Efficacy and tolerability of valsartan in patients with mild to moderate essential hypertension

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ABSTRACT

Objectives: To assess the efficacy of valsartan in a different ethnic population than that studied in international trials. Also to compare the adverse experiences reported in this trial with those reported internationally.

Methods: A total of 2940 patients with newly diagnosed or established uncomplicated mild-to-moderate essential hypertension participated in this open-label study. Each participating investigator was asked to enrol 12 patients, 10 on valsartan and 2, serving as controls, on any other anti-hypertensive. The control group included patients of similar clinical setting, disease severity, and overall health profile using alternative anti-hypertensive treatments was enrolled for tracking of patients receiving any anti-hypertensive other than valsartan.

Results: Both valsartan and the control medications showed a clear-cut antihypertensive effect. However, valsartan showed significantly better antihypertensive efficacy compared to the control group at the final visit. Twenty-four percent of patients in the control group compared to 3.9% in the valsartan group reported adverse experiences ($P<0.001$). Dizziness and headache were the most common treatment-related reported adverse experiences. Dry cough was more commonly reported in the control group compared to patients in the valsartan group.

Conclusion: Data from this study suggest, in line with data from international clinical studies, that valsartan is well tolerated and is at least as effective as other commonly used medications in the treatment of patients with mild to moderate hypertension.

Keywords: Renin-angiotensin system, angiotensin II, angiotensin II receptors, angiotensin II receptor blockers, valsartan, essential hypertension.

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The renin-angiotensin system (RAS) plays a fundamental role in the maintenance and regulation of extracellular fluid volume and blood pressure (BP).[1] Renin is secreted from the kidney in response to a decrease in circulating blood volume and BP, and cleaves the substrate angiotensinogen to form the inactive decapeptide angiotensin I. By the action of angiotensin converting enzyme (ACE), angiotensin I is converted to the active octapeptide angiotensin II which interacts with cellular receptors inducing vascular constriction, the release of catecholamines from the adrenal medulla and pre-junctional nerve endings, and promotes aldosterone secretion and sodium reabsorption. The RAS can be inhibited both by blocking the effects of ACE and renin and by preventing the interaction of angiotensin II with cellular receptors. At this point, 2 distinct subtypes of angiotensin II receptors have been described, angiotensin receptors type I (AT_1)

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and angiotensin receptor type II (AT_2). The AT_1 receptor appears to mediate all the above mentioned actions of angiotensin II. To date, the role of the AT_2 receptor is unknown. Since ACE inhibitors have been shown to be effective and safe in the treatment of hypertension and congestive heart failure,[2,3] angiotensin II receptor antagonists should have the potential for the same clinical indications as well as an adequate safety profile. Moreover, angiotensin II receptor antagonists do not interfere with the kininase II (ACE) responsible for the degradation of bradykinin. Bradykinin is implicated in the pathogenesis of cough and angioneurotic edema, both are class-specific side-effects of ACE inhibitor therapy. Hence, blockade of angiotensin II receptors represents a more specific means of blocking the RAS, and this approach may produce effective anti-hypertensive agents devoid of the side effects of ACE inhibitors. Valsartan (manufactured by Novartis Pharma as Diovan®) is an orally active, potent and specific competitive angiotensin II antagonist at the level of the AT_1 receptor subtype.[4] Valsartan has been shown to be as effective as other leading anti-hypertensives in treatment of high BP with an excellent tolerability profile, with an overall incidence of side effects comparable to placebo. The primary aim of this trial is to collect safety data and to assess the systemic tolerability of valsartan 80mg and 160mg capsules once a day during 8 weeks of treatment, under daily practice conditions in a large unselected patient sample. The secondary aim of the trial is to evaluate the degree of BP control (according to the VI report of the Joint National Committee on Detection, Evaluation and Treatment of High BP,[5] and the 1999 World Health Oraganization-International Society of Hypertension Guidelines),[6] during the 8 weeks follow-up.

Methods. The study was performed according to current medical practice in the Kingdom of Saudi Arabia (KSA). Co-operative outpatients, of either sex, aged 18 years and above, with newly diagnosed or established uncomplicated mild-to-moderate essential hypertension (mean sitting diastolic BP [SDBP] between 90-109mm Hg and mean sitting systolic BP (SSBP) between 140-179mm Hg on inclusion day) were eligible for enrollment in the study. All patients gave their consent to participate in the study. The study was performed according to Good Clinical Practice requirements. A control group was enrolled for tracking of patients receiving any anti-hypertensive other than valsartan. The control group included patients of similar clinical setting, disease severity, and overall health profile using alternative anti-hypertensive treatments. Blood pressure was measured at all visits, using a mercury sphygmomanometer. Before beginning the BP measurement, the patient remained seated for 5 minutes. Measurements were performed twice with 3 minutes apart. The 2 values were recorded and their mean value was calculated for the analysis. Two hundred and forty-five medical practitioners including Internists, Cardiologists and General Practitioners from the private hospitals and polyclinics in the 3 different zones of KSA were selected to participate in the study (Central = 84, Western = 125, Eastern = 43). Each participating investigator was asked to enrol 12 patients (10 on valsartan and 2, serving as controls, on any other anti-hypertensive). A total of 2940 patients were enrolled in the study. Eligible patients whose SDBP was $\geq$ 90 and $\leq$ 109mm Hg were given one valsartan 80mg capsule, once a day or any other anti-hypertensive (for the control group) for 4 weeks. Those who did not have their BP normalized (SDBP $\geq$ 90mm Hg) had the therapeutic dose of the assigned medication doubled for 4 additional weeks. Patients whose BP was normalized (SDBP < 90mm Hg) during the first 4 week period continued therapy on the same dosage for the remaining period of the study. The primary efficacy variable was the change from baseline (visit one) in mean SDBP. The secondary variables included the change from baseline in mean SSBP together with an investigator's overall assessment of efficacy based on a predefined 4-point scale (excellent, good, fair and poor). To evaluate safety and tolerability, adverse events (AE) were recorded. The type, date and time of onset, intensity and relationship to the trial treatment of all the symptoms observed by the investigator, and those subjective symptoms reported by the patient in response to a general enquiry from the investigator at visits 2 and 3 were assessed as a primary variable. The secondary variable was the investigator's overall assessment of tolerability based on a predefined 4-point scale (excellent, good, fair and poor). Statistical analysis was carried out using non-parametric and parametric 2-way repeated measure analysis of variance (ANOVA) to determine the tolerability of the investigational products and degree of BP control, respectively. Within-subject and between-subject factors were the visits and patients (control versus experimental). Simple contrast with visit one as reference was used as post hoc test. Descriptive statistics were calculated for all the measurements along with the final overall investigators' assessments of tolerability and efficacy. A total of 2940 patients with newly diagnosed or established mild-to-moderate hypertension were enrolled into the trial in the ratio of 5:1 (valsartan, N=2450; control, N=490). Demographic characteristics and medical history were similar in both treatment groups, as were their baseline measurements (**Table 1**). One thousand three hundred and ninety patients (47.2%) were newly diagnosed while 1550 patients (52.8%) were established mild-to-moderate hypertensives (**Table 1**). Out of the 1550 patients with established

diagnosis, 1095 (70.5%) were actually on anti-hypertensive medication before enrollment in the study. The reason for switch to valsartan or the control group for those patients with established hypertension and were on anti-hypertensive medication at the time of enrollment is listed in **Table 2**. The different classes of anti-hypertensive therapies prescribed to patients in the control group are listed in **Table 3**. A total of 2845 patients completed the full 8 weeks study period. Ninety-five patients discontinued the trial prematurely (**Table 4**). Of those, 30 patients discontinued prematurely due to adverse experiences, 33 for unsatisfactory therapeutic effect, 14 lost to follow-up, 2 consent withdrawals and 16 non-compliance.

Results. Analysis of the primary efficacy variable (change from baseline in mean SDBP) showed statistically significant difference in mean percent reduction of SDBP at visits 2 and 3 compared to baseline levels, in favor of valsartan (**Table 5**). Analysis of the secondary efficacy variables showed that valsartan also significantly reduced the mean SSBP at visit 3 compared to the control group (**Table 5**). Twenty-five percent of patients in the valsartan group compared to 28% in the control group needed doubling of their therapeutic doses at visit 2. As for the investigator's overall assessment of efficacy, 94.2% of patients compared to 89% in the valsartan and the control groups respectively were rated as excellent by the investigators (**Figure 1**). A total of 205 patients (7.1%) reported adverse experiences, 95 (3.9%) in the valsartan group and 110 (24.1%) in the control group, ($P < 0.0001$). The most common reported drug-related adverse experiences were headache, dizziness, fatigue and cough (**Table 6**). As for the investigator's overall assessment of tolerability, 96.1% of patients compared to 77.6% in the valsartan and the control groups respectively were rated as excellent by the investigators (**Figure 2**).

Table 1 - Comparability of treatment groups: demographic and baseline data.

Patients	**Valsartan (%)**	**Control (%)**
All patients	2450	490
Sex		
Males	1604 (65.5)	320 (65.3)
Females	846 (34.5)	170 (34.7)
Age (years)	55.7 ± 10.9	55.20 ± 10.5
Obesity	737 (30.1)	127 (26)
Smoking	648 (26.5)	115 (23.4)
Diabetes	574 (23.4)	77 (15.7)*
Dyslipidemia	576 (23.5)	93 (18.9)
LVH	264 (10.7)	52 (10.6)
Hypertension		
Newly diagnosed	1146 (46.8)	254 (51.9)
Established	1304 (53.2)	236 (48.1)
Baseline BP (mm Hg)		
Mean SDBP	100.27 ± 5.61	99.76 ± 5.08
Mean SSBP	159.44 ± 11.29	159.02 ± 10.79
Severity of hypertension		
Mild	532 (21.8)	116 (24)
Moderate	1908 (78.2)	368 (76)

* P<0.0001, LVH - left ventricular hypertrophy, BP - blood pressure, SDBP - sitting diastolic blood pressure, SSBP - sitting systolic blood pressure.

Table 2 - Patients on anti-hypertensives before enrollment.

Reason for switch	**Valsartan (%)**	**Control (%)**
All patients	933	162
Lack of efficacy	624 (66.8)	92 (56.7)
Adverse experience	223 (23.9)	35 (21.6)
Other causes	86 (9.2)	35 (21.6)

Table 3 - Control group-prescribed anti-hypertensives.

Class	**N of patients (%)**
All patients	490
Diuretics	73 (14.8)
Beta blockers	134 (27.3)
CCB	93 (18.9)
ACE inhibitors	166 (33.8)
Others	24 (4.8)

N - number, CCB - calcium channel blockers, ACE - angiotensin converting enzyme.

Table 4 - Patients prematurely discontinuing the trial.

Reason	Valsartan (%)	Control (%)	Total
Adverse experience	10 (0.4)*	20 (4.1)*	**30**
Unsatisfactory therapeutic efficacy	24 (0.1)	9 (1.8)	**33**
Lost for follow-up	13 (0.5)	1 (0.2)	**14**
Consent withdrawal	2 (0.1)	0 (0)	**2**
Non-compliance	10 (0.4)	6 (1.3)	**16**
Total	**59**	**36**	**95**

* P<0.001

Table 5 - Mean percentage change of sitting systolic and diastolic blood pressure compared to baseline.

Percentage change in blood pressure	Treament	Mean	SD	p-value
Percent change of SDBP visit 1 - visit 2	Valsartan Control	10.9558 10.2944	6.2380 6.0375	0.033*
Percent change of SDBP visit 1 - visit 3	Valsartan Control	15.6621 14.3919	6.1677 6.6580	0.0001*
Percent change of SSBP visit 1 - visit 2	Valsartan Control	10.5424 10.2113	6.6765 6.2882	0.317
Percent change of SSBP visit 1 - visit 3	Valsartan Control	15.4446 14.6907	7.0585 6.9986	0.034*

* - statistically significant difference, SD - standard deviation,
SDBP - sitting diastolic blood pressure,
SSBP - sitting systolic blood pressure.

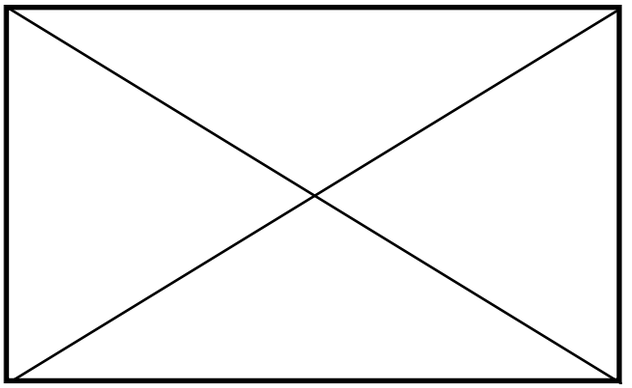

Figure 1 - Investigators' assessment of efficacy. * excellent efficacy = patients with sitting diastolic blood pressure < 90 mmHg, namely patients controlled.

Table 6 - Most common reported drug-related adverse experiences.

Adverse experience	Valsartan N (%)	Control N (%)
Dizziness	36 (1.5)	8 (1.8)
Headache	23 (1)	22 (4.8)
Dry cough	10 (0.4)	22 (4.8)
Fatigue	5 (0.2)	1 (0.2)
Others	21 (0.8)	57 (12.5)
Total	**95 (3.9)***	**110 (24.1)***

*P<0.001, N - number.

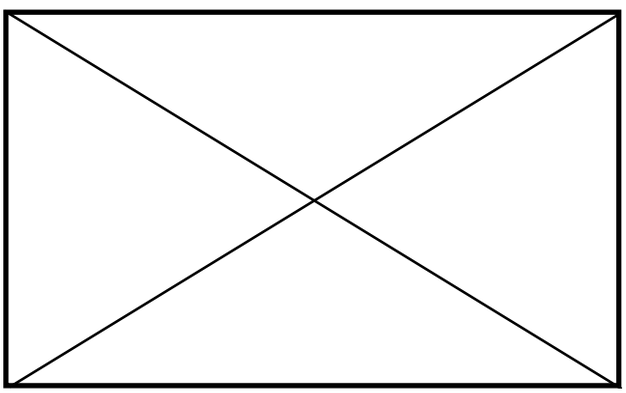

Figure 2 - Investigators' assessment of tolerability.

Discussion. Cardiovascular disease is the major cause of death in industrial societies, and hypertension is one of its most common modifiable risk factors.[7] Although, a number of classes of drugs are available to control BP, treatment compliance may be poor, and associated with unacceptable side-effects.[7] Valsartan is a new, highly selective angiotensin II antagonist for the treatment of hypertension.[8] Recent clinical trials have shown that a single daily dose of valsartan 80mg or 160mg is effective, safe and well tolerated.[9-11] This 8-week study aimed to further establish the safety and efficacy of valsartan 80mg and 160mg in a different ethnic population. The results of the present study confirm that valsartan 80mg and 160mg were as effective as other antihypertensives in patients with mild-to-moderate essential hypertension. The effect of valsartan on the reduction from baseline levels in mean SDBP and mean SSBP showed a statistically significant difference in favor of valsartan compared to the control group. As for the tolerability, valsartan showed a significantly superior safety and tolerability profile compared to the control group in the overall incidence of adverse experiences. The incidence of cough, a common side-effect frequently encountered with the use of ACE inhibitors, was very low in the valsartan group compared to the control group. The reported side-effects in the valsartan group were generally well in line with those reported in international trials.

In conclusion, the results of this study suggest that in patients with mild-to-moderate essential hypertension, valsartan was significantly more effective than the control group in terms of systolic and diastolic BP reduction at the end of the study compared to baseline levels, with a significantly superior safety and tolerability profile compared to the control group.

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