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Influence of the Renin Profile on the Blood Pressure Response to Different Doses of Hydrochlorothiazide plus either Quinapril or Captopril

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Summary The antihypertensive efficacy and safety of quinapril 20mg plus hydrochlorothiazide 6.25mg were compared over 8 weeks with captopril 50mg plus hydrochlorothiazide 15mg in 52 patients with mild to moderate essential hypertension (27 men and 25 women age 49.7 ± 8.4 years). The study also evaluated the relationship between antihypertensive efficacy and plasma renin activity/blood pressure sensitivity to changes in dietary sodium intake. The combination of quinapril or captopril with hydrochlorothiazide showed similar antihypertensive effects and tolerability. Neither blood pressure salt sensitivity nor renin profile were predictive of blood pressure response to either therapy. These results suggest that the antihypertensive efficacy of an angiotensin converting enzyme inhibitor when administered in fixed ratio with a thiazide diuretic is independent of salt sensitivity in hypertension.

Angiotensin converting enzyme (ACE) inhibitors are widely accepted as safe and effective therapy for hypertension (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1983, 1984; Santucci et al. 1989), and are often coadministered with thiazide diuretics to potentiate their antihypertensive effects (Giarrizzo et al. 1988; Townsend & Holland 1990). Moreover, several placebo-controlled studies have shown the efficacy of ACE inhibitors when administered once daily (Santucci et al. 1990), and similar antihypertensive effects have been noted for ACE inhibitors when administered once daily in combination with hydrochlorothiazide 15 to 25mg (Raule et al. 1991; Santucci et al. 1990). Nevertheless, in spite of the evident synergism between ACE inhibitors and thiazide diuretics, baseline plasma renin activity is not predictive of blood pressure response to their combination (Biollaz et al. 1981). This may reflect variation in sodium intake and consequent disparate changes in renin secretion for patients with hypertension.

This double-blind randomised study compared the efficacy and tolerability of captopril 50mg plus hydrochlorothiazide 15mg with quinapril 20mg plus hydrochlorothiazide 6.25mg in patients with mild to moderate hypertension. A lower hydrochlorothiazide dose was chosen for combination with quinapril because the elimination half-life of the latter is greater than that of captopril. Therefore, enhanced antihypertensive activity might be evident. This study also evaluated the relationship between the blood pressure response to antihypertensive therapy and plasma renin activity determined with a diet of either 'normal' or 'low' sodium content.

Patients and Methods

Patients

This study recruited 52 Caucasian outpatients with mild to moderate hypertension seen consecutively in the Andrea Cesalpino Foundation Institute of I Clinica Medica, University 'La Sapienza', Rome. Patient characteristics are given in table I. The mean duration of hypertension was 2.6 ± 2.4 years, and 34 patients (65.4%) were being treated with antihypertensive medication when referred to the Foundation.

To be eligible for enrolment, patients were required to have a diastolic blood pressure between 95 and 114mm Hg on 3 visits at weekly intervals. Patients had normal renal morphology and/or function, as determined by serum creatinine level, renal ultrasonography and [^{131}I]*O*-Orthoiodohippurate radionephroscintigram. The presence of concomitant disease (e.g. heart failure, liver cirrhosis, chronic obstructive pulmonary disease, diabetes) was also discounted. In particular, patients were required to demonstrate a normal blood glucose response to an oral glucose load (1 g/kg bodyweight). Other antihypertensive medication was withdrawn 5 weeks before the study commenced. No other medications were allowed during the study.

Methods

At the first visit to the Foundation, a nutritionist advised each patient on how to prepare a diet containing 'low' sodium (40 mmol/day) or 'normal' sodium (120 mmol/day) levels; written instructions were also provided. On each subsequent visit patients were required to bring a 24-hour urine sample to determine sodium excretion and to assess compliance with dietary sodium intake.

Patients were treated with placebo once daily for 5 weeks commencing at the first visit to the Foundation (8am). For the first 3 weeks of this regimen, patients followed a diet with 'normal' sodium levels, but were subsequently switched to a 'low' sodium diet for the last 2 weeks. Plasma renin activity was determined in blood samples obtained at the end of the 'low' and 'normal' dietary sodium periods from patients remaining supine (after 1 hour's bed rest) and following 1 hour of spontaneous activity.

On completion of the placebo run-in period, patients were randomly assigned in double-blind fashion to receive either quinapril 20mg plus hydrochlorothiazide 6.25mg or captopril 50mg plus hydrochlorothiazide 15mg daily at 8am for 8 weeks. The first active dose was administered in hospital, and patients were maintained under observation for 2 hours to ensure that first-dose acute hypotension did not occur. During active treat-

Table I. Patient characteristics of the treatment population

Variable	Quin + HCTZ (n = 27)	Capt + HCTZ (n = 25)	Total (n = 52)
Gender			
Male	15	12	27
Female	12	13	25
Age			
Median (y)	48.8 ± 8.5	50.6 ± 8.3	49.7 ± 8.4
Range (y)	24-63	28-64	24-64
Body mass index	23.6 ± 2.1	24.2 ± 2.0	23.8 ± 2.0
Smoker	5	3	8
Previous antihypertensive therapy	16 (59.3%)	18 (72%)	34 (65.4%)

Abbreviations: Capt + HCTZ = captopril 50mg + hydrochlorothiazide 15mg; Quin + HCTZ = quinapril 20mg + hydrochlorothiazide 6.25mg.

Table II. Antihypertensive efficacy of quinapril (Quin) plus hydrochlorothiazide (HCTZ) or captopril (Capt) plus HCTZ in patients with mild to moderate hypertension

Week/treatment	No. of patients	Change from baseline (mm Hg)		
		DBP	SBP	response rate (%)
Week 2[a]				
Capt + HCTZ	25	−4.0 ± 1.1	−7.2 ± 2.2	20
Quin + HCTZ	27	−7.0 ± 1.0	−10.6 ± 2.3	37
Week 4[a]				
Capt + HCTZ	25	−5.5 ± 1.1	−9.3 ± 2.3	28
Quin + HCTZ	27	−8.7 ± 1.2	−11.1 ± 2.0	48
Week 8[a]				
Capt + HCTZ	25	−5.3 ± 1.3	−11.0 ± 2.0	40
Quin + HCTZ	27	−8.3 ± 1.2	−10.2 ± 2.0	44

a The last observation available.

Abbreviations: Capt + HCTZ = captopril 50mg + hydrochlorothiazide 15mg; DBP = diastolic blood pressure; Quin + HCTZ = quinapril 20mg + hydrochlorothiazide 6.25mg; SBP = systolic blood pressure.

ment, patients were again placed on a 'normal' sodium diet (120 mmol/day).

Blood pressure measurements were taken by the same investigator (who was unaware of the study design) using a mercury sphygmomanometer. The blood pressure at which all sounds disappeared (Korotkoff phase V) was recorded as the diastolic blood pressure. Blood pressure measurements were taken at 2-week intervals during active therapy at the end of the dosing interval (trough blood pressure) 22 to 24 hours after the previous dose. On each occasion 3 recordings were made at 3-minute intervals with the patient in the sitting position; the average blood pressure was calculated and recorded as the definitive measurement.

A thorough medical examination (patient history, general and cardiological examinations including 12-lead electrocardiogram) was performed at the start and completion of the study. Plasma renin activity was determined by a commercially available radioimmunoassay (RENCTK, Sorin Biomedica, Vercelli, Italy) and 24-hour urinary sodium levels measured concomitantly and at study completion using standard laboratory methods. Patients with plasma renin activity < 0.28 ng/L/sec after normal exercise while following a 'low' sodium diet were considered to be 'low renin patients' (Williams et al. 1992). Routine laboratory tests on blood and urine samples (including lipids, electrolytes and serum glucose) were carried out at the time of screening, at the end of the placebo period, and at the end of the study, using standard laboratory methods. All adverse events were recorded, together with assessment of their relationship to the drug and their severity.

All withdrawals from the study were evaluated blindly by the study chairman and classified as administrative or medical. Medical withdrawals were further analysed blindly to determine whether they were due to an adverse drug reaction.

The primary outcome measure was the treatment success rate: the percentage of patients considered to have responded to therapy. A response to treatment was defined as a reduction in sitting diastolic blood pressure of 10mm Hg and/or a sitting diastolic blood pressure < 90mm Hg. Treatment success rates were analysed by the Cochran-Mantel-Haenszel test using a SAS™ Statistical package (version 6.04) for personal computers (SAS Institute, Cary, North Carolina, USA).

Results

Of the 52 patients randomised to therapy, 8 withdrew from the investigation; 6 because of adverse events and 2 for unrelated causes. Thus, 44 patients completed the study; 21 received quinapril plus hydrochlorothiazide and 23 received captopril plus hydrochlorothiazide.

During placebo run-in, evaluation of 24-hour urinary sodium excretion confirmed compliance with the dietary sodium regimen. Values were between 80 and 130 mEq/24h with 'normal' sodium intake and < 40 mEq/24h with sodium restriction. After the 2-week period of sodium dietary restriction, plasma renin activity significantly increased (quinapril/hydrochlorothiazide group: from 0.19 ± 0.1 to 0.4 ± 0.2 ng/L/sec, $p < 0.002$; captopril/hydrochlorothiazide group: from 0.2 ± 0.1 to 0.36 ± 0.1 ng/L/sec, $p < 0.001$), but only minimal changes in blood pressure were observed.

During the active treatment phase, no significant hypotensive event occurred with first-dose administration, and both treatments showed equivalent efficacy in terms of diastolic blood pressure reduction commencing on week 2. On completion of the treatment period, 44% of patients receiving quinapril plus hydrochlorothiazide and 40% receiving captopril plus hydrochlorothiazide were considered to have responded to therapy (table II). Basal plasma renin activity did not influence diastolic blood pressure response to therapy (table III). Similarly, subgroup comparison of patients showing a diastolic blood pressure reduction of ≥ 5mm Hg (n = 11) with those that showed no such difference at this timepoint (n = 40) revealed no significant difference in blood pressure response to either drug regimen (table IV). Moreover, no significant relationship was found between plasma renin activity during 'normal' or 'low' sodium intake and diastolic blood pressure changes to drug therapy.

Table III. Antihypertensive efficacy based on plasma renin activity (PRA) in patients with mild to moderate hypertension (orthostatic position) evaluated on completion of the placebo run-in period

	DBP (mm Hg)					
	Quin + HCTZ		Capt + HCTZ		All patients	
	PRA > 0.28 (n = 20)	PRA < 0.28 (n = 6)	PRA > 0.28 (n = 18)	PRA < 0.28 (n = 7)	PRA > 0.28 (n = 38)	PRA < 0.28 (n = 13)
Baseline values	101.8 ± 1.0	101.4 ± 1.8	100.0 ± 1.0	100.5 ± 2.8	100.9 ± 0.7	100.9 ± 1.7
Week 2[a]	94.5 ± 1.5	95.8 ± 1.1	95.1 ± 1.4	98.6 ± 3.5	94.8 ± 1.0	97.3 ± 1.9
Change	−7.4 ± 1.3	−5.5 ± 1.6	−4.8 ± 1.3	−1.9 ± 2.2	−6.2 ± 0.9	−3.6 ± 1.5
p (among groups)	< 0.001	0.015	0.001	0.401	< 0.001	0.022
p (between groups)	0.503		0.245		0.151	
Week 4[a]	93.2 ± 1.4	92.7 ± 2.7	94.4 ± 1.5	95.0 ± 4.3	93.8 ± 1.0	93.9 ± 2.6
Change	−8.6 ± 1.5	−8.6 ± 2.3	−5.6 ± 1.1	−5.5 ± 2.9	−7.1 ± 1.0	−6.9 ± 1.8
p (among groups)	< 0.001	0.002	< 0.001	0.020	< 0.001	< 0.001
p (between groups)	0.929		0.984		0.917	
Week 8[a]	93.6 ± 1.2	93.6 ± 1.6	94.5 ± 1.5	95.5 ± 4.2	94.0 ± 0.9	94.6 ± 2.3
Change	−8.3 ± 1.5	−7.7 ± 2.4	−5.5 ± 1.5	−5.0 ± 2.8	−6.9 ± 1.0	−6.3 ± 1.9
p (among groups)	< 0.001	0.001	0.002	0.061	< 0.001	< 0.001
p (between groups)	0.963		0.855		0.752	

a The last observation available.

Abbreviations: DBP = diastolic blood pressure; Capt + HCTZ = captopril 50mg + hydrochlorothiazide 15mg; Quin + HCTZ = quinapril 20mg + hydrochlorothiazide 6.25mg.

Table IV. Antihypertensive efficacy in patients with mild to moderate hypertension based on the reduction in diastolic blood pressure evaluated on completion of placebo run-in

	DBP (mm Hg)					
	Quin + HCTZ		Capt + HCTZ		All patients	
	ΔDBP ≥ 5 (n = 3)	ΔDBP < 5 (n = 23)	ΔDBP ≥ 5 (n = 8)	ΔDBP < 5 (n = 17)	ΔDBP ≥ 5 (n = 11)	ΔDBP <5 (n = 40)
Baseline values	99.4 ± 2.4	102.0 ± 0.9	99.8 ± 1.8	100.3 ± 1.3	99.7 ± 1.4	101.3 ± 0.8
Week 2[a]	95.0 ± 1.3	93.3 ± 1.0	93.9 ± 2.4	97.1 ± 1.7	93.7 ± 1.8	95.9 ± 1.0
Change	–6.1 ± 2.0	–7.0 ± 1.2	–5.8 ± 2.6	–3.1 ± 1.1	–5.9 ± 1.9	–5.4 ± 0.9
p (among groups)	0.038	< 0.001	0.008	0.034	< 0.001	< 0.001
p (between groups)	0.981		0.263		0.600	
Week 4[a]	93.3 ± 1.7	93.1 ± 1.4	93.7 ± 2.4	95.0 ± 2.0	93.6 ± 1.7	93.9 ± 1.2
Change	–6.1 ± 3.9	–8.9 ± 1.3	–6.0 ± 1.7	–5.3 ± 1.4	–6.1 ± 1.5	–7.4 ± 1.0
p (among groups)	0.055	< 0.001	0.007	0.001	0.001	< 0.001
p (between groups)	0.670		0.768		0.648	
Week 8[a]	92.2 ± 1.5	93.7 ± 1.1	95.2 ± 2.1	94.6 ± 2.1	94.4 ± 1.6	94.1 ± 1.1
Change	–7.2 ± 2.2	–8.3 ± 1.4	–4.6 ± 2.3	–5.7 ± 1.6	–5.3 ± 1.8	–7.2 ± 1.0
p (among groups)	0.007	< 0.001	0.059	0.001	0.002	< 0.001
p (between groups)	0.725		0.723		0.608	

a The last observation available.

Abbreviations: DBP = diastolic blood pressure; Capt + HCTZ = captopril 50mg + hydrochlorothiazide 15mg; Quin + HCTZ = quinapril 20mg + hydrochlorothiazide 6.25mg.

All adverse events were considered drug-related and were moderate in severity; the most common were cough and asthenia (2 patients), dizziness (2 patients), nonpostural hypotension (1 patient), and headache (1 patient) in patients taking quinapril plus hydrochlorothiazide, and dizziness (1 patient) and headache (1 patient) in patients taking captopril plus hydrochlorothiazide. No significant differences in routine laboratory parameters were observed with either combination.

Discussion

In this study, low dose hydrochlorothiazide (6.25mg) plus quinapril was comparable to higher dose hydrochlorothiazide (15mg) plus captopril in reducing blood pressure among patients with mild to moderate hypertension. Furthermore, the incidence of adverse events was similar for both combination therapies.

In accordance with the findings of this study, the antihypertensive effects of ACE inhibitors have previously been reported in a large subpopulation of normal-renin salt sensitive patients with hypertension, so-called 'nonmodulators' (Redgrave et al. 1985; Williams & Hollenberg 1991). Diuretics have also shown antihypertensive efficacy in 'low-renin' patients (Laragh & Brenner 1990), who are often referred to as a sodium sensitive subgroup (Weinberger et al. 1986). In 'low-' and 'normal-renin' patients in whom ACE inhibitors alone are ineffective, diuretic therapy may induce renin release, thereby causing renin-dependent vasoconstriction and thus enhancing the antihypertensive efficacy of converting enzyme inhibition (Gavras et al. 1976; Laragh & Brenner 1990).

The above observations suggest that ACE inhibition might induce hypotension and possibly renal failure in patients with excessive sodium depletion due to low sodium intake and/or diuretic therapy. Indeed, animal and human studies have demon-

strated that sodium depletion is often followed by an excessive antihypertensive response to ACE inhibition, with marked hypotension and even acute renal failure (Menard et al. 1987).

In this study, first dose hypotension did not occur in response to administration of a low dose diuretic and ACE inhibitor. This indicates that such a regimen may be used in patients with mild to moderate hypotension without danger of excessive response to ACE inhibition.

Conclusion

This study showed that quinapril plus low dose hydrochlorothiazide is as effective and safe as the more usual combination of captopril plus hydrochlorothiazide in patients with mild to moderate essential hypertension. Antihypertensive efficacy was not related to the renin profile or sodium sensitivity of blood pressure.

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