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SHORT COMMUNICATION

EFFICACY AND TOLERABILITY OF TRANDOLAPRIL IN MILD TO MODERATE HYPERTENSION - A DOUBLE BLIND COMPARATIVE CLINICAL TRIAL WITH ENALAPRIL IN INDIAN POPULATION

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Abstract : Several large scale clinical trials have demonstrated that angiotensin converting enzyme inhibitors offer cardiovascular and renal protection independent of their effects on systolic BP. Trandolapril is a new angiotensin converting enzyme inhibitor approved for the treatment of hypertension. The potential advantages of this drug are long duration of action and better tolerability. The objective of the study was to compare the efficacy and tolerability of trandolapril with that of enalapril in mild to moderate hypertension in Indian population. In this double blind, multicentric, parallel comparative clinical study, 120 patients with mild to moderate hypertension were randomly assigned to receive trandolapril 2 mg or enalapril 5 mg once daily for 8 weeks. The attainment of sitting diastolic blood pressure <90 mmHg at the end of 8th week was considered as primary outcome measure and attainment of diastolic blood pressure <90 mmHg or reduction of at least 10 mmHg diastolic blood pressure compared to baseline at any visit was considered as secondary outcome measures. 98.4% patients treated with trandolapril and 92.6% patients treated with enalapril fulfilled the primary outcome measure. 54, 72 and 62% patients on trandolapril and 52, 61 & 64% patients on enalapril fulfilled secondary outcome measure at the end of 2nd, 4th and 8th week respectively. Also trandolapril was better tolerated than enalapril with no significant abnormality in lab parameters.

Key words : tandolapril efficacy safety hypertension

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INTRODUCTION

The aim of antihypertensive therapy is to prevent morbidity and mortality associated with persistently raised BP by lowering it to an acceptable level, with minimum inconvenience to the patient. Up to one half of hypertensive patients will fail to achieve appropriate BP goals with monotherapy, regardless of the class of antihypertensive agent used (1). The multiple drug therapy adversely affects the compliance, which has a significant impact on the treatment success in terms of quality of life (2). Recent data suggest that long term compliance is improved when the initial antihypertensive agent prescribed is both efficacious and well tolerated (3) Inhibition of renin angiotensin aldosterone system (RAAS) by angiotensin converting enzyme inhibitors (ACEI) has been proved to provide substantial cardiovascular and renal protection, independent of their effects on systolic BP (SBP) (4, 5). ACEI alone normalize blood pressure in approximately 50% of patients with mild to moderate hypertension and many consider ACEI as the first line drugs for the treatment of high blood pressure except for elderly African-American patients (6). Trandolapril is a prodrug that is hydrolyzed to the active diacid, trandolaprilat, after oral administration. The distinguishing characteristics of trandolapril are its high binding affinity to ACE, high lipophilicity and long elimination half-life of 16-24 hours (7).

Trandolapril has comparable antihypertensive efficacy to enalapril given once daily in two studies with almost equal response rate (65% with trandolapril and 67% with enalapril) in a large Japanese study (8), 47% and 40% respectively in a smaller study using 24 hour ambulatory BP (AMBP) monitoring (9). The objective of the present study is to compare the efficacy and tolerability of trandolapril 2 mg with enalapril 5 mg at 2, 4 & 8 weeks of treatment in patients with mild to moderate hypertension among Indian population. Although trandolapril has been approved in other countries, this multicentric trial has been has been under taken as it is recquired by the drug regulatory authorities to establish its effect in Indian population before being marketed.

Patients and methodology

The present study is a randomized, double blind, multicentric, parallel comparative study conducted in three centers in India over a period of 6 months. The study protocol was approved by the institutional review boards of the participating centers. Patients of either sex in the age group of 18–60 yrs with mild to moderate hypertension (sitting diastolic between 90–110) were included into the study. Patients who were previously receiving antihypertensive medications were given 2 weeks of washout prior to the entry into the study. A written informed consent was obtained prior to the study. Patients were excluded from the study if they had secondary or malignant hypertension, sitting diastolic blood pressure (DBP) >110 mm Hg , significant cardiovascular, hepatic, renal or neurological disease, suspected bilateral renal artery stenosis or those with a single kidney and renal artery stenosis, poorly controlled diabetes mellitus with a HbAlc ≥9%, known hypersensitivity to ACE inhibitors, alcohol or drug abuse. Pregnancy,

lactation and women of child bearing potential were also excluded unless adequate contraception was used and intake of any investigational drug within 30 days prior to entry into the active treatment period.

One hundred twenty patients who fulfilled the above criteria were enrolled into the study. A detailed medical history was obtained and baseline laboratory investigations were carried out. Patients received the blinded study medication either trandolapril 2 mg or enalapril 5 mg. The efficacy and tolerability parameters were evaluated at the end of 2, 4 and 8 weeks. Blood pressures were recorded at fixed time before the morning dose of the test drug. The same person using the same sphygmomanometer at the same time of the day recorded three BP measurements at each visit and the mean value of three readings were calculated and used for statistical analysis. All adverse events reported by the patient or observed by the investigator were recorded throughout the study. The primary efficacy variable was attainment of normal blood pressure i.e. sitting DBP <90 mm Hg at the end of 8th week. Secondary outcome measures was attainment of DBP <90 mmHg or reduction of at least 10 mmHg DBP compared to baseline at any visit.

Statistical methods

A sample size of 120 patients was required to achieve 80% power at a two tailed ∝ level of 0.05. Baseline parameters were compared by Chi-square and paired 't' test. The primary and secondary endpoints were analysed by using Chi square test. The change in blood pressure and heart rate as compared to base line, at 2, 4 and 8 weeks were analysed individually by ANOVA and paired't' test in each group and the difference between the two groups were analyzed by using parametric unpaired 't' test. Chi-square test was employed to analyze the adverse events and repeated measures ANOVA to analyze the laboratory parameters. Graphpad software was used to carry out the statistical analysis.

RESULTS

One hundred twenty patients were randomized to the treatment schedule, out of which five patients were lost to follow up, leaving behind 115 patients (61 in trandolapril and 54 in enalapril group). The two treatment groups were comparable with respect to demographic and baseline variables (Table I) suggesting that the study sample was homogenous with respect to age, sex, baseline BP and pulse rate.

The proportion of patients who satisfied the primary outcome was similar for both trandolapril and enalapril group (60 patients i.e. 98.36% with trandolapril and 50 patients

TABLE I: Patient demographics and baseline characteristics.

	Trandolapril	*Enalapril*
Total no. of patients	61	54
Sex Male	29	20
Female	32	34
Age (Mean±SD) years	51±9	52±10
Basal Systolic BP (Mean±SD) mm Hg	154±6.0	152±10
Basal Diastolic BP (Mean±SD) mm Hg	95±6	95±7
Basal Pulse Rate (Mean±SD) rate/min	79±8	76±7

Statistical method: Chi-square test: not significant.

i.e. 92.6% with enalapril without any significant difference between them. At the end of 2nd, 4th and 8th week 54, 72 and 62% of patients on trandolapril and 52, 61 and 64% of patients on enalapril fulfilled the secondary outcome measure i.e. reduction of DBP of at least 10 mmHg compared to baseline at the respective visits.

Treatment with trandolapril showed a significant decrease in mean SBP and DBP after 2, 4 & 8 weeks compared to baseline and this decrease in BP was comparable to the enalapril treated group (Table II). The mean SBP reduced from 154±16 mmHg (baseline) to 137±15, 131±12 & 130±9 mmHg and the mean DBP also reduced significantly from 95±6 mmHg (baseline) to 86±9, 82±7 and 82±6 mmHg at the end of 2, 4 and 8 weeks respectively (P<0.001) (Table II) with trandolapril. The absolute fall in diastolic BP was 9, 13 & 14 mmHg at the end of 2nd, 4th & 8th week respectively.

Treatment with enalapril also achieved significant decrease in mean SBP and DBP after 2, 4 and 8 weeks compared to baseline. The mean SBP decreased significantly from 152±10 mm Hg (baseline) to 137±15, 134±17 & 133±15 mmHg and mean DBP also decreased significantly from 95±7 mmHg (baseline) to 86±10, 82±7 and 82±8 mmHg at the end of 2,4 and 8 weeks respectively (P<0.001) with enalapril. The absolute fall in diastolic BP was 9, 13 & 14 mmHg at the end of 2nd, 4th& 8th week respectively (Table II). There was no statistically significant difference between the two groups as far as SBP and DBP were concerned at the end of 8th week.

During 8 weeks treatment with trandolapril 2 mg once daily and enalapril 5 mg once daily, all patients tolerated the drug without any serious side effects. Adverse events were experienced overall by 20 patients (33%) in trandolapril group and 25 patients (46%) in enalapril group. The common adverse events seen in both the groups were dry cough, dizziness, headachae and abdominal discomfort. The incidence of dry cough, dizziness headache, were experienced in 4.9, 8.1 and 4.9% respectively in patients receiving trandolapril and 12.9, 9.2 and 7.4% respectively in patients receiving enalapril without any statistical significance between them (Table III). In addition, there was no clinically relevant

TABLE II: Changes in blood pressure (mm Hg) and pulse (rate/min) from baseline to different time intervals by trandolapril and enalapril.

	Systolic BP (SBP)		*Diastolic BP (DBP)*		*Pulse rate*	
Visits	*Trandolapril*	*Enalapril*	*Trandolapril*	*Enalapril*	*Trandolapril*	*Enalapril*
Basal	154±16.0	152±10	95±6	95±7	79±8	76±7
Week 2	137.0±15*	137±15†	86±9*	86±10†	76±6	77±7
Week 4	131±12*	134±17†	82±7*	82±7†	77±6	74±7
Week 8	130±9*	133±15†	82±6*	82±7†	77±6	75±6

Values are expressed as (Mean±SD).
*P<0.001, between baseline and 2nd, 4th and 8th week in trandolapril treated patients. ANOVA and paired 't' test. df = 60.
†P<0.001, between baseline and 2nd, 4th and 8th week in enalapril treated patients. ANOVA and paired 't' test. df = 53.

change in mean laboratory data including creatinine, urea, blood glucose and liver enzymes and serum potassium levels during treatment.

TABLE III: Various adverse events recorded in two groups.

Sl. No.	*Adverse event*	*Trandolapril*	*Enalapril*
		No. of patients (%)	*No. of patients (%)*
1.	Abdominal discomfort	2(3.28)	3(5.55)
2.	Nausea	1(1.64)	1(1.85)
3.	Vomiting	0(0)	1(1.85)
4.	Headache	3(4.9)	4(7.41)
5	Dizziness	5(8.12)	5(9.26)
6.	Hypotension	0	1(1.85)
7.	Dry cough	5(8.12)	7(12.96)
8.	Fatigue	1(1.64)	2(3.7)
		n=20(33)	n=25(46)

Statistical method: Chi-square test: (not significant between trandolapril and enalapril)

DISCUSSION

In the present study, we have compared trandolapril 2 mg with enalapril 5 mg using trough level DBP for the primary efficacy analysis. The data generated from this study clearly shows that trandolapril is equally efficacious as enalapril as an antihypertensive at the dose level tested. There are reports saying that trandolapril has a comparable antihypertensive efficacy to enalapril when given once daily (9, 10, 11). Vaur et al reported that trandolapril (2 mg/day) was able to sustain a greater BP reduction than perindopril 4 mg/day (12). Early comparative trials have also shown that trandolapril had antihypertensive effect similar to lisinopril (13), calcium channel blocker amlodipine (14), nitrendipine (15), atenolol, hydrochlorthiazide & nifedipine (16, 17). There is also evidence to indicate that there is increased prevalence of coronary artery disease in India (18) and also it is known to occur in younger age groups (19). According to HOPE study, ramipril reduced the incidence of stroke in patients at high risk, despite a modest reduction in systolic BP of 3.8 mmHg and diastolic BP of 2.8 mmHg (20). Trandolapril being a more potent ACEI should afford greater protection against both coronary and cerebrovascular accidents on long term use. Though there is no such long term study with this drug at this point of time, such a hypothesis would merit investigation.

The most frequently reported adverse events in both groups were headache, dry cough and dizziness, which were commonly reported in clinical trials with ACEI. Dry cough being one of the common adverse vents with the ACEI, so one with less incidence of the above adverse event could be a better option. This will increase the patient compliance. There was no change evidenced in hepatic, renal and hematological parameters. There were also no electrocardiography changes seen in the study population. These observations may have important implications in terms of not only minimizing potential adverse events but also maximizing the patient compliance. As suggested by Caro et al (3) the initial choice of antihypertensive agent is a key determinant in maximizing long term adherence to therapy. So we conclude that trandolapril would be an alternative to enalapril in hypertensive patients as it is equally efficacious as enalapril and better tolerated than enalapril. Since the sample size was small, we could not draw the significance as far as tolerability was concerned. Hence a well planned clinical trial involving wider cross section of patient population will definitely answer this.

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