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Controlled Multicenter Study with Quinapril, Hydrochlorothiazide, and Combination in Patients with Moderate to Severe Hypertension

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Summary: In an 8-week, double-blind, randomized, active-controlled, multicenter study with three parallel treatment groups, we compared the efficacy and safety of once-daily 20 mg quinapril plus 12.5 mg hydrochlorothiazide (HCTZ) with each drug as monotherapy in patients with moderate to severe hypertension. Hypertensive outpatients with supine diastolic blood pressure (DBP) ≥105 and ≤120 mm Hg at the end of a 2- to 4-week placebo-baseline period were randomly assigned to one of the treatment groups. Of the 323 patients who were randomized to double-blind medication, 297 completed the study, but 6 patients were excluded for violations of protocol; therefore, statistical analysis was performed in 291 patients. Only 7 patients withdrew owing to lack of efficacy (2 receiving combination therapy). In all three treatment groups, clinically significant reductions in DBP were achieved. Combination therapy was statistically more effective than each component in both evaluable data and intent-to-treat analyses. The incidence of adverse events (AE) was 24% in the quinapril monotherapy group, 14% in the combination therapy group, and 11% in the HCTZ monotherapy group. Orthostatic hypotension with related symptoms was observed in 4 patients (2 receiving quinapril monotherapy, 1 receiving HCTZ monotherapy, and 1 receiving combination therapy). Once-daily quinapril plus HCTZ provided increased reduction of DBP as compared with the monotherapies and was well tolerated in patients with moderate to severe hypertension. **Key Words:** Hypertension—Quinapril—Hydrochlorothiazide—Monotherapy—Combination therapy.

Quinapril hydrochloride (quinapril) is a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor which is administered as a prodrug and converted in the liver to quinaprilat, the major active metabolite. This mechanism provides a more gradual onset of antihypertensive effect. In addition, the effective elimination half-life (1½) of quinapril (3 h) is shorter than that of other once-daily ACE inhibitors (1); therefore, the risk of drug accumulation is reduced. However, due to the high affinity for ACE, both in plasma and tissues, the duration of action of quinapril is sufficient to provide 24-h blood pressure (BP) control with once-daily dosing (2). Quinapril is well absorbed when taken with food. Excretion of quinapril and its metabolites is ~66% urinary and ~33% fecal (2,3).

Adequate control of high BP is generally considered not to be achieved in all patients with a single-drug approach. In these patients, the addition of a second antihypertensive drug is required. The antihypertensive efficacy of ACE inhibitors is enhanced by concurrent therapy with diuretics. Furthermore, this combination has proven particularly beneficial in reducing metabolic side effects of diuretics (4–11).

The objective of our study was to compare the efficacy, in terms of reduction in BP and safety of combination therapy with quinapril 20 mg and hydrochlorothiazide (HCTZ) 12.5 mg administered once daily with the efficacy and safety of each drug administered as monotherapy in patients with moderate to severe hypertension.

PATIENTS AND METHODS

Data were collected from a controlled, multicenter study in 26 centers (11 countries) of 323 patients who had

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moderate to severe hypertension. Men and women aged at least 18 years with supine diastolic BP (DBP) ≥105 and ≤120 mm Hg at two consecutive visits during the placebo period qualified for randomization to double-blind treatment. All patients gave verbally witnessed or written informed consent; the study was conducted in accordance with the Declaration of Helsinki, and approval was given by the local ethics committees.

Study design

The study design was 8-week, double-blind, randomized, active-controlled multicenter with three parallel treatment groups. Patients discontinued all antihypertensive medication and received placebo medication for at lest 2 weeks but not longer than 4 weeks before being randomized to 8 weeks of double-blind treatment. The dosing during double-blind phase was once-daily quinapril 20 mg plus HCTZ placebo, or quinapril 20 mg plus HCTZ 12.5 mg, or quinapril placebo plus HCTZ 12.5 mg. BP was recorded during placebo washout period weekly and at weeks 1, 2, 4, and 8 during treatment phase. Patients were considered to have completed the study if they had been in the double-blind period ≥54 days, but patients with a minimum follow-up of 26 days of treatment were included in the analysis for efficacy.

Therapy was discontinued, and patients were withdrawn from the study at the patient's request or if the following occurred: DBP increase to >120 mm Hg, intolerable adverse events (AE), development of serious disease, not allowed concurrent medication, or repeated noncompliance.

Baseline BP value was defined as the average of the means of three supine readings at each of the last two consecutive visits during the placebo-baseline phase. Trough BP measurements were performed at each clinic visit three times with the patient in supine position (after 5, 8, 11 min) and 30 s and 3 min after the patient stood.

The primary measure of efficacy was supine DBP at trough (24 h postdose). The following recordings or measurements were evaluated for safety: AE, serum potassium, first-dose effect on BP (for a minimum of 2 h postdose), hypotension defined as systolic BP (SBP) <100 mm Hg with symptoms, orthostatic hypotension defined as a decrease in standing SBP of >20 mm Hg from the last of the three supine SBP measurements with symptoms, heart rate (HR) at trough (measured after 5 min supine and 3 min standing), changes in physical examination findings, changes in the 12-lead ECG, and clinical laboratory measurements.

Data analysis

The total number of 110 patients per study arm to be enrolled was calculated assuming a 20% overall dropout rate and an SD of 7 mm Hg. This provided a 95% power to detect a mean difference of 3–5 mm Hg between combination and each monotherapy when a one-sided test at the 5% level of significance was performed.

All efficacy parameters were based on change from baseline. The intent-to-treat analysis included all patients randomized to treatment who had both baseline and double-blind data, with the data of the last available double-blind visit as endpoint. The evaluable data analysis included all patients without protocol deviations who had received ≥26 days of double-blind treatment, with the data of the last evaluable double-blind visit as endpoint. Although statistical subgroup analysis was not planned in the protocol, exploratory analysis [stratifications by age (<65/≥65 years), by baseline supine DBP (≤110/>110 mm Hg), and by sex] without any testing were conducted with data of the last evaluable visit.

Responses to treatment were also evaluated in terms of rates of antihypertensive response: response rates (percentage of evaluable patients who had a decrease in supine DBP at the last evaluable visit of ≥10 mm Hg from baseline), and global response rates (percentage of all randomized patients who completed the study on day 54 or later and who had a decrease in supine DBP at the last available visit of ≥10 mm Hg from baseline).

In the interferential analyses, both monotherapies versus combination therapy were selected for one-side significance testing with the null hypothesis "the effect of the combination therapy is not superior to the effect of both monotherapies," since a combination therapy must demonstrate superiority over each of its components. Interferential testing in BP was performed with an analysis of covariance (ANCOVA). Treatment of effects on response rates were tested with the Cochran-Mantel-Haenszel procedure. All randomized patients were evaluated for safety.

RESULTS

Demographical data

In all, 323 patients were randomized to quinapril (106 patients), HCTZ (109 patients), and quinapril + HCTZ (108 patients). Table 1 shows the demographic characteristics of randomized patients. Nine (3%) black patients (3 in each treatment group) and one Arabian patient participated in the study; all other patients were white. No clinically significant baseline differences were apparent between the treatment groups. Twenty-six patients withdrew from the study for different reasons (Table 2). Eleven percent of the patients had at least one concurrent metabolic disease diagnosed before the preselection period (diabetes, 13 patients; hyperli-

TABLE 1. *Demographic characteristics of 323 randomized patients*

Patients	QP	QP + HCTZ	HCTZ
Total	106	108	109
Sex [n (%)]			
Men	55 (52)	63 (58)	67 (61)
Women	51 (48)	45 (42)	42 (39)
Age [n (%)]			
<65 yr	85 (80)	94 (87)	88 (81)
≥65 yr	21 (20)	14 (13)	21 (19)
Mean	53	52	55
Range	21–84	22–86	26–84
Baseline hypertension state			
Median duration (yr)	4.9	4.6	4.0
Mean duration (yr)	5.8	6.4	6.1
Range	0–30	0–30	0–34
Mean supine DBP (mm Hg)	109.1	108.8	108.6
Range	102–118	95–120	95–119
Mean supine SBP (mm Hg)	167.9	166.7	167.0
Range	136–235	136–232	135–214

QP, quinapril; HCTZ, hydrochlorothiazide; DBP and SBP, diastolic and systolic blood pressure.

TABLE 2. *Patients randomized and withdrawn in each treatment group*

Patients/reason for withdrawal	QP, n (%)	QP + HCTZ, n (%)	HCTZ, n (%)
Randomized to treatment	106	108	109
Withdrawals			
Adverse events	6 (5.7)	0 (0.0)	2 (1.8)
Lack of efficacy	2 (1.9)	2 (1.9)	3 (2.8)
Lost to follow-up	2 (1.9)	0 (0.0)	2 (1.8)
Personal reasons	0 (0.0)	0 (0.0)	2 (1.8)
Noncompliance	0 (0.0)	0 (0.0)	1 (0.9)
Other	3 (2.8)	0 (0.0)	1 (0.9)
Total	13 (12.3)	2 (1.9)	11 (10.1)

Abbreviations as in Table 1.

pemia, 10; hypercholesterolemia, 8), and 7% had an illness related to the cardiovascular system. In all, 101 patients (31%) received at least one concurrent medication at some time during the double-blind phase. None of the concurrent medications were excluded by the study protocol, and none was considered to have impact on the evaluation of the antihypertensive effects of quinapril or HCTZ.

Sixty-five percent of patients who started double-blind therapy had been treated for hypertension before entering the study. The previous antihypertensive therapy most frequently prescribed was ACE inhibitors (29.7%), diuretics (27.2%), and β-blockers (22.6%), calcium-channel blockers (16.1%), and α-blockers (4.3%).

Efficacy

Table 3 summarizes the number of patients included in the efficacy analyses. Six patients were excluded from all efficacy analyses: 1 patient had no baseline data, and 5 patients had no double-blind data. Therefore, 317 patients were available for the intent-to-treat analysis of efficacy. Twenty-six other patients were excluded from the evaluable data analysis, resulting in 291 evaluable patients. The most frequent reasons for exclusion were inadequate baseline DBP (16 patients) and time treated with study drug <26 days (12 patients).

BP values at baseline were comparable for all treatments. An overview of the results in supine DBP and supine SBP is shown in Table 4. In the inferential analyses for the patient sample with evaluable data, combination therapy produced greater mean reductions in supine DBP and SBP as compared with both monotherapies. The percentage of responders was highest for the combination therapy (69%), which was significantly different only from HCTZ monotherapy (53%) but not from quinapril monotherapy (65%). The inferential analysis for the intent-to-treat sample confirmed these conclusions.

BP responses were analyzed descriptively to explore whether age, sex, and severity of hypertension significantly influenced the response to treatment. Response rates tended to be higher in elderly patients than in younger patients: quinapril monotherapy 63 and 72%, HCTZ monotherapy 51 and 60%, and combination therapy 66 and 86% in young and elderly patients, respectively. However, the number of elderly patients was relatively small (14–20 patients per treatment group). Within groups of patients with a baseline DBP ≤110 mm Hg and a baseline DBP >110 mm Hg, the combination therapy produced greater mean reductions in supine BP from baseline than did either monotherapy. Comparison of the results between groups showed that patients with lower baseline (DBP <110 mm Hg) values had the greatest response in DBP reduction of all three treatment groups. The BP was more reduced in women than in men in all treatment groups. No differences between women and men were observed with regard to age and mean baseline DBP. However, a treatment/sex interaction was not evident. The 3-min readings of standing BP were used as a secondary measure of efficacy. Raw mean changes from baseline were slightly smaller (1 or 2 mm Hg) as compared with those in supine BP. The greatest reduction in BP was obtained with the combination therapy.

HR was not significantly modified in any of the treatment groups. Changes from baseline in standing HR were similar to those in the supine position.

TABLE 3. *Number of patients in each efficacy analysis*

Phase/analysis	QP	QP + HCTZ	HCTZ	Total
Randomized to treatment	106	108	109	323
Intent-to-treat analysis	101	108	108	317
Evaluable data analysis	96	99	96	291

Abbreviations as in Table 1.

TABLE 4. *Supine DBP and SBP (mm Hg) at trough and response rate on the last evaluable visit in evaluable patients (n = 291)*

Parameter	QP (n = 96)	QP + HCTZ (n = 99)	HCTZ (n = 96)
Supine DBP			
Mean baseline	109.1	109.2	109.1
Change from baseline			
Adjusted mean	−12.1	−14.4[a]	−11.0
SE	0.8	0.8	0.9
p-Value[b]	0.022	0.002	
Supine SBP			
Mean baseline	168.4	167.4	167.0
Change from baseline			
Adjusted mean	−13.2	−17.6[a]	−12.4
SE	1.4	1.3	1.4
p-Value[b]	0.01	0.003	
Response rate			
No. of responders (%)	62 (65)	68 (69)	51 (53)
p-Value[b]	0.209	0.02	

Abbreviations as in Table 1.
[a] Significantly different from both monotherapies.
[b] One-sided for the difference between QP + HCTZ and each of the monotherapies.

Safety

All study medications were well tolerated, with the percentage of patients with AE receiving combination therapy (14%) ranging between that occurring with the quinapril monotherapy (24%) and the HCTZ monotherapy (11%). Most AE were categorized as mild to moderate in severity. No conclusions can be drawn for an increased incidence of a specific AE in one of the treatment groups. Of the 52 patients with AE, 31 (60%) had events related to study drugs, as attributed by the investigators. The AE occurring frequently (≥3 patients) were headache (5 patients, 4.7%), and cough (3 patients, 2.8%) in the quinapril monotherapy group; cough in the combination group (4 patients, 3.7%); and none in the HCTZ monotherapy group. Nine patients (6 in the quinapril monotherapy group, 2 in the HCTZ monotherapy group, and 1 in the combination therapy group) withdrew from the study as a result of one or more AE.

Orthostatic hypotension (a decrease in SBP of >20 mm Hg from supine to standing position) is a potential AE of any hypertensive treatment. Twenty-one patients after the first active dose and 34 patients at trough during the double-blind phase reported hypotension, with no relevant differences between the treatment groups. Four of these patients (2 after the first dose of quinapril monotherapy, 1 at trough on HCTZ monotherapy, and 1 after the first dose of combination therapy) reported symptoms related to hypotension. Overall, the incidence of hypotension was similar (~10%) during both the placebo baseline phase and the active treatment phase.

Table 5 shows the median differences between baseline and final value of selected laboratory parameters. Although there was a trend for quinapril monotherapy to increase potassium levels and for HCTZ monotherapy to decrease them, no relevant changes were observed in the combination therapy group. No possibly clinically important increase of uric acid values was reported throughout the study. The median differences between baseline and final value were +10.5 μM in the HCTZ monotherapy group and −6.5 μM in the quinapril monotherapy group, with almost no change in the combination group, indicating that concomitant quinapril tended to blunt adverse changes in uric acid due to HCTZ treatment. No clinically important increase in creatinine levels was observed during the study. Overall, in all treatment groups, median changes from baseline at the final visit indicated no clinically significant trends in hematological parameters and in renal and liver function.

TABLE 5. *Median differences between baseline and final value for selected laboratory parameters*

Parameter	QP	QP + HCTZ	HCTZ
Glucose (mM)	−0.05	0	0.2
Blood urea nitrogen (mM)	0.3	0.4	0.13
Creatinine (μM)	−1	0	1
Uric acid (μM)	−6.5	0	10.5
Potassium (mM)	0.1	0	−0.2

Abbreviations as in Table 1.

DISCUSSION

Combined quinapril plus HCTZ was statistically significantly more effective in reducing BP than was either monotherapy. The greater response observed with combination therapy was expected because each active agent affects a different but interrelated mechanism of BP control. Although the mechanism of the antihypertensive action of diuretics is not yet clearly understood, diuretics are believed to reduce plasma volume by impairing the ability of the collective mass of renal tubules to reabsorb specific ions, such as sodium and chloride, plus the water associated with these ions. They also have a vasodilatory action. These effects result in the promotion of renin release. The increase in plasma renin activity renders the BP more renin dependent and limits the antihypertensive effect of the diuretic. Concomitant administration of ACE inhibitors, by blocking the renin–angiotensin axis, enhances the antihypertensive effect of HCTZ (12–14).

The medication was well tolerated in all treatment groups. The low incidence of AE in the HCTZ monotherapy group indicates that 12.5 mg is a relatively low dose that often requires uptitration or concomitant medication for management of essential hypertension in many patients. On the other hand, quinapril is a potent antihypertensive drug, and a dose of 20 mg is sufficient to control BP in many hypertensive patients as monotherapy (2). The tolerability of the combination therapy ranked between that of both monotherapies in this study.

Orthostatic hypotension or hypotension after the first dose or at trough occurred infrequently during the study. No relevant differences between treatment groups were observed. None of the clinical laboratory assessments showed significant AE of the combination therapy with quinapril plus HCTZ.

Despite the relatively low diuretic dose in this study, the loss of potassium was highest, but not significant, in the HCTZ monotherapy group. The addition of quinapril to HCTZ appears to blunt this AE on potassium levels, as previously observed for this class of drugs (15). The same benefit of quinapril on HCTZ therapy was observed with regard to the increase of uric acid usually caused by HCTZ, also confirming results of another study with quinapril and HCTZ (17).

These results demonstrate the principle advantage of the combination of an ACE-inhibitor with a diuretic, which has important implications for the

management of patients with moderate to severe hypertension. In such patients, a single drug often does not produce the desired reduction in BP. Combining a truly effective dose of an ACE inhibitor with a low dose of the diuretic should reduce the prevalence of hypokalemia, glucose intolerance, gout, and other AE frequently associated with "high-dose" thiazide diuretics and allow the patient's BP to adjust to the appropriate level. Even doses of quinapril as low as 2.5 mg ameliorated the decrease in potassium induced by HCTZ (18), indicating that high doses of quinapril are not necessarily required for development of its beneficial effects in combination with HCTZ. With regard to the BP-lowering potency of the combination, the same study demonstrated that the optimal dose range of quinapril in combination with HCTZ (5–25 mg HCTZ was used in that study) is 10–30 mg (18). The suitability of the combination of 20 mg quinapril and 12.5 mg HCTZ was confirmed in the present study.

An exploratory subgroup analysis of the results of this study showed a trend to higher response rates in patients aged >65 years as compared with younger patients. Particularly for the combination therapy, the same trend was observed in another study in which the combination of quinapril and HCTZ was used (16). For the purpose of these two clinical trials, the study drugs were administered as initial therapy to all patients. Thus, although this was not an objective of this study, the lack of orthostatic hypotension after the first dose and during the study and the overall safety and efficacy profile of combination therapy support the use of ACE inhibitor–diuretic combination as initial therapy in subgroups of patients with moderate to severe hypertension, e.g., in elderly patients as previously suggested (19,20). Combined therapy with once-daily 20 mg quinapril plus 12.5 mg HCTZ significantly reduced BP more than did either monotherapy in patients with moderate to severe essential hypertension and no complicated hypertension and was well tolerated.

STUDY SITES AND PARTICIPANTS

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