Does blood pressure reduction necessarily compromise cardiac function or renal hemodynamics? Effects of the angiotensin-converting enzyme inhibitor quinapril

Clinical studies indicate that the angiotensin-converting enzyme inhibitor quinapril is an effective antihypertensive agent when administered once daily. At the end of a 4-week, double-blind crossover trial comparing quinapril and placebo, patients were admitted for a hemodynamic profile study 12 hours after taking the previous dose. A final 20 mg dose of quinapril had no additional effect on blood pressure. This is interesting inasmuch as the plasma half-life of the active metabolite quinaprilat is approximately 2 hours and the effective accumulation half-life is approximately 3 hours. The blood pressure reduction in patients with mild hypertension receiving long-term quinapril therapy may be more closely related to prolonged angiotensin-converting enzyme inhibition or to an effect on tissue angiotensin II concentration than to the plasma half-life. This may be the case particularly for cardiac output and renal circulation, because quinapril lowers total vascular resistance without increasing cardiac output or disturbing autoregulation of renal blood flow. Reduced ventricular wall stress, improved diastolic function, and lower renal perfusion pressure may spare cardiac function and glomeruli from hypertensive vascular damage. (AM HEART J 1992;123:1433-8.)

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Currently available antihypertensive drugs lower blood pressure through widely different hemodynamic mechanisms. In general, β-blockers tend to produce chronic depression of cardiac output, particularly during exercise,1 and consequently may induce reduction of physical endurance during severe work loads.5-4 In contrast, α-blockers, calcium-channel blockers, and angiotensin-converting enzyme (ACE) inhibitors reduce vascular resistance and maintain blood flow,5-11 but the degree of counteracting reflex tachycardia and the increase in cardiac output vary widely.

The antihypertensive effect of ACE inhibitors is likely mediated largely by withdrawal of the vaso-

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lished diastolic blood pressure at home of greater than 95 mm Hg when untreated (i.e., no “white coat” phenomenon). Here we obtain detailed records from the daily home blood pressure and heart rate measurements of the 10 patients, and we also present individual patient changes in cardiac index and renal blood flow as well as evidence of improved diastolic function.

METHODS

Patients. Ten white men averaging 42 ± 3 years (range, 32 to 61 years) with uncomplicated mild to moderate essential hypertension were studied.21 After informed consent was obtained, all antihypertensive medications were discontinued for 3 weeks, and patients were included in the study if they had stable diastolic blood pressures between 95 and 115 mm Hg at home (sitting) and in the outpatient clinic (supine) at the end of this period. One patient was stable on thyroid hormone replacement. Aside from essential hypertension, no subject had any other acute or chronic illness. All patients were nonsmokers and did not abuse alcohol or drugs. They were urged not to change their dietary or drinking habits during the study period.

Protocol. After the initial 3 weeks without antihypertensive treatment, patients were randomly assigned to a double-blind, two-period crossover trial comparing quinapril and placebo. Quinapril, 20 mg, or matching placebo was each given twice daily for 4 weeks. On the last day of each 4-week period, 12 hours after taking the next to last dose of medication, and having fasted for 12 hours (i.e., overnight), patients were admitted to the University of Michigan Clinical Research Center for 4 hours for hemodynamic profiling.

Subjects were placed at supine rest in a quiet room. Baseline blood pressure was measured in the right arm as the average of two readings by a newly calibrated mercury sphygmomanometer, and baseline heart rate was calculated from the average of 20 to 40 beats taken from the ECG tracing. After baseline blood pressure and heart rate were measured, the morning dose of medication (quinapril or placebo) was given. Thereafter, blood pressure and heart rate were measured every half hour throughout for 4 hours, and hemodynamic profiling was performed 2 to 4 hours after the last dose. The echocardiographic and Doppler procedures used in this study are described in detail elsewhere.22, 23

Plasma clearance of paraaminohippuric acid (PAH), an estimate of effective renal plasma flow, was measured at 3½ hours after the administration of the morning dose of placebo or quinapril by a steady-state infusion method.24, 25 A plasma blank was first obtained, after which an intravenous priming dose of 8 mg/kg of PAH was administered over a 10-minute period. PAH was then infused for 1 hour, from 2½ to 3½ hours after the dose of placebo or quinapril was given, at a rate calculated to achieve a target PAH plasma concentration of 0.02 mg/ml. A single blood sample was drawn for measurement of PAH concentration.25 Hematocrit level was obtained with a Coulter counter M4 30 (Coulter Electronics, Inc., Hialeah, Fla.), and renal blood flow was calculated as renal plasma flow/(1 – hematocrit). Endogenous urinary creatinine clearance was measured to estimate average glomerular filtration rate during the 24-hour period that preceded the hemodynamic profiling. Plasma catecholamine values were obtained at the same time as the PAH plasma blank and analyzed with the radioenzymatic method of Peuler and Johnson.26

The study was approved by the Human Subject Review Committee of the University of Michigan.

Statistical analysis. The data were tested for an order of treatment effect. Because none could be found, further analyses compared the quinapril-treatment with the placebo-treatment period, regardless of the order in which they were given. Blood pressure and vascular resistance were postulated to fall; therefore differences in these variables were tested by one-tailed tests. Other differences were tested by two-tailed parametric tests for single or repeated measurements. A value of p < 0.05 was considered the limit for statistical significance. Data are presented as means ± SE.

RESULTS

Blood pressure. Blood pressure was significantly lowered by treatment with quinapril compared with placebo. As shown in Fig. 1, A and B, home blood pressures, both systolic and diastolic, averaged 10 to 15 mm Hg lower for those receiving quinapril compared with placebo (p < 0.001, analysis of variance) for most of the 4-week period. However, at the beginning and end of each treatment period, differences leveled out because of the crossover design and slightly different lengths of individual treatment periods. Blood pressure recordings and differences between quinapril and placebo were of the same levels and magnitudes in the clinic as those measured by the patients at home. Also, the single dose of quinapril administered 12 hours after the last long-term drug dose had no discernible additional effect on blood pressure at the expected peak pharmacodynamic action, that is, 3 hours after the dose of quinapril.

Heart rate and plasma catecholamines. There was no significant difference in home heart rate between the quinapril and placebo treatments (Fig. 1, C). There was also not a significant difference in plasma catecholamine values between the two treatment groups: plasma norepinephrine drawn 2½ hours after the dose averaged 220 ± 25 versus 202 ± 16 ng/L (NS) with quinapril and placebo, respectively, and plasma epinephrine was 45 ± 5 versus 47 ± 10 ng/L (NS).

Cardiac function. Cardiac index was not altered by treatment with quinapril in the 10 patients (Fig. 2). Thus all the blood pressure-lowering effect of quinapril was the result of a decrease in total vascular resistance (49 ± 2 versus 43 ± 2 arbitrary units.
Fig. 1. Effects of quinapril (circles) and placebo (squares) on (A) home systolic blood pressure (top panel, \( p < 0.001 \)), (B) home diastolic blood pressure (middle panel, \( p < 0.001 \)), and (C) home heart rate (lower panel, NS).
for placebo and quinapril, respectively; \( p < 0.01 \). Left ventricular wall stress decreased significantly with quinapril compared with placebo (149 ± 9 versus 170 ± 8 \( \times 10^3 \) dynes/cm\(^2\), \( p < 0.01 \)). Previously unanalyzed records of the Doppler sonography showed improvements in diastolic function: the peak E/A ratio increased in 8 of the 10 patients, and the overall increase was significant (from 1.12 ± 0.11 to 1.31 ± 0.10 arbitrary units for placebo and quinapril, respectively; \( p < 0.02 \)).

**Renal hemodynamics.** Renal blood flow remained unchanged in the 10 patients (907 ± 36 vs 896 ± 28 ml/min for quinapril and placebo, respectively) (Fig. 3). However, renal vascular resistance was significantly (\( p < 0.05 \)) lower when taking quinapril (12.2 ± 0.8 arbitrary units) compared with placebo (13.6 ± 0.6), which suggests that reduced renal vascular resistance may partly explain the reduction in total vascular resistance during treatment with quinapril. Glomerular filtration rate and filtration fraction remained unchanged, which resulted in a lower glomerular filtration pressure.

**DISCUSSION**

ACE inhibition induces a decrease in total and renal vascular resistance without changing cardiac output.\(^9\)-\(^11\),\(^27\)-\(^29\) Quinapril lowers blood pressure by the same mechanism. The changes induced by quinapril differ from the reduced cardiac output and unchanged total peripheral resistance observed with \( \beta \)-blockade.\(^1\) \( \beta \)-Blockade may worsen the already depressed cardiac function in hypertension.\(^30\)-\(^32\) In contrast, vasodilation, as with an ACE inhibitor, may reverse the established vascular changes in hypertension and may be preferable for long-term treatment of hypertension.

The degree of counteracting reflex tachycardia and the increase in cardiac output vary widely with vasodilator therapy of hypertension.\(^5\)-\(^11\) Even though quinapril produced a substantial fall in blood pressure, heart rate and plasma catecholamines remained virtually unchanged. The same observation has been made for captopril,\(^9\),\(^10\),\(^27\),\(^29\),\(^33\) enalapril,\(^11\),\(^34\) and lisinopril,\(^34\) and appears to be a class effect of ACE inhibition. It has been shown that with captopril,\(^35\),\(^36\) enalapril,\(^37\),\(^38\) and lisinopril,\(^38\) the absence of reflex tachycardia with blood pressure reduction may be related to increased parasympathetic tone. It is likely that the absence of tachycardia with quinapril has a similar mechanism.

The reduction in systemic vascular resistance by long-term ACE inhibition appears to be unevenly distributed in the circulation. Lisinopril did not change the splanchnic vascular resistance,\(^39\) and we\(^21\) did not detect a significant decrease in forearm vascular resistance with quinapril. However, captopril\(^28\),\(^29\),\(^40\),\(^41\) and lisinopril\(^39\) and in the present study quinapril reduced renal vascular resistance. This
may be explained by the particularly pronounced vasoconstricting action of angiotensin II in the renal circulation, especially in patients with essential hypertension.

Long-term treatment of essential hypertension with captopril or enalapril has been associated with no change or a relatively small increase in renal blood flow and unchanged glomerular filtration rate. An increase in renal blood flow may possibly be related to withdrawal of the effect of angiotensin, which is more potent in constricting the efferent than the afferent glomerular arteriole. However, a fall in filtration fraction may also indicate a redistribution of renal blood flow to more superficial nephrons known to have a low filtration fraction or relate to reduction in glomerular capillary hydraulic pressure. In the present study, the fall in blood pressure and renal vascular resistance was not accompanied by a change in renal plasma flow, glomerular filtration rate, or filtration fraction. Presumably, the failure of renal blood flow to increase was caused by a reduction in perfusion pressure. Thus the effect of quinapril on renal function is consistent with intact autoregulation of renal hemodynamics. This conclusion is in agreement with studies in laboratory animals, in which angiotensin II was not required for renal autoregulation.

We found left ventricular peak systolic wall stress in the same range as reported by others. Although we demonstrated a significant reduction in wall stress and, as estimated by the peak E/A ratio, an improvement in diastolic function, we did not find a significant reduction in left ventricular mass. ACE inhibition may decrease left ventricular mass. However, a 4-week treatment period may be too brief to detect such changes and longer studies will be required.

Oral administration of quinapril 12 hours after a previous dose produced no significant acute hemodynamic effects. This may seem somewhat surprising, because the plasma half-life of the active metabolite, quinaprilat, is approximately 2 hours and the effective accumulation is 3 hours after a single 20 mg dose and quinaprilat is minimally detectable in plasma 8 to 12 hours after administration. However, quinapril-induced plasma ACE inhibition is almost complete at 8 to 12 hours and is still depressed by 25% at 24 hours after administration, suggesting tight binding of the drug to the enzyme. In addition, quinaprilat has been demonstrated to inhibit tissue ACE even after plasma ACE activity has returned to near-normal levels. Although the precise contribution of tissue angiotensin II production to hypertension is not yet defined, the antihypertensive effect of ACE inhibition more closely parallels tissue than plasma ACE inhibition during long-term administration in some models. The prolonged antihypertensive effect of quinapril in humans at a time when plasma drug concentration of quinaprilat is minimal may relate either to sustained plasma ACE inhibition or to effects mediated by the endogenous tissue renin-angiotensin system.

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REFERENCES


