Patients of Southern Asian descent treated with valsartan (POSATIV) study

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Abstract

Southern Asians in the UK have a substantially increased (50%) risk of coronary heart disease compared with the general population, in part due to a high prevalence of hypertension and diabetes. This patient group has not been specifically studied in a clinical trial using modern antihypertensive therapy such as the angiotensin II receptor antagonists (AIIRAs). A multi-centre, double-blind, randomised, parallel-group study compared the effects of treatment with valsartan 80 mg once daily (o.d.) with control therapy (bendrofluazide 2.5 mg o.d.) in 116 patients with mild hypertension (diastolic blood pressure [DBP] $\geq$ 90 mmHg and $\leq$ 105 mmHg) after a four-week run-in period. Sitting blood pressure was measured at baseline (end of run-in) and after four and eight weeks of treatment using the OMRON automatic oscillometric blood pressure monitor. The study medication dosage was doubled if patients had < 4 mmHg decrease in DBP after four weeks. Compared with the control group (n=62), the addition of valsartan 80/160 mg o.d. (n=51) resulted in a significantly greater reduction in blood pressure at eight weeks (mean change in blood pressure -15.6 mmHg [95% CI -19.9 to -11.2 mmHg] for systolic blood pressure [SBP] and -9.3 mmHg [95% CI -11.8 to -6.8 mmHg] for DBP; p<0.001). Both treatments were well tolerated. Valsartan is effective and well tolerated, and would be an appropriate treatment option in Southern Asian hypertensive patients.

Key words: valsartan, angiotensin II receptor antagonist, hypertension, Southern Asians, thiazide diuretic.

Introduction

Individuals of Southern Asian descent (i.e. Indians, Bangladeshi, Pakistanis and Sri Lankans) living in the UK have a substantially increased risk of cardiovascular disease, with mortality due to coronary heart disease (CHD) up to 50% higher than that of the general population.[1,2] This increased risk is, in part, due to the high prevalence of hypertension and diabetes in this population (adjusted Hazard ratio for diabetes ranging from 6.1 in Bangladeshi women to 2.9 in Indian women).[1,3,4] Apart from the increase in blood pressure, hypertension is often associated with various factors that potentiate the risk of poor cardiovascular outcome, including insulin resistance, hypercoagulability, vascular hypertrophy, endothelial dysfunction and left ventricular hypertrophy.[5] The prevalence of a number of these factors is known to be increased in this patient group.[4,6]

As the difference in cardiovascular mortality between Southern Asians and the general population in the UK is increasing,[2] the importance of effective clinical management, targeted to the needs of ethnic groups, has been emphasised[7] and, indeed, recognised by recent government guidelines.[8] However, there are few clinical studies that have specifically investigated this patient group on which to base therapeutic recommendations.

Valsartan is an orally active, potent and selective AIIRA that is safe and effective in the treatment of mild to moderate essential arterial hypertension at licensed doses of up to 160 mg daily.[9-11] The aim of this short-term, placebo-controlled study was to investigate the efficacy and tolerability of valsartan in Southern Asians in the UK.

Table 1. Exclusion criteria for the POSATIV study

- Malignant hypertension or disease secondary to hypertension
- Grade III or IV hypertensive retinopathy
- History of heart failure, unstable angina pectoris, serious/life threatening arrhythmias
- Hypersensitivity to angiotensin II receptor antagonists or intolerance to thiazide diuretics
- Myocardial infarction, invasive procedures, hypertensive encephalopathy or cerebrovascular accident in the last six months
- Uncontrolled type 1 or type 2 diabetes mellitus
- Clinically significant hepatic or renal impairment, hypnonatraemia, hyper- or hypokalaemia, or gout
- Women who were pregnant or likely to become pregnant or breast-feeding

Materials and methods

Patients of Southern Asian descent (i.e. grandparents from India, Pakistan, Bangladesh or Sri Lanka) with uncomplicated mild

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Table 2. Patient characteristics, all treated patients in the POSATIV study

	Valsartan (n=52)	Control (n=64)
Male; n (%)	33 (64)	33 (52)
Age; years (range)	52.3 (37 to 71)	54.4 (35 to 70)
Weight; kg (range)	73.9 (47 to 123)	72.3 (45 to 109)
Prior antihypertensive therapy; n (%)		
Diuretic	7 (13)	10 (16)
ACE inhibitor	14 (27)	5 (8)
Beta blocker	9 (17)	2 (3)
Angiotensin II receptor antagonist	1 (2)	1 (2)
Calcium antagonist	8 (15)	3 (5)
Other	1 (2)	-

Table 3. Mean sitting systolic and diastolic blood pressure and pulse rate (± SD) at baseline and week eight in patients treated with valsartan 80–160 mg once daily or control therapy

	Valsartan (n=51)	Control (n=62)
Systolic blood pressure (mmHg)		
Baseline	154 ± 15.8	154 ± 14.2
Week eight	139 ± 21.5	151 ± 14.9
Diastolic blood pressure (mmHg)		
Baseline	97 ± 4.6	96 ± 4.4
Week eight	88 ± 10.5	94 ± 7.6
Pulse rate (beats/min)		
Baseline	84 ± 12.7	82 ± 12.9
Week eight	81 ± 12.5	82 ± 13.9

essential hypertension and aged 18–75 years were screened for the study. Exclusion criteria for the study are specified in table 1. Concomitant treatment with other antihypertensive therapy, excluding bendrofluazide, or the use of potassium-containing salt substitutes was prohibited. The study was approved by the ethics committee responsible for each centre and was conducted in accordance with the Declaration of Helsinki (revised, South Africa 1996). All patients gave written informed consent prior to entry.

Study design

This was a multi-centre, double-blind, randomised, parallel-group study. At screening, a medical history was taken and all patients underwent a physical examination and had blood samples taken for measurement of routine haematology and biochemistry safety variables. At entry to the four-week run-in period, treatment with bendrofluazide 2.5 mg once daily (o.d.) was initiated after discontinuation of other antihypertensive medication. At the end of this period (baseline), patients who satisfied the diastolic blood pressure (DBP) criteria ($\geq$ 90 mmHg and $\leq$ 105 mmHg) were randomised to double-blind treatment with valsartan 80 mg o.d. or matching placebo (control group), in addition to bendrofluazide, for eight weeks. If patients failed to show at least a 4 mmHg decrease in DBP after four weeks, the dose of study medication was doubled for the remainder of the study. The total duration of the study was 12 weeks. Valsartan (Diovan®) 80 mg capsules, matching placebo capsules and bendrofluazide 2.5 mg tablets were supplied by Novartis Pharma AG.

Sitting blood pressure and pulse rate were measured at entry, after two and four weeks of the run-in period, and at four-weekly intervals during the double-blind treatment period using the OMRON automatic oscillometric blood pressure monitor. On each occasion, blood pressure was measured by the same trained personnel using the left arm, after the patient had rested quietly for five minutes. Sitting blood pressure was measured three times with an interval of at least two minutes between measurements. Spontaneously observed and reported adverse events were noted during the treatment phase, and blood sampling for measurement of biochemistry and haematology safety variables was repeated at the end of the study.

Statistical analysis

Data from all randomised patients with at least one post-baseline measurement were included in the intention-to-treat (ITT) analysis. Changes from baseline to week eight or end point (last visit on double-blind treatment) in sitting DBP, SBP and pulse rate were compared between treatment groups using analysis of variance (ANOVA) with treatment as a factor. The proportion of patients on each dose level was compared between groups using Fisher's exact test. A p-value of < 0.05 was considered clinically significant. All treated patients were included in the safety analysis.

Results

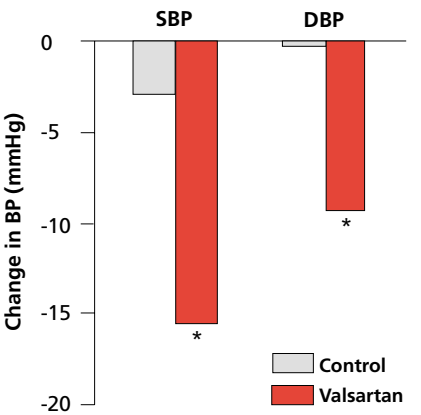
A total of 116 of 188 patients screened for the study were randomised and treated; 52 patients received valsartan and 64 patients received control therapy. Ten patients in each treatment group were withdrawn during the study. This left 96 patients (42 in the valsartan group and 54 in the control group) to complete the study. Overall, the reasons for withdrawal were adverse events (seven patients), protocol violation (five patients), lack of efficacy (three patients), withdrawal of consent (two patients), lost to follow-up (two patients) and abnormal blood results (one patient). The demographics of the two treatment groups were similar at baseline (table 2).

Efficacy

A total of 113 patients, 51 in the valsartan group and 62 in the control group, were included in ITT efficacy analyses. Three patients, one in the valsartan group and two in the control group, were excluded from analysis due to lack of post-baseline data.

Blood pressure at baseline and week eight is summarised by treatment group in table 3. Compared with the control group, treatment with valsartan 80–160 mg o.d. produced a significantly greater decrease in both SBP and DBP at eight weeks (figure 1). The mean change in SBP was -15.6 mmHg (95% CI -19.9 to -11.2 mmHg) for valsartan compared with -3.0 mmHg (95% CI -6.9 to -3.0 mmHg) for placebo; and for DBP was -9.3 mmHg (95% CI -11.8 to -6.8 mmHg) for valsartan compared with -0.2 mmHg (95% CI -2.9 to 2.5 mmHg) for control ($p<0.001$, ANOVA). There was no difference between the two groups in the change from baseline to week eight in pulse rate (table 3). Significantly more patients in the valsartan group than the control group were considered responders (73% *vs.* 44%, $p=0.0046$) and therefore not requiring dose titration.

Figure 1. Mean change in sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to week eight in patients treated with valsartan 80-160 mg once daily (n=51) or control therapy (n=62)



Key: * Statistically different from control, $p<0.001$, ANOVA

Safety and tolerability

Both treatments were generally well tolerated. Adverse events considered possibly related to treatment were reported for eight patients in the valsartan group (15%) and six patients in the control group (9%). The most commonly reported treatment-related adverse events were headache and dizziness in the valsartan group and hypotension in the control group. Three patients were hospitalised for adverse events; none of these events were considered related to the study treatment. One patient in the valsartan group developed high blood pressure and, in the control group, one patient developed empyema and cholelithiasis and one patient developed Bell's palsy, dizziness and dyspnoea.

Discussion

As far as we are aware, this is the first study that has specifically investigated the efficacy of an AIIRA in hypertensive patients of Southern Asian descent. The results of this study clearly show that valsartan is an effective treatment in this patient group with mild hypertension. The addition of valsartan to control therapy produced a significantly greater decrease in blood pressure after eight weeks when compared to the control group (mean change from baseline in blood pressure: 15.6 mmHg/9.3 mmHg SBP/SDP). Interestingly, the magnitude of the blood pressure lowering response was greater than the 12.4 mmHg/9.6 mmHg (SBP/SDP) reported in a meta-analysis of studies of patients of predominately European descent treated with valsartan 80–160 mg.[12] The addition of valsartan to control therapy was shown to be well tolerated, and is consistent with its known tolerability profile.[13,14]

A study of this nature does have the limitation of the potential introduction of investigator bias when a pronounced drop in blood pressure is observed with the active treatment compared to placebo. Thus, further trials using an active comparator would be valuable.

There is clear evidence[1,2] that Southern Asians living in the UK are at substantially increased risk of mortality due to CHD. Moreover, despite the availability of effective antihypertensive therapy, mortality due to CHD is not decreasing as rapidly in this patient group as in the general population. From 1971 to 1991, the CHD mortality rate in individuals aged 20–69 years decreased by 29% in men and 17% in women in the general population; however, amongst Southern Asians, CHD mortality only decreased by 20% for men and 7% for women.[15] This finding may be explained by less than effective targeting of this patient group, as borne out by recent data from the Health Survey for England 1999.[1]

The implementation and audit of new blood pressure guidelines[16,17] incorporated within the CHD National Service Framework (NSF) emphasises the need for effective blood pressure control in all patients with mild hypertension. To date, there is a paucity of studies[18,21] that have investigated the efficacy of treatment in ethnic groups, such as Southern Asians, on which to base clinical decisions. Moreover, none of these studies have been conducted with modern pharmacological therapies, such as AIIRAs, which have potential mode of action advantages over other antihypertensive treatments, including angiotensin-converting enzyme (ACE) inhibitors. *In vitro* data have shown that valsartan has markedly greater selectivity for the AT_1 than AT_2 receptor[22] when compared to that of other AIIRAs,[23-28] and this may contribute to the pronounced reduction in blood pressure observed in the current study. Thus, on the basis of these findings, valsartan would be an appropriate antihypertensive therapy for use in hypertensive Southern Asians, particularly in view of the National Service Framework for Coronary Heart Disease[29] requirements.

In conclusion, the results of the current study demonstrate that valsartan is effective and well tolerated and would be an appropriate treatment option in Southern Asian hypertensive patients.

Acknowledgements

The authors wish to acknowledge the support of Novartis Pharma AG for the study. We also thank the following for their advice on protocol design: Dr F Cappuccio, Dr J Kooner, Professor G Lip.

Key messages

- POSATIV is the first hypertension study in UK patients of Southern Asian descent using modern day therapy
- Hypertensive patients of Southern Asian descent are at high risk of CHD and their blood pressure is often under treated
- Valsartan has been shown to be an effective antihypertensive treatment and to significantly reduce blood pressure in this high risk group

Appendix

The following investigators participated in the POSATIV study: M Adler, V Agarval, M Ahmad, B Baskaran, J Chambers, F Docrat, C Gibbs, K Gunawardena, S Handa, J Kooner, A Lahiri, G Patel, J Patel, A Sennik.

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