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MULTIPLE-DOSE PROPRANOLOL ADMINISTRATION DOES NOT INFLUENCE THE SINGLE DOSE PHARMACOKINETICS OF QUINAPRIL AND ITS ACTIVE METABOLITE (QUINAPRILAT)

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ABSTRACT

To evaluate the influence of multiple dose propranolol administration on the single dose pharmacokinetics of quinapril and its active metabolite, quinaprilat, a drug–drug interaction study was performed in ten healthy volunteers. Each subject received a single 20 mg quinapril oral dose on Days 1 and 16 of the study. Oral propranolol doses of 40 mg BID were initiated on Day 3, titrated gradually to 80 mg TID by Day 10, and continued at 80 mg TID through Day 17. Comparable mean quinapril pharmacokinetic parameter values as well as comparable mean quinaprilat pharmacokinetic parameter values determined following quinapril administered alone and following quinapril administered with propranolol, indicate that propranolol does not alter the single dose pharmacokinetics of quinapril or quinaprilat.

KEY WORDS Quinapril ACE inhibitor Propranolol Pharmacokinetic interaction

INTRODUCTION

Quinapril is a second generation nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor being studied in patients with hypertension and congestive heart failure.[1-3] Previous studies with enalapril and lisinopril, two ACE inhibitors structurally similar to quinapril, have shown reduced bioavailability in the presence of propranolol.[4-6] Like enalapril, quinapril is rapidly and extensively de-esterified by hepatic and/or gastrointestinal esterases to quinaprilat, a more

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potent ACE inhibitor and the compound responsible for therapeutic effect.[7] Quinapril also undergoes limited oxidative metabolism to an inactive metabolite.

Propranolol, a commonly prescribed beta-adrenergic blocking agent used in the treatment of hypertension, is known to inhibit oxidative metabolism[8–10] and to reduce hepatic blood flow.[11–12] Thus, if quinapril de-esterification is hepatic blood flow limited, the rate and extent of quinaprilat formation may be altered directly in response to propranolol-induced alterations in hemodynamics. Alternatively, a propranolol-induced reduction in oxidative metabolic processes may reduce the elimination of quinapril by the parallel oxidative pathway, increasing the availability of quinapril for de-esterification and, thus, the extent of quinaprilat formation.

Since quinapril and propranolol may be administered concomitantly, the potential influence of propranolol on the pharmacokinetic profiles of quinapril and its active metabolite, quinaprilat, was investigated in healthy volunteers.

SUBJECTS AND METHODS

The study was carried out using ten healthy male volunteers, aged 19 to 29 years (mean 24 years) and weighing 72 to 97 kg (mean 81 kg). Biochemical indices of hepatic and renal function were within normal ranges as were all other hematological and clinical chemistry laboratory values.

Concomitant medications were excluded from 2 weeks prior to the study until its completion. Each subject gave written informed consent to take part in the study which was approved by an ethical committee.

Each subject received propranolol: 40 mg BID on Days 3 through 6, 40 mg TID on Days 7 through 9, and 80 mg TID on Days 10 through 17. On Day 1, prior to the first dose of propranolol, each subject received a single 20 mg quinapril capsule at 08.00 h. On Day 16 at 08.00 h each subject received a second 20 mg dose of quinapril concomitantly with propranolol. Each dose of quinapril was administered with 200 ml water after an overnight fast and subjects abstained from drinking caffeine-containing liquids for 48 h post-quinapril administration. Subjects continued to fast for an additional 4 h after quinapril dosing. Blood samples were taken before and 0·5, 1, 1·5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 h after each quinapril dose. Plasma was collected and stored frozen until assayed for quinapril and quinaprilat using a validated, sensitive, and specific gas chromatographic method with electron capture detection.[13]

Peak plasma quinapril and quinaprilat concentrations (C_{max}) and the times at which these occurred (t_{max}) were obtained from individual plasma profiles by inspection. Apparent elimination rate constants (λ_z) were obtained by linear regression of the log-linear terminal phases of plasma concentration–time profiles. Elimination half-life ($t_{1/2}$) was determined as $0{\cdot}693/\lambda_z$. The areas under the plasma quinapril and quinaprilat concentration vs time curves from 0 to time of the last detectable concentration (AUC_{0-tldc}) were calculated by linear trapezoidal approximation. Area under the plasma concentration–time curve from zero to

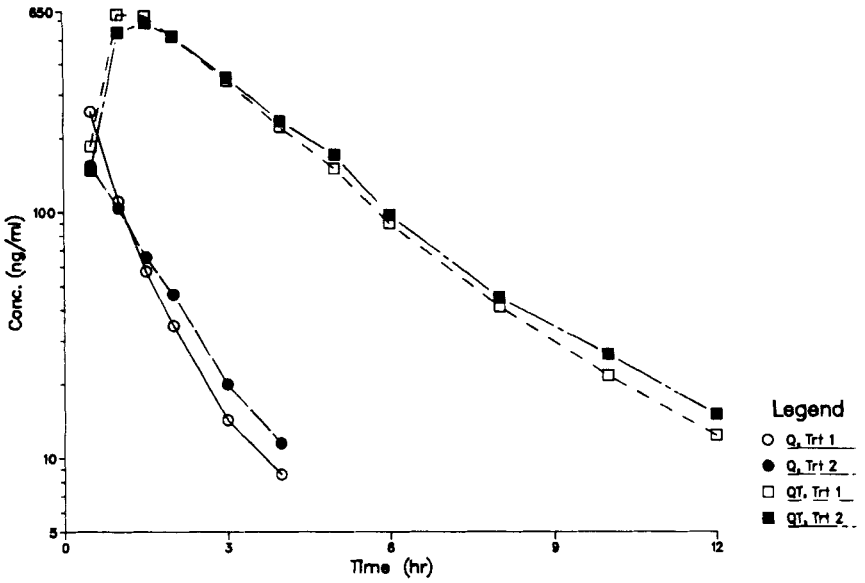

Figure 1. Mean quinapril (Q) and quinaprilat (QT) concentration–time profiles following Q administered alone (Trt 1) and Q administered with propranolol (Trt 2)

infinity ($AUC_{0-\infty}$) was calculated by summing AUC_{0-tldc} with the last detectable plasma concentration divided by λ_z. Pharmacokinetic data were compared by analysis of variance using the Statistical Analysis System (Cary, NC). All tests were conducted at the 0·05 significance level.

RESULTS

No adverse events were reported during the study. No significant treatment-induced changes in hematology or clinical chemistry laboratory values were observed. Systolic blood pressure, diastolic blood pressure, and heart rate were recorded both sitting and standing at entry, Day 19, and Days 4 to 17 inclusive. Propranolol reduced blood pressure and heart rate by 12 per cent on Days 10 to 17 (80 mg propranolol TID) as compared to prestudy values. This reduction in blood pressure and heart rate is expected for a beta-blocker. There were no reports of hypotension after quinapril was administered concomitantly with propranolol.

Mean plasma concentration–time profiles of quinapril and quinaprilat following administration of quinapril alone and in combination with propranolol are shown in Figure 1. Mean pharmacokinetic parameters are summarized in Table 1. No statistically significant differences were detected between mean quinapril t_{max}, λ_z or AUC values obtained following quinapril administration alone or during multiple-dose propranolol administration. Quinapril mean C_{max} values

Table 1. Quinapril and quinaprilat pharmacokinetic parameter mean values (per cent RSD)

Parameter	Quinapril administered alone (Q)	Quinapril administered with propranolol (Q and P)	Ratio (Q and P)/Q
C_{max}			
Quinapril	257 (42)	184 (41)	0·72
Quinaprilat	675 (37)	639 (42)	0·95
t_{max}			
Quinapril	0·5 (0)	0·7 (37)	1·30
Quinaprilat	1·3 (27)	1·5 (44)	1·15
AUC $0\text{-}\infty$			
Quinapril	263 (36)	235 (34)	0·89
Quinaprilat	2159 (33)	2154 (28)	1·00
λ_z			
Quinapril	0·95 (16)	0·93 (39)	0·97
Quinaprilat	0·38 (14)	0·36 (20)	0·94
$t_{1/2}$			
Quinapril	0·7	0·8	1·03
Quinaprilat	1·8	1·9	1·06

C_{max} = maximum plasma concentration (ng ml^{-1}).
t_{max} = time (h) of C_{max}.
AUC_∞ = area under the plasma concentration–time curve from time zero to infinity (ng.h ml^{-1}).
λ_z = apparent elimination rate constant (1 h^{-1}).
$t_{1/2}$ = harmonic mean of the apparent elimination half-life (h).

were approximately 28 per cent lower when quinapril was administered with propranolol than when administered alone and this difference was statistically significant. Due to sampling times chosen it is not possible to attribute the quinapril C_{max} difference to propranolol rather than to imprecise characterization of the plasma quinapril peak. The lack of a propranolol effect on t_{max}, λ_z, and AUC further supports the argument that the C_{max} difference may be artifactual rather than due to hemodynamic or metabolic effects of propranolol.

No statistically significant differences were detected between mean quinaprilat C_{max}, t_{max}, λ_z or AUC values obtained following quinapril administration alone or during multiple-dose propranolol administration. These results would suggest that neither the formation or subsequent clearance of quinaprilat are affected by propranolol.

DISCUSSION

Propranolol has been shown to reduce hepatic blood flow by approximately 25 per cent[11-12] and to impair hepatic microsomal activity in healthy subjects when

administered according to multiple-dose regimens similar to the one used in the present study.[8-10] Either of these effects of propranolol has the potential to alter the rate and/or extent of quinapril de-esterification to quinaprilat. While the hepatic extraction ratio for quinapril has not been determined it is not unlikely that extraction is high, providing the necessary conditions for perfusion-rate limited hepatic clearance. As quinaprilat is known to be the only major metabolite, alterations in hepatic clearance of quinapril, hypothetically produced by propranolol-induced alterations in hepatic blood flow, could be reflected as alterations in quinaprilat formation.[7] With this situation, the effect of propranolol, that of reducing blood flow, would be expected to reduce the rate of quinaprilat formation.

The second effect of propranolol, that of inhibiting hepatic microsomal activity, could alter the availability of quinapril for conversion to quinaprilat. Approximately 10 to 15 per cent of an oral dose of quinapril is excreted in urine as the ethyl ester and di-acid diketopiperazine metabolites.[7] These compounds have been observed as metabolites following incubation of quinapril in hepatic microsomal preparations (unpublished data). Furthermore, diketopiperazine formation preferentially occurs through the parent quinapril rather than through the di-acid quinaprilat, suggesting that this metabolic pathway offers a parallel, competing route for quinapril clearance. Inhibition of this pathway would be equivalent to providing additional quinapril for de-esterification, thus increasing the extent of quinapril conversion to quinaprilat. Additionally, while inhibition of hepatic microsomal activity may inhibit diketopiperazine formation, de-esterification may be inhibited by propranolol as well. The end result in terms of rate and extent of quinaprilat formation is unclear without direct pharmacokinetic evaluation.

A third effect of propranolol, although somewhat speculative, is perhaps more consistent with the observed interaction of propranolol with lisinopril.[6] As propranolol-induced reductions in hepatic clearance are attributed to reductions in cardiac output,[14] similar reductions in gastrointestinal blood flow probably occur. Lisinopril bioavailability is reported to be slightly decreased when administered concomitantly with propranolol. This finding is interesting in light of the fact that lisinopril undergoes no metabolism and may suggest that absorption of lisinopril is impaired in the presence of propranolol because of reductions in gastrointestinal blood flow just as de-esterification of quinapril and other ACE inhibitors may be impaired through reductions in hepatic blood flow. It is possible that reduced gastrointestinal blood flow could reduce quinapril absorption as well.

In a study to evaluate the influence of propranolol on the pharmacokinetics of enalapril, enalaprilat AUC was reduced by one-third when propranolol and enalapril were coadministered.[4-5] Whether or not this reduction in enalaprilat AUC was accompanied by a change in pharmacokinetic disposition for the parent enalapril is not known. It is unlikely, however, that the reduced enalaprilat AUC reflects an increase in clearance as enalaprilat, like quinaprilat,

is essentially completely excreted in urine in unchanged form. The reduced enalaprilat AUC may, therefore, reflect a reduction in the absorption and/or subsequent de-esterification of the parent enalapril. Similarly, coadministration of propranolol and lisinopril was determined to slightly reduce the lisinopril AUC. As lisinopril is not metabolized but rather excreted intact in the urine, this reduction in AUC probably reflects a change in the extent of lisinopril absorption. Potential interactions of propranolol with other ACE inhibitors have not been reported until now. Neither the rate nor extent of quinapril conversion to quinaprilat, assessed in terms of quinaprilat C_{max}, t_{max}, and AUC, were influenced by multiple dose propranolol. It is not known if the small reduction in quinapril C_{max} reflects a change in quinapril absorption. This change, however, does not translate into changes in the quinaprilat pharmacokinetic profile. Finally, and not surprisingly, the subsequent rate of quinaprilat elimination, a process known to be essentially completely renal, was not influenced by propranolol.[7]

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