff, H. (1986). Radioimmunoassay and characterization of atrial natriuretic peptide in human plasma. *J. clin. Endocrinol. Metab.*, **63**, 72–78.

(Received 19 October 1989, accepted 4 April 1990)