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Quinapril, hydrochlorothiazide, and combination in patients with moderate to severe hypertension

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KEY WORDS: Essential hypertension, quinapril, hydrochlorothiazide, combination therapy.

This 8-week, double-blind, multicentre study compared the efficacy and safety of the combination of quinapril and hydrochlorothiazide (HCTZ) with each drug as monotherapy. Outpatients with moderate to severe hypertension defined as supine diastolic blood pressure (DBP) ≥105 mmHg and ≤120 mmHg at the end of a 2 to 4-week placebo-baseline period were randomly assigned to one of the three treatments: once-daily 10 mg quinapril plus 12·5 mg HCTZ or monotherapy with these doses. After 4 weeks, the doses were to be doubled for the remaining 4 weeks. Three hundred and sixty-eight patients were randomized to double-blind medication; 346 completed the study. Seven patients withdrew due to lack of efficacy. Four patients withdrew due to side effects. In all three treatment groups, clinically significant reductions in DBP were achieved. Combination therapy was statistically more effective than each component taken as monotherapy. Adverse events were infrequent in all treatment groups. No patients experienced symptomatic hypotension or orthostatic hypotension.

Introduction

Several compounds have been developed[1–3] since the first orally active angiotensin converting enzyme (ACE) inhibitor, captopril, was synthesized in 1977. Quinapril hydrochloride is a new once-daily nonsulfhydryl ACE inhibitor, characterized by a strong binding affinity for the converting enzyme, which potently and specifically blocks the conversion of angiotensin I to II[4]. Quinapril has been shown to produce a dose-dependent inhibitory effect on human plasma ACE[5]. It is a monoethylester and is hydrolysed in vivo to the pharmacologically active form quinaprilat, which has a three-fold stronger inhibitory effect on guinea pig serum ACE than the parent substance[4]. Clinical studies in hypertensive patients have demonstrated the efficacy and safety of once-daily quinapril[5–7].

ACE inhibitors have been widely used for the treatment of hypertension in patients with normal[2,8] and impaired renal function[9], and have gained acceptance by many clinicians as first-line antihypertensive agents[10]. It is generally agreed, however, that adequate control of high blood pressure is not achieved in all patients with a single-drug approach, irrespective of the antihypertensive agent used[11]. Thus, adequate control of high blood pressure in many hypertensive patients will require the addition of a second antihypertensive drug. Concurrent therapy with diuretics enhances the antihypertensive efficacy of ACE inhibitors[9,12,13]. Furthermore, the combination of ACE inhibitors with diuretics tends to attenuate the metabolic side effects of diuretics[13]. In general, the prescription of a combination of two active drugs for the treatment of hypertension may allow the use of lower doses of either drug, which might reduce the incidence of side effects and thus increase patient compliance.

In the present study the antihypertensive efficacy and safety of once-daily quinapril and hydrochlorothiazide (HCTZ) as monotherapy and in combination were assessed in patients with essential moderate to severe hypertension.

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Materials and methods

EXPERIMENTAL DESIGN

The study design was multicentre, double-blind, randomized, forced-titration with three parallel treatment groups (Fig. 1). Throughout the investigation, patients maintained their usual salt intake. At the end of the 2- to 4-week placebo-baseline period, patients were randomized to double-blind treatment. Men and women, at least 18 years old, with supine diastolic blood pressure (DBP) ≥105 mmHg and ≤120 mmHg at two consecutive visits at the end of the placebo phase were included. Patients took their medication once-daily in the morning and, on clinic visit days, after measurement of trough blood pressure. During the first 4 weeks of double-blind treatment, patients received once-daily quinapril 10 mg plus placebo or quinapril 10 mg plus HCTZ 12·5 mg or placebo plus HCTZ 12·5 mg. After 4 weeks of therapy, the doses were to be doubled and the treatment

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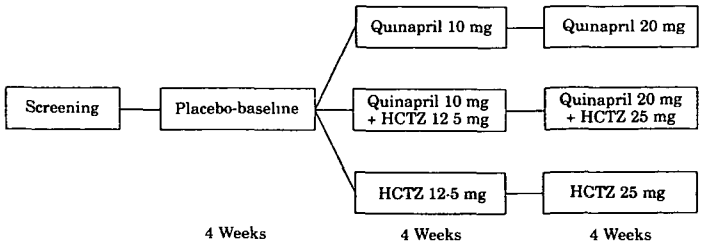

Figure 1 Study design. Medication was randomized given once-daily, double-blind. Patients with supine diastolic pressure <80 mmHg or supine systolic pressure <120 mmHg at the end of week 4, or if there were any other clinical reasons, did not have their doses doubled for safety reasons but maintained the low dose.

continued for another 4 weeks. If the supine DBP was below 80 mmHg or the supine systolic blood pressure (SBP) below 120 mmHg at the end of week 4, or if there was any other clinical reason, the doses were not doubled.

Blood pressure measurements were performed in the clinic using a mercury sphygmomanometer, until the disappearance of all sound (Korotkoff Phase V), to identify the diastolic blood pressure. Following a 5 min rest in the supine position, three measurements were taken 3 min apart and their averages used for evaluation; then patients stood quietly and blood pressure was recorded after 30 s and after 3 min. After the first dose, the procedure was repeated hourly up to 4 h.

STATISTICS

The total number of 110 patients per study arm to be enrolled was calculated assuming a 20% overall drop-out rate and a standard deviation of 7 mmHg. This provided a 95% power to detect a mean difference of 3·5 mmHg between combination and each monotherapy when a one-sided test at the 5% level of significance was performed.

Inferential testing of supine DBP and SDP was done by an analysis of covariance using baseline blood pressure as the covariate, and included treatment group and centre as classification variables in the model. Change from baseline was regarded as the dependent variable, and baseline was defined as the average of the measurements from the last two consecutive visits during the placebo-baseline phase.

Treatment effects on response rates were tested with the Cochran–Mantel–Haenszel procedure using centres as strata. Only the two tests of combination therapy vs each monotherapy were done. Both tests were performed one-sided at the 5% level of significance, as specified in the protocol. Since combination therapy must demonstrate superiority over each of its components, an adjustment for multiple testing is not necessary. An intent-to-treat analysis of efficacy data was performed on all patients having data from the placebo-baseline phase and from the double-blind phase.

The global response was evaluated for each treatment group. Global response is a measure of tolerance and efficacy, in that it is the percent of all patients who completed study week 8 and responded to treatment with a reduction in supine DBP of $\geq$ 10 mmHg from baseline. In this analysis all other patients were considered to be non-responders.

Statistical subgroup analyses were not planned in the study protocol. Exploratory subgroup analyses were done without any testing.

SUBJECTS

This multicentre study was conducted in seven European countries (29 centres) in accordance with the declaration of Helsinki, and approval was given by the local ethics committees. After informed consent was obtained, outpatients with moderate to severe hypertension underwent a screening period during which antihypertensive medications were withdrawn. Women of child-bearing potential had to be using reliable birth control. A total number of 368 patients (165 men, 203 women; 364 white, 1 black, 3 Asian) were enrolled in the study. Demographic data for all 368 randomized patients are summarized in Table 1. While the percentage of women in the HCTZ group (60%) was slightly higher than in other groups (53% and 52%), no other differences were apparent between the treatment groups.

PREVIOUS ANTIHYPERTENSIVE MEDICATION

In the 3 months before the study, 272 patients (74%) were treated for hypertension. The most frequently used medications were beta-blockers, diuretics, and ACE inhibitors.

Results

CLINICAL OUTCOME

Of the 368 patients who entered the double-blind phase, 22 (6%) withdrew and 346 completed the study. In general, no relevant differences could be detected

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Table 1 Characteristics for randomized patients (n=368)

Variable	Quinapril monotherapy (n=120)	Quinapril +HCTZ (n=124)	HCTZ monotherapy (n=124)	Total (n=368)
Sex [N(%)]				
Men	56 (47)	59 (48)	50 (40)	165 (45)
Women	64 (53)	65 (52)	74 (60)	203 (55)
Age group [n(%)]				
<65 years	83 (69)	89 (72)	79 (64)	251 (68)
≥65 years	37 (31)	35 (28)	45 (36)	117 (32)
Age (years)				
Mean	58	57	59	58
Range	23–86	22–79	26–80	22–86
Baseline hypertension state				
Median duration (years)	4 0	4·4	4·9	4·1
Range	0–39	0–43	0–22	0–43
Mean DBP* (mmHg)	109·5	109·7	109·2	109 5
Range*	99–119	100–120	97–120	97–120
Mean SBP* (mmHg)	173·5	169·8	170·9	171·3
Range*	134–223	137–217	141–213	134–223

*n=118 (quinapril), n=122 (quinapril+HCTZ), n=123 (HCTZ), n=363 (total) due to five patients with no placebo-baseline measurements.

Table 2 Patient distribution [Number (%) of patients]

	Quinapril monotherapy	Quinapril +HCTZ	HCTZ monotherapy	Total
Randomized to treatment	120	124	124	368
Withdrawals				
Adverse events	3* (2·5)	0 (0·0)	1 (0·8)	4* (1·1)
Lack of efficacy	2 (1·7)	2 (1·6)	3 (2·4)	7 (1·9)
Personal reasons	1 (0·8)	1 (0·8)	2 (1·6)	4 (1·1)
Loss to follow-up	0 (0·0)	1 (0·8)	0 (0·0)	1 (0·3)
Non-compliance	0 (0·0)	1 (0·8)	0 (0·0)	1 (0·3)
Missing baseline phase†	2 (1·7)	2 (1·6)	1 (0 8)	5 (1·4)
Total	8 (6·7)	7 (5·6)	7 (5·6)	22 (6·0)

*One patient withdrew due to dizziness, but he had complained of dizziness over the past 3 years.
†Five patients started the study erroneously without a placebo-baseline phase. After this protocol violation was detected, treatment was stopped in the third week.

between the treatment groups in the number of withdrawals and the reasons for withdrawal. The number of patients who entered and withdrew from the study, including the reasons for withdrawal, are summarized in Table 2. No patient in the combination therapy group, two in the quinapril and one in the HCTZ monotherapy group withdrew from the study as a result of one or more adverse events that began during the double-blind phase of the study. In one patient the adverse event (heart palpitation) was attributed to the study medication (quinapril). According to the study design, all patients were to be force-titrated to the high dose. However, for safety reasons only 323 patients (88%) were titrated to the high doses. More patients received high doses in the HCTZ group (93%) than in the quinapril monotherapy (85%) or combination group (86%).

EFFICACY

Altogether, data from 318 patients in the low dose group and from 284 patients in the high dose group were used for efficacy evaluation. Reasons for exclusion from efficacy evaluation were inadequate baseline blood pressure, concomitant medication that had not been approved, late discontinuation of prior antihypertensive medication, blood pressure measurements taken outside the 20–28 h postdose limit, or within fewer than 19 days on the respective dose. The data from all 368 patients who entered the double-blind phase were evaluated for safety.

Low dose

After 4 weeks of low-dose treatment (10 mg quinapril: 12·5 mg HCTZ; combination), all treatment groups had

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Table 3 Supine and standing blood pressure (mmHg) at trough and response rate on the last evaluable visit (day 19 to 39) with low-dose treatment (n=318) and with following high-dose treatment (n=284)

	Low dose				High dose			
	Quinapril 10 mg monotherapy (n=101)		Quinapril 10 mg +HCTZ 12·5 mg (n=108)	HCTZ 12 5 mg monotherapy (n=109)	Quinapril 20 mg monotherapy (n=91)		Quinapril 20 mg HCTZ 25 mg (n=94)	HCTZ 25 mg monotherapy (n=99)
Supine DBP								
Mean baseline	109·8		110·1	109·6	109 9		110·4	109·7
Change from baseline								
Adjusted mean	− 12·1		− 14·6	− 12·5	− 17·0		− 19·5	− 17·2
Standard error	0·8		0·8	0·8	0·9		0·9	0·8
P-value*		0·019		0·033		0·017		0·026
Supine SBP								
Mean baseline	172·7		169·6	171·0	173·3		171·3	171·9
Change from baseline								
Adjusted mean	− 13·1		− 17·7	− 11·6	− 19·7		− 27·1	− 20·4
Standard error	1·5		1·4	1·4	1·3		1·4	1·3
P-value*		0·013		0·0012		<0·001		<0·001
Standing DBP								
Mean baseline	110·4		110·6	110·2	110·5		110·8	110·1
Raw mean change from baseline	− 11·0		− 13·7	− 10·7	− 15·8		− 18·3	− 16·4
Standing SBP								
Mean baseline	170·8		168 7	170·5	171·1		171·0	171·0
Raw mean change from baseline	− 12·1		− 18·0	− 11·1	− 17·8		− 27·6	− 20·3

*One-sided for the difference between quinapril+HCTZ and each of the monotherapies.

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clinically significant mean reductions from baseline in supine DBP and SDP. Reductions with combination therapy were significantly ($P<0.05$) greater than with either monotherapy (Table 3).

In an exploratory subgroup analyses, combination therapy tended towards a greater response in older (≥ 65 years) than in younger patients (<65 years). The corresponding mean reductions from baseline with combination therapy in supine DBP (SBP) were 18·0 (17·7) mmHg for the older patients and 13·6 (17·1) mmHg for the younger patients with the same baseline of 110 mmHg in both age groups. A similar trend was seen for HCTZ monotherapy, but not for quinapril monotherapy.

High dose

After the forced titration of 88% of patients to the high dose (20 mg quinapril; 25 mg HCTZ; combination), greater mean reductions from baseline in supine DBP and SBP were seen in all three treatment groups (Table 3). Reductions with combination therapy were significantly ($P<0.05$) greater than with either agent alone. In regard to age-related differences in efficacy, similar results with both the low and high doses were apparent. Mean reductions with the combination therapy in supine DBP (SBP) were 20·7 (28·5) mmHg for the older and 18·9 (25·7) mmHg for the younger patients. The same trend was observed with HCTZ monotherapy, while quinapril monotherapy was equally effective in both age groups.

Standing blood pressure

Thirty-second readings of standing blood pressure were used to detect orthostatic hypotension for safety reasons and the 3 min readings were used as a measure of efficacy. The raw mean changes in standing blood pressure from baseline with the low and high dose were similar to those seen in supine blood pressure with either monotherapy or combination therapy. Greater efficacy for both low and high dose was obtained with the combination therapy (Table 3).

INTENT-TO-TREAT ANALYSIS

The intent-to-treat analysis performed with supine diastolic and systolic blood pressure at trough with the low dose (n=362), and the analysis performed in all patients' final double-blind measurement, independent of dose, confirmed the results of the evaluable data analysis. There were statistically significantly higher mean reductions produced by combination therapy than with either monotherapy.

GLOBAL RESPONSE

All 368 patients in the study were included in the analysis of global response. Global response rates under combination therapy, quinapril monotherapy and HCTZ monotherapy were 72%, 66% and 70% , respectively. Differences were not statistically significant.

SAFETY

The incidence of adverse events was low in all treatment groups. The proportion of patients with adverse events on quinapril monotherapy (9·2%) was similar to proportion of patients on HCTZ monotherapy (9·7%), whereas the proportion of patients with adverse effects while on combination therapy was somewhat lower (6·5%). Percents of patients with associated adverse events (considered by the investigator as possibly, probably, or definitely related to study drug) were lowest in the HCTZ monotherapy group (1·6%), 4·0% in the combination group, and 6·7% in the quinapril monotherapy group. Associated adverse events reported by more than one patient in any treatment group were cough, dizziness, hypoglycaemia, and nausea, each in two patients of the quinapril monotherapy group. Concomitant quinapril plus HCTZ did not cause any adverse events in elderly patients (≥ 65 years). In two patients with high dose treatment (one in the combination treatment group and one in the quinapril monotherapy group), adverse events related to low blood pressure resulted in a reduction of study medication.

Adverse events did not appear to be dose-related. The numbers of first occurrences of adverse events under quinapril monotherapy, combination therapy, and HCTZ monotherapy were 10, 3, and 9, respectively, during therapy with the low dose, and 8, 5, and 10, respectively, during therapy with the high dose.

An analysis of blood pressure data as regards hypotension or orthostatic hypotension revealed 51 patients with decreases in systolic blood pressure >20 mmHg from supine to standing. However, none of these patients reported concurrent clinical symptoms of postural hypotension. One case of syncope that was considered unrelated to study medication occurred on quinapril monotherapy. The addition of quinapril to HCTZ appeared to attenuate the potassium loss and the increase of uric acid which was observed under HCTZ monotherapy. The percents of patients who had decreases of potassium below the lower limit or increases of uric acid above the upper limit of the normal range at the end of the study are listed in Table 4. Clinical laboratory assessments revealed no clinically significant adverse effects. No patient died during the study.

Discussion

The blood pressure lowering efficacy of the new once-daily ACE inhibitor quinapril has been shown in patients with mild to severe hypertension[5–7,15–17]. In patients with moderate to severe hypertension resistant to quinapril monotherapy, diuretic can be safely added for additional blood pressure control[7,16,17]. This is consistent with the literature findings, in that in most patients when a diuretic is added to an ACE inhibitor, the blood pressure lowering effect is increased[12,13,18–20]. In the present study of moderately to severely hypertensive patients, using quinapril alone in two different doses or in combination with a diuretic, similar

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Table 4 Percent of patients with decreases in potassium below or increases of uric acid values above the normal range at the end of the study

	Quinapril monotherapy	Quinapril +HCTZ	HCTZ monotherapy
Potassium	1·9	3·6	12·8
Uric acid	6·0	12·9	20·2

observations were made. Both low- and high-dose treatment with concomitant quinapril plus HCTZ was significantly more effective in lowering blood pressure than either monotherapy within each respective dose level. Although the mechanism of the antihypertensive action of diuretics is not yet clearly understood, it is believed that reduction of plasma volume which subsequently activates the renin-angiotensin system is involved. This activation, however, counteracts the reduction of blood pressure and is the reason why persistent elevated blood pressure in diuretic-treated, uncontrolled patients becomes particularly angiotensin II-dependent[2,21]. In this situation, blockade of the renin-angiotensin system by ACE inhibitors is a powerful approach to reducing elevated blood pressure.

As would be expected, the global response rate tended to be higher in the combination therapy group (72%), followed by 70% in the HCTZ monotherapy group, and 66% in the quinapril monotherapy group. However, the differences were not statistically significant. In this forced-titration study, the relatively high global response rate in the HCTZ monotherapy group might be due to the fact that 93% of the patients in this group received the high dose at the end of the study, whereas this percentage was lower in the quinapril monotherapy group (82·5%) and in the combination therapy group (84%). The comparatively small dose of HCTZ (12·5%) received by patients during the pre-titration phase of the study may not have been sufficient antihypertensive with the single-drug approach. Notably, however, although combination therapy with quinapril plus HCTZ can achieve higher reductions in blood pressure than either monotherapy alone within the respective dose levels, many patients can be treated satisfactorily with the monotherapy.

An exploratory subgroup analysis has been performed on age-related effects on blood pressure reduction. Since such an analysis was not planned in the study protocol, no statistical evaluation was done and the results are only of descriptive nature. Nevertheless, it is noteworthy that combination therapy tended to be more effective in reducing supine blood pressure in elderly patients than in patients younger than 65 years of age. The higher reduction of blood pressure, especially systolic blood pressure, in older patients was achieved with virtually no side effects. It has been documented in previous studies that quinapril is effective and well tolerated in elderly hypertensives[14,22,23]. For elderly hypertensives who are not adequately controlled on monotherapy, the combination may provide other benefits such as attenuating the undesirable metabolic side effects of diuretic therapy, particular hypokalaemia[11,13]. In a retrospective analysis of three double-blind Veterans Administration Cooperative Studies that enrolled persons 55 years of age and older, it was found that response to combination therapy in this group of patients did not diminish with age and this response was greater than with either agent alone[24]. Combination therapy with low doses of an ACE inhibitor has been shown to be effective in elderly hypertensive patients in several studies[23,25]. Thus, our data agree with the use of an ACE inhibitor–diuretic combination as initial therapy in elderly, moderate to severely hypertensive patients[11].

The medication was well tolerated in all treatment groups. Metabolic adverse reactions to potassium and uric acid levels were lowest in the quinapril monotherapy group and highest in the HCTZ monotherapy group, whereas the combination ranged between the two groups. Thus, these results confirm previously reported findings that ACE inhibitors attenuate metabolic side effects of diuretics[13,18]. The lowest percent of patients reporting adverse events was found in the combination therapy group. The lowest incidence of adverse events was found in patients 65 years or older who were treated with combination therapy. In this subgroup, no adverse events were reported. In patients below 65 years of age, the incidence was slightly lower in the combination therapy group compared to either monotherapy group. With regard to side effects of combination therapy, similar favourable observations were also made by other investigators. They reported a particularly low incidence of adverse drug reactions when elderly patients were treated with combination therapy[23,25].

In summary, once-daily quinapril monotherapy and HCTZ monotherapy effectively reduced blood pressure in patients with moderate to severe hypertension. Concomitant quinapril plus HCTZ provided additional efficacy over either monotherapy within each dose level. Once-daily administration of both 10 mg quinapril plus 12·5 mg HCTZ and 20 mg quinapril plus 25 mg HCTZ was effective and well tolerated. Quinapril appears to attenuate the adverse effects of HCTZ on potassium and uric acid.

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List of study sites

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