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CLINICAL TRIALS

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Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy and safety compared to hydrochlorothiazide

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Abstract *Objective:* To compare the antihypertensive efficacy of a new angiotensin II antagonist, valsartan, with a reference therapy, hydrochlorothiazide (HCTZ). *Methods*: In this double-blind study, 167 adult outpatients with mild-to-moderate essential hypertension were randomly allocated in equal number to receive valsartan 80 mg or HCTZ 25 mg for 12 weeks. In patients whose blood pressure (BP) remained uncontrolled after 8 weeks of monotherapy, atenolol 50 mg was added to the initial treatment. Patients were assessed at 4, 8 and 12 weeks. The primary efficacy variable was change from baseline in mean sitting diastolic BP (SDBP) at 8 weeks. Secondary variables included change in sitting systolic BP (SSBP) and responder rates (percentage of patients with SDBP <90 mmHg or drop ≥10 mmHg compared to baseline) at 8 weeks.
Results: Valsartan and HCTZ were both effective at lowering diastolic and systolic blood pressure at all time points. Similar falls were seen in both groups with no significant differences between treatments. For the primary variable (decrease in SDBP) there was no significant difference between treatments. For SSBP there was also no significant difference observed. Responder rates at 8 weeks were 74% for valsartan and 62% for HCTZ ($P = 0.10$). Both treatments were well tolerated, both as monotherapy, and when combined with atenolol 50 mg per day.
Conclusion: The data show valsartan 80 mg to be as effective as HCTZ in the treatment of mild-to-moderate hypertension. The results also show valsartan to be well tolerated when taken alone or in combination with atenolol.

Key words Hydrochlorothiazide, Valsartan; angiotensin II receptor antagonist, essential hypertension, thiazide diuretic

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Introduction

The benefits of treating essential hypertension are well established [1–3]. Both lifestyle measures and drug treatment play an important part in management [4]. With respect to drug therapy, initial treatment is generally with monotherapy and there are currently a wide choice of classes of antihypertensive agents available for first-line treatment. These include diuretics, β-adrenoceptor blockers, calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors. The efficacy of all these classes is well established and generally accepted to be similar [5]. However, all are associated with well-recognised adverse effects which may limit their use in some patients.

Angiotensin II receptor antagonists are the newest class of antihypertensives. These agents reduce blood pressure by selective and specific blockade of the action of angiotensin II at the AT1 receptor, the last step in the renin-angiotensin-aldosterone cascade [6]. Angiotensin II is well recognised to play a central role in hypertension via its potent vasoconstrictor action and stimulation of aldosterone secretion [7, 8]. Selective and specific inhibition of this pathway would be anticipated to result in effective antihypertensive agents with a good tolerability profile.

Valsartan is a new orally active specific angiotensin II receptor antagonist [9]. It has been shown to be effective

at reducing blood pressure at a dose of 80 mg once daily and to be as effective as amlodipine [10]. A direct comparison of the efficacy and safety with diuretics has not been previously reported.

The primary aim of this study was to compare the efficacy of valsartan 80 mg with hydrochlorothiazide 25 mg in the treatment of mild to moderate essential hypertension. A secondary aim was to compare the tolerability of valsartan with HCTZ either as monotherapy or when taken in combination with atenolol 50 mg.

Patients and methods

Patients

Male and female outpatients of any race with mild to moderate essential hypertension, between the ages of 18–80 years, were eligible to participate in the study. Mild to moderate hypertension was defined as sitting diastolic blood pressure (SDBP) of >95 mmHg and <115 mmHg after a 2-week single-blind placebo run-in period. The most important exclusion criteria were presence of overt heart failure, history of cerebrovascular accident, heart failure in the preceding 6 months or myocardial infarction in the preceding 3 months, presence of angina pectoris, significant valvular heart disease, second- or third-degree heart block, malignant hypertension, evidence of significant hepatic, renal or gastrointestinal disease, pregnancy and use of oestrogen/progestogen preparations.

Patients could be withdrawn from the trial for intolerable adverse events, lack of therapeutic response resulting in intolerable symptoms and/or mean SDBP of ≥120 mmHg, major violation of the trial protocol or withdrawal of consent. The study was conducted according to the revised Declaration of Helsinki and Good Clinical Practice requirements. All patients gave written consent to participate in the study, which was approved by the relevant local Ethics Review Boards.

Study design

The study was conducted in Germany, in general practice and in outpatients from a general hospital. It was a multicentre (19 centres), randomised, double-blind, comparative trial. After a 2-week placebo run-in period (to confirm the presence of raised BP prior to randomisation), during which all other antihypertensive medication was stopped, patients who met the inclusion criteria were randomised in equal numbers to receive either valsartan 80 mg once daily (o.d.) or HCTZ 25 mg o.d. Both medications were given in the form of capsules which were identical in size and colour. Following 8 weeks of therapy, patients in either group whose blood pressure was not adequately controlled (SDBP ≥95 mmHg) received, in addition to their initial therapy, atenolol tablets 50 mg o.d. in an open fashion for a further 4 weeks. Patients whose SDBP was controlled at 8 weeks continued on their initial therapy.

Assessment visits were at 4, 8 and 12 weeks. Weight, pulse rate, systolic and diastolic blood pressures were recorded at each assessment. Measurements were carried out at each visit at the same time of day before daily dosing to provide consistent through measurements. Systolic and diastolic blood pressures were measured with the patient in the sitting position according to WHO guidelines (two measurements in the sitting position after 5 min resting followed by one measurement in the standing position after at least 2 min of equilibration [1]). All measurements were to the nearest 2 mmHg. Phase V (disappearance of the Korotkoff sound) was used for measurement of diastolic BP. Blood pressure (BP) was measured by the same clinician using the same mercury sphygmomanometer on the same patient in the dominant arm.

At each visit details of any adverse experiences were elicited by direct questioning and recorded in the case record form. Measurements of routine haematological, biochemical and urinary parameters were carried out at baseline and at the 8- and 12-week visits. The use of any antihypertensive medication other than study drugs was prohibited during the study period.

The primary efficacy variable was the change from baseline in mean SDBP at end point of monotherapy (8 weeks). Secondary variables analysed included change from baseline at end point of monotherapy in mean sitting systolic blood pressure (SSBP) and responder rates (defined as the percentage of patients at end point with SDBP <90 mmHg or drop in SDBP ≥10 mmHg compared to baseline).

Statistical methodology

A sample size of 80–90 evaluable patients per group was calculated to be necessary for a treatment difference in SDBP to be estimated, with a precision in terms of a 95% confidence interval, of ±2.5 mmHg, assuming the standard deviation of SDBP measurement to be 8 mmHg [11].

The primary analysis was based on the ''intent-to-treat'' data set, which included all randomised patients who had a baseline measurement and at least one post-randomisation measurement for the variable to be analysed. A secondary analysis was performed for the ''acceptable patient'' data set. This data set excluded major protocol violators (blood pressure measurements <12 or >30 h from last dose, mean SDBP ≤ 95 mmHg at baseline, interval between post-randomisation visits of <21 or >36 days in patients continuing on therapy, trial treatment for <25 days, use of forbidden concomitant medication). For both analyses the end point measurement was after 8 weeks of monotherapy or, in the case of premature discontinuation, the last post-baseline observation carried forward.

Changes in SDBP and SSBP from baseline were analysed by analysis of covariance, fitting treatment, baseline, treatment-by-baseline interaction, centre and treatment-by-centre interaction. Two centres with three and four patients each were pooled so that each centre in the analyses contained at least two patients with post-baseline assessments for primary and secondary variables in each treatment group. The estimated mean treatment difference and confidence intervals (CIs) were calculated from the analysis of covariance model. Responder rates were analysed by means of a chi-square test. All statistical tests were carried out at the two-sided 5% level. Efficacy data at 12 weeks (after possible titration) were summarised.

All randomised patients were included in the safety evaluation, which was descriptive. The main criterion for tolerability was the incidence of adverse experiences. Secondary criteria were sitting and standing pulse rate, weight and laboratory results.

Results

Patients

A total of 167 patients were randomised. All patients were in the age range 25–80 years. All patients were Caucasian with the exception of one black patient in the valsartan group. Fifty-nine per cent had received antihypertensive medication in the previous 3 months. Of the randomised patients, 12 discontinued prematurely, with 155 patients completing the 8-week double-blind monotherapy period. A total of six patients discontinued therapy with valsartan: one due to an adverse experience; one due to a laboratory abnormality; three due to administrative problems; and one patient withdrew

Table 1 Patient demographics and baseline measurements

Randomised patients	Valsartan (n = 82)	HCTZ (n = 85)
Sex (% female)	47.6%	43.5%
Age (years, mean ± SD)	57.9 (11.3)	56.4 (10.8)
Weight (kg, mean ± SD)	81.3 (15.7)	81.6 (13.5)
Height (cm, mean ± SD)	169.9 (8.5)	169.7 (8.1)
Duration of hypertension (years, mean ± SD)	5.0 (5.6)	4.6 (5.2)
Antihypertensive treatment over previous 3 months (%)	62.2%	55.3%
Significant medical history (%)	84.1%	81.2%
Baseline blood pressure (mmHg)		
Sitting diastolic BP (mean ± SD)	103.6 (5.2)	103.1 (4.9)
Sitting systolic BP (mean ± SD)	165.3 (16.0)	166.1 (15.6)
Sitting pulse (beats/min, mean ± SD)	78.0 (7.9)	75.5 (7.3)

consent. In the HCTZ group, two patients discontinued due to adverse experiences: one due to a laboratory abnormality; one due to an unsatisfactory therapeutic effect; and two patients were lost to follow up.

Table 1 shows that there were no relevant differences between the valsartan and HCTZ treatment groups with respect to demographics and baseline measurements. Six patients from one centre were excluded from the primary intent-to-treat analysis and the acceptable patient analysis because of data irregularities discovered during an audit of the centre. A total of 18 patients were also excluded from the acceptable patient analysis due to major protocol violations (10 in the valsartan group, 8 in the HCTZ group).

After 8 weeks of monotherapy, 16 (20%) valsartan patients and 17 (20%) HCTZ patients required addition of atenolol 50 mg for blood pressure control.

Efficacy

Both treatments were effective at lowering SDBP and SSBP (Table 2). Similar mean changes from baseline were seen in the two groups after 4 and 8 weeks of monotherapy and at 12 weeks with additional therapy in non-responders (SDBP 8 weeks: valsartan −13.6 mmHg, HCTZ −12.0; SDBP 12 weeks: valsartan −15.3, HCTZ −14.3. SSBP 8 weeks: valsartan −16.6, HCTZ −18.5; SSBP 12 weeks: valsartan 18.6, HCTZ −20.3).

Table 2 Mean (standard deviation) sitting diastolic and sitting blood pressure (mmHg) (intent-to-treat data set, n = 161)

	Diastolic Valsartan	HCTZ	Systolic Valsartan	HCTZ
Baseline	103.8 (5.2)	103.4 (4.8)	165.2 (16.1)	165.3 (15.3)
Four weeks	93.3 (8.1)	93.7 (7.3)	152.7 (17.2)	152.0 (16.6)
Eight weeks	90.4 (6.4)	90.7 (7.2)	149.1 (15.4)	145.5 (15.1)
Twelve weeks	88.6 (6.7)	88.3 (6.2)	147.0 (13.3)	143.7 (14.0)

The analysis of covariance showed no statistically significant difference between the groups for either SDBP or SSBP after 8 weeks of monotherapy (SDBP: estimate of mean difference in favour of valsartan −1.8 mmHg; 95% CI −3.9, 0.2; P = 0.08. SSBP: estimate of mean difference in favour of HCTZ 1.9-mmHg; 95% CI −1.6, 5.5; P = 0.28).

A supplementary intent-to-treat analysis including the six patients from the centre found to have data irregularities was performed and produced similar results for all variables studied. Results from the secondary analysis using the acceptable patient data set were comparable to those seen for the intent-to-treat data set.

Similar decreases in SDBP and SSBP were observed in both men and women for the two treatment groups. Furthermore, similar decreases in diastolic and systolic BPs were also observed for patients aged <65 years and those ≥65 years.

After 8 weeks of monotherapy, the responder rate was 73.8% in the valsartan group and 61.7% in the HCTZ group, with no significant difference between the two groups (P = 0.10). The responder rates also support valsartan as being as effective as HCTZ.

Tolerability and safety

Both trial medications were generally well tolerated both during the monotherapy phase and also in non-responders receiving additional therapy. Of the 167 patients randomised, a total of 46 (27.5%) reported one or more adverse experiences regardless of relationship to trial medication. Of these, 19 patients were taking valsartan monotherapy, 2 were taking valsartan and atenolol 50 mg, 25 were taking HCTZ monotherapy and 1 was taking HCTZ and atenolol. Five patients discontinued therapy due to adverse experiences or abnormal laboratory values. In the valsartan group one patient discontinued due to raised liver enzymes which were present at baseline and one patient discontinued due to complications of ischaemic heart disease assessed as unrelated to therapy. Three patients in the HCTZ group discontinued prematurely: one due to an increase in eosinophil count and dyspepsia; one due to cephalgia and heart pain; and one due to palpitations, tinnitus, headache, gastritis and vomiting. All three cases were assessed as being related to study medication.

A total of 13 patients (7.8%) reported adverse experiences which were considered to be related to trial medication. Five patients (6.1%) taking valsartan monotherapy reported a total of seven adverse experiences. No adverse experiences were reported by patients taking valsartan in combination with atenolol. Seven patients (8.2%) on HCTZ monotherapy reported a total of 14 adverse experiences, of which headache and dyspepsia occurred most frequently. One patient on combination therapy (HCTZ and atenolol) had a mild disturbance in hepatic function. Table 3 shows all ad-

Table 3 Incidence of adverse experiences considered drug related

	Valsartan		HCTZ	
	Monotherapy	+ atenolol 50 mg	Monotherapy	+ atenolol 50 mg
Total patients	*n* = 82	*n* = 16	*n* = 85	*n* = 17
Patients (%) with an adverse experience	5 (6.1%)	0	7 (8.2%)	1 (5.9%)
Number of adverse experiences	7	0	14	1
Angina pectoris	1		1	
Dizziness	1			
Dyspnoea			1	
Dyspepsia			2	
Eosinophilia			1	
Gastritis			1	
Headache			2	
Hepatic dysfunction				1
Hot flushes			1	
Increased appetite	1			
Leg oedema	1			
Nail disorder	1			
Palpitations			1	
Pyuria	1			
Raised glucose			1	
Rash	1			
Sweating			1	
Tinnitus			1	
Vomiting			1	

verse experiences assessed as being possibly or probably related to study medication.

All valsartan-related adverse experiences were mild to moderate in severity. Four adverse experiences with HCTZ were graded as severe: one case of palpitations; one case of gastritis; one case of eosinophilia; and one case of headache. Only one patient reported a cough and this occurred in the HCTZ group.

Orthostatic hypotension was defined in this study as a fall in BP on standing (after at least 2 min equilibration) of ≥10 mmHg diastolic and/or ≥20 mmHg systolic with concomitant symptoms of cerebral hypoperfusion [12]. At 8 weeks no patients in either group had a measurable drop in BP on standing ≥ 10 mmHg diastolic and/or > 20 mmHg systolic, and at 12 weeks (where patients may have been on combination treatment) only one patient (1.3%) on valsartan and two patients (2.5%) on HCTZ showed such a postural decrease. No patients at any time point in either treatment group experienced symptoms associated with a postural blood pressure change and therefore did not fulfil the criteria for orthostatic hypotension. These data suggest that neither valsartan 80 mg nor HCTZ 25 mg produce clinically significant changes in diastolic BP on rising from sitting.

No clinically or statistically significant changes in sitting or standing pulse rates from baseline were observed during the study in either group. No significant effect on body weight was seen for either treatment. Similar non-specific changes in laboratory parameters were seen during the study for both treatment groups. For serum potassium, six patients on HCTZ monotherapy and three patients on valsartan monotherapy had >20% change from baseline (percentage of patients with increase >20% from baseline: valsartan 2.6%, HCTZ 3.8%; percentage of patients with decrease >20% from baseline: valsartan 1.3%, HCTZ 3.8%). However, the changes seen were considered to be of no clinical relevance. For other changes in laboratory parameters from baseline, most values remained within the normal range and the majority were considered to be of no clinical relevance.

There were no deaths or serious adverse experiences related to study medication reported during the study.

Discussion and conclusions

The study shows valsartan 80 mg o.d to be as effective as HCTZ 25 mg o.d in reducing blood pressure in patients with mild to moderate essential hypertension.

Valsartan and HCTZ produced reductions in both SDBP and SSBP of similar magnitude. When comparing two antihypertensive agents, the range of clinical equivalence can be considered to be ±2 mmHg. For the primary efficacy variable (change in SDBP from baseline) the confidence interval for the difference between valsartan and HCTZ was −3.9 to 0.2 (negative number in favour of valsartan, positive number in favour of HCTZ). Although the study was not designed to demonstrate equivalence between the two therapies, the data demonstrate that valsartan is as effective as HCTZ in the treatment of mild-to-moderate essential hypertension.

Both medications were generally well tolerated both as monotherapy and when combined with atenolol 50 mg. The incidence of trial drug-related adverse experiences was somewhat lower on valsartan (7 for valsartan, 14 for HCTZ), as was the incidence of severe adverse experiences (0 vs 4) and discontinuations for drug-related adverse experiences/laboratory abnormalities (0 vs 3). However, the numbers were small and are therefore not conclusive.

No cases of orthostatic hypotension were recorded in either treatment group. No cases of cough occurred with valsartan treatment, confirming previous findings that angiotensin II receptor antagonists, due to their mechanism of action, do not have the unwanted effects associated with agents such as ACE inhibitors which interfere with the renin-angiotensin-aldosterone pathway at a more proximal point [13].

The results of this study are in keeping with reported results compared to established agents for the first angiotensin II antagonist, losartan [14].

In summary, the study demonstrates that valsartan, a new angiotensin II receptor antagonist, is as effective as a well-established thiazide diuretic, hydrochlorothiazide, in the treatment of mild-to-moderate hypertension.

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