ORIGINAL ARTICLE

A Comparison of Valsartan and Perindopril in the Treatment of Essential Hypertension in the Malaysian Population

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Summary

This study was conducted to determine the safety, tolerability and efficacy of valsartan (DIOVAN®) compared to perindopril (COVERSYL®) in Malaysian patients with mild to moderate hypertension. Two hundred and fifty adult Malaysian patients with a mean sitting diastolic blood pressure of more than 95 mmHg and less than 115 mmHg after a 14 day washout period were randomized to receive either valsartan 80 mg once daily (n=125) or perindopril 4mg daily (n=125) for eight weeks. The primary end point for efficacy was the change in mean sitting systolic and diastolic blood pressure (SiSBP and SiDBP). The primary criteria for evaluation of tolerability was the incidence of adverse events. There were no significant differences between the two groups with respect to sex, age, weight, baseline sitting and standing systolic and diastolic blood pressure. At 0, 4 and 8 weeks the mean SiDBP in the valsartan group were 101.4, 92.8 and 91.0 mmHg respectively. The corresponding BP for the perindopril treated group was 102.6, 93.8 and 93.2 mmHg, (95% CI -1.39 to +3.27). There were no significant differences in the mean BP measurements between the valsartan and perindopril group at 0, 4 and 8 weeks. In each group there were significant differences between the BP at 4 and 8 weeks compared to baseline. A similar pattern was seen with SiSBP. At 4 weeks 28.7% of the valsartan and 25% of the perindopril group had their BP normalized (SiDBP < 90 mmHg) The percentages of patients who responded (SiDBP reduction > 10 mmHg but SiDBP > 90 mmHg) were 21.3 in the valsartan group and 20.8 in the perindopril group. At 8 weeks, 31.1% of the valsartan group and 30.8% of the perindopril group had their BP normalized. The response rate was 27% and 22.5% for valsartan and perindopril respectively. The major adverse event was cough which occurred in 18 patients (14.4%) in the perindopril and 1 (0.8%) in the valsartan group at 4 weeks. At 8 weeks the figures were 24 (19.2%) and 2 (1.6%) respectively. The results indicate that Valsartan is safe and efficacious in the treatment of mild to moderate hypertension. It is equally efficacious to Perindopril and not associated with any major adverse event. It has a better tolerability profile with respect to dry cough.

Key Words: Hypertension, ACE Inhibitor, Angiotensin Receptor Blocker, Tolerability, Efficacy

Introduction

Hypertension is a prevalent condition. In USA it affects about one in four adult persons[1]. In the Malaysian National Health and Morbidity survey, the prevalence of hypertension in adults above 30 years of age was 30%[2]. Blood pressure is directly and continuously related to the risk of cardiovascular disease and stroke [3-6]. Better control of blood pressure results in reduction in age adjusted mortality for stroke and coronary heart

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disease[7]. However, a number of studies have shown that blood pressure in hypertensives is not well controlled. The percentage of patients with controlled blood pressure ranged from 6% to 27%[8]. A number of factors contribute to the low rates of controlled blood pressure in hypertensives. The choice of antihypertensive agents plays an important role in fostering compliance. The Angiotensin II receptor antagonist (AII antagonist) is a recently introduced class of antihypertensives which has minimal side effects. The renin angiotensin system (RAS) plays a pivotal role in the pathogenesis of hypertension[9]. The AII antagonist blocks the actions of Angiotensin II on the AT1 receptors unlike the angiotensin converting enzyme inhibitor (ACEI) which prevents the conversion of Angiotensin I to II[10]. Its efficacy as an antihypertensive has been well studied and shown to be comparable with existing classes of antihypertensives[11]. However, most of the data available for this new class of agents comes from studies with predominantly Caucasian patients with relatively scanty data from Asia. Drug pharmacokinetics and pharmacodynamics may vary in different ethnic groups[12-15]. In view of the multiethnic composition of Malaysia, the purpose of this study was to collect data pertinent to our own local population in terms of comparing the efficacy and tolerability of valsartan (DIOVAN®) an AII antagonist against perindopril (COVERSYL®) an angiotensin converting enzyme inhibitor (ACEI) in patients with essential hypertension.

Materials and Methods

Patients

Male and female adult outpatients > 18 years of age, with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure (DBP) > 95 mmHg and < 115 mmHg were included in the study. Major exclusion criteria were heart failure, second or third degree heart block, history of myocardial infarction, concomitant angina, previous coronary artery bypass graft surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA), clinically significant hepatic, renal or gastrointestinal disease, malignancy and pregnancy.

Prior approval of the National Ethics Committee was obtained and all patients gave their written consent to participate in the study. The study was conducted in conformance to good clinical practice guidelines.

Study Design

The study was conducted in five centres in Malaysia. These centres were at Kuala Lumpur, Penang, Ipoh, Seremban and Johor Bharu. This was an open-label, randomised, parallel-group, comparative trial comparing the tolerability and efficacy of valsartan 80 mg and perindopril 4 mg given once daily. After a washout period of 2 weeks, patients were enrolled in the study if their BP was within the inclusion criteria. Patients randomly received either valsartan 80 mg once daily or perindopril 4 mg once daily. Concomitant medication with other antihypertensives was not allowed for the duration of the study.

Patients were assessed at baseline, at 4 and 8 weeks (end of treatment). The assessment included body weight, pulse rate, systolic and diastolic blood pressure and any adverse events experienced. Routine laboratory investigations included haematology, blood chemistry and urinary parameters measured at run-in period and at week 8. Systolic and diastolic blood pressures were measured in the sitting position according to WHO guidelines[16].

The primary safety variable was presence of cough (self-volunteered or elicited by direct questioning of the patients) and other adverse events at week 4 and at the end of the treatment period (week 8). The analysis of efficacy was in terms of reduction of DBP and SBP, based on intent to treat all randomised patients at week 8. Responders were defined as patients in whom a reduction in SiDBP ≥ 10 mmHg compared to baseline was achieved although SiDBP remained >90 mmHg at endpoint. BP was considered normalized if mean SiDBP was lowered below 90 mmHg.

Statistical methodology

Change from baseline in sitting DBP was analysed by covariance, fitting treatment, baseline and centre. The mean treatment difference was estimated from this model together with 95% confidence interval. Chi-square test was used to compare the incidence of cough and a p value of <0.05 was considered to indicate statistical significance.

Results

Patients

A total of 292 patients were initially recruited at 5 centres. However, 42 patients were not randomised due to multiple reasons such as DBP < 95 mmHg, abnormal biochemistry, withdrawal of consent, or loss to follow-up. The remaining 250 patients were randomised to 125 patients in each arm. The patient demographics are given in Table I. There are no significant differences in the distribution of sex, age,

body weight, sitting DBP and sitting SBP between two groups.

A total of 242 patients (valsartan 122 and perindopril 120) completed the study. Eight patients (4 in each arm) were excluded from analysis due to following reasons: violation of inclusion/exclusion criteria (4), absence of informed consent (1), loss to follow-up (2), no BP recording at visit 1 (1).

The analysis of efficacy was based on intent to treat all randomised patients who had baseline and at least one post baseline BP measurement.

Efficacy

Both valsartan and perindopril reduced DBP compared to the baseline at all points measured, with similar reduction in two groups (Table II). Mean change in sitting DBP at week 4 and 8 were 8.7 mmHg and 10.4 mmHg respectively for valsartan. Corresponding figures for perindopril were 8.8 mmHg and 9.5 mmHg respectively. There was no significant difference between valsartan and perindopril. (95% CI -1.48 to 6.26)

Mean change in sitting SBP at week 4 and 8 was 12.4 mmHg and 14.3 mmHg for valsartan while the change for perindopril was 9.5 mmHg and 11.9 mmHg. The normalisation of BP at week 4 and week 8 was similar in both groups (at week 4, 28.7% for valsartan and 25% perindopril; at week 8, 31.1% valsartan and 30.8% perindopril). The responder rate was also similar at 21.3% for the valsartan group and 20.8% in the perindopril group at 4 weeks, and 27% and 22.5% respectively at 8 weeks.

Tolerability and Safety

The major focus of observation on tolerability and safety was the incidence of cough. Cough occurred in 18 patients (14.4%) at week 4 and in 24 patients (19.2%) at week 8 in the perindopril group. The corresponding figures for valsartan were 1 patient (0.8%) and 2 patients (1.6%) (p=0.01)(Table III). Five patients in the perindopril group had to discontinue medication due to cough while no patient discontinued therapy in valsartan group. Apart from cough being significantly more prominent in the perindopril group there were only a few other non-specific adverse events in both groups.

Table I: Patient demographics and baseline characteristics

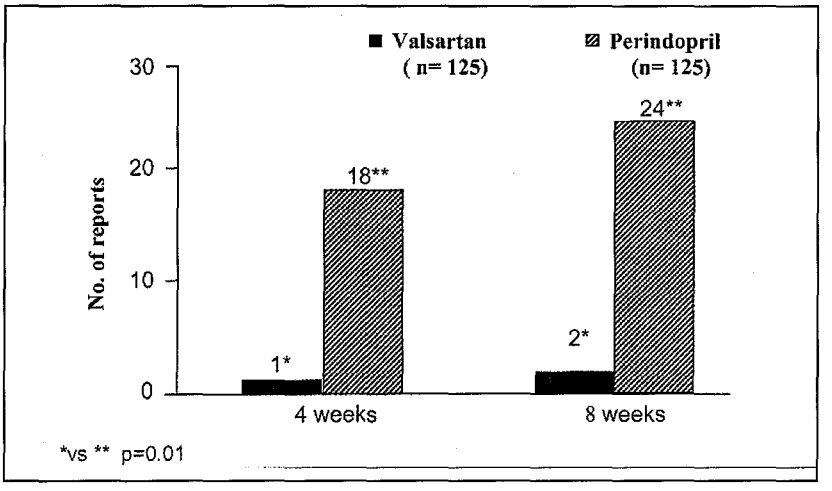
		Valsartan n = 125	Perindopril n = 125
Sex	Male	59 (47%)	71 (57%)
	Female	66 (53%)	54 (43%)
Age in years (mean ± SD)		48.6 ±10.22	48.6 ± 10.37
Body weight in kg (mean ± SD)		69.8 ± 13.69	72.3 ± 13.21
Sitting diastolic blood pressure in mmHg (mean ± SD)		101.4 ± 5.32	102.6 ± 5.66
Sitting systolic blood pressure in mmHg (mean ± SD)		159.0 ± 17.25	157.1 ± 15.82

Table II: Sitting blood pressure in both groups

	Systolic Blood Pressure (mmHg)				Diastolic Blood Pressure (mmHg)			
	Valsartan		Perindopril		Valsartan		Perindopril	
	Mean	Change From Baseline	Mean	Change From Baseline	Mean	Change From Baseline	Mean	Change From Baseline
Baseline	159 ±17.25		157.1 ±15.82		101.4 ±5.32		102.6 ± 5.66	
Week 4	146.6 ± 18.61	-12.4*	147.7 ±16.07	-9.5*	92.8 ±8.05	-8.7**	93.8 ± 9.02	-8.8**
Week 8	144.8 ± 17.54	-14.3*	145.3 ±17.84	-11.9*	91.0 ± 8.97	-10.4**	93.2 ± 9.80	-9.5**

* = No significant difference **= No significant difference
95% CI -1.48 to +6.26 (at week 8)

Table III: Incidence of Cough



Discussion

This study has demonstrated that valsartan and perindopril are equally effective in lowering blood pressure in patients with mild to moderate hypertension. However, valsartan was better tolerated due to the significantly lower incidence of cough in Malaysian patients.

Blood pressure reduction of the same magnitude with valsartan has been shown in other studies. Oparil et al [17] in a study with 736 patients showed DBP reduction of 7.2 mmHg and SBP reduction of 8.6 mmHg. Antihypertensive effects of similar magnitude was found in a comparative study of valsartan and enalapril by Holwerda et al [18] and Mallion et al [19]. As in our study, the reported incidence of cough with valsartan was low, compared to ACE inhibitors [18]. More cases of cough were also reported with enalapril in the Mallion study. Among Asian patients, similar results to ours was shown in an earlier study by Prabowo et al [20] in Indonesia.

One major difference between our study and published data from this geographic region i.e. the Indonesian study is a somewhat lower normalization rate with both drugs (~ 30% vs ~ 50%). This may reflect differences in factors such as dietary salt intake or a more heterogenous population in terms of racial composition in our study. DNA sequence variations have been shown to influence drug effects and certain polymorphisms have significant ethnic variation [13,14,21,22]. We postulate therefore that between Malays, Chinese and Indians there may be subtle differences in drug responses that affected the normalization rate overall. However, no definite pharmacogenetic data for valsartan or perindopril is available. The design of this study only allowed monotherapy. Hence, the failure to achieve normalization of BP in the majority of patients is not that surprising in view of current medical literature that shows most hypertensive patients will require 2 or more antihypertensives to achieve their BP goals [7,23]. Patients in the HOT study [23], for example, had a baseline diastolic BP comparable to our study patients (105 ± 3 mmHg vs 101.4 ± 5.32 in the valsartan group and 102.6 ± 5.66 in the perindopril group). This study showed that to achieve a target diastolic blood pressure < 90 mmHg combination therapy was required in up to 57% of hypertensive patients.

Conclusion

Valsartan is effective in lowering blood pressure in mild to moderate hypertension in Malaysian patients. It is equally effective as perindopril. However, perindopril has a significantly higher incidence of dry cough, leading to discontinuation of treatment in some patients.

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References

1. American Heart Association: 1999 Heart and Stroke Statistical Update. Dallas, Taxas, American Heart Association, 1998; 1-29.
2. Lim, TO, Ding LM, Goh BL, Zaki M et al. Distribution of Blood Pressure in a national sample of Malaysian adults. Med J Malaysia 2000; 55(1).
3. Flack JM, Neaton J, Grimm R Jr et al., for the Multiple Risk Factor Intervention Trial research Group. Blood pressure and mortality among mean with prior myocardial infarction. Circulation 1995; 92: 2437-445.
4. MacMahon S. Blood pressure and the prevention of stroke, J Hypertens 1996; 14 (suppl): S39-S46.
5. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and coronary heart disease BMJ 1994; 50: 272-98.
6. Rodgers A, MacMahon S, Gamble G, Stattery J et al., for the United Kingdom Transient Ischaemic Attack Collaborative Group. Blood pressure and risks of stroke in patients with cerebrovascular disease BMJ 1996; 313: 147.
7. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 2003; 289: 2560-572.
8. Burt VL, Culter JA, Higgins M et al. Trends in prevalence, awareness, treatment and control of hypertension. Hypertension 1995; 50: 272-98.
9. Jackson EK, Garrison JC. Renin and angiotensin. In: Goodman and Gilman's pharmacological basis of therapeutics. 9th edition New York, NY : McGraw Hill: 1996: 733-58.
10. Goodfriend TL, Elliot ME, Calt KJ. Angiotensin receptors and their antagonists. N Eng J Med 1996; 334: 1649-654.
11. Bauker JH, Reams GP. Angiotensin II type 1 receptor antagonists: a new class of antihypertensive drugs. Arch Intern Med 1995; 155: 1361-368.
12. Mathew HW. Racial, ethnic and gender differences in response to medicines. Drug Metabolism and Drug Interactions 1995; 12: 77-91.
13. Weinshilboum R. Inheritance and Drug Response. N Engl J Med 2003; 348(6): 529-37.
14. Evans WE, McLeod HL . Pharmacogenomics - Drug Disposition, Drug Targets, and Side Effects. N Engl J Med 2003; 348(6): 538-49.
15. Lin HJ, Han C-Y, Lin BK, Hardy S. Slow acetylator mutations in human polymorphic N-acetyltransferase gene in 786 Asians, blacks, Hispanic, and whites: application to metabolic epidemiology. Am J Hum Genet 1993; 52: 827-34.
16. Subcommittee of WHO/ISH. Clin Exp Hypertens 1993; 15: 1363-395.
17. Oparil S, Dyke S, Harris F et al. Efficacy and Safety of Valsartan compared with placebo the treatment of patients with essential hypertension. Clin Ther 1996; 18(5): 797-810.
18. Holwerda NJ, Fogardi R, Angets P et al. Valsartan, a new angiotensin II antagonists for treatment of essential hypertension: efficacy and safety compared with placebo and enalapril. J Hypertens 1996; 14: 1147-51.
19. Mallion JM, Boutelant S, Chabaux P et al. Valsartan ; blood pressure reduction in essential hypertension compared with enalapril. Blood Pressure Monitoring 1997; 2: 179-84.
20. Prabowo P, Arwanto A, Soemantri D, Sukardar E et al. A comparison of Valsartan and Captopril in patients with essential hypertension in Indonesia. Int J Clin Pract 1999; 53 (4): 268-72.
21. Zhou HH, Koshakji RP, Silberstein DJ et al . Racial differences in drug response: Altered sensitivity to and clearance of propranolol in men of Chinese descent as compared to American whites. N Engl J Med 1989; 320: 565-70.
22. McInnes GT. Clinical advantage of Valsartan. Cardiology 1999; 91 (Suppl 1): 14-1.
23. Hansson L, Zanchetti A et al. Effects of intensive blood pressure lowering and low dose aspirin in patients with hypertension (Hypertension Optimal Treatment (HOT) study). Lancet 1998; 351: 1755-762.