

Clinical Study

Assessment of the Efficacy, Safety, and Tolerability of Perindopril/Indapamide (2mg/0.625mg) In Adult Patients of Mild to Moderate Hypertension

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Abstract

Aim of the study

The aim of this study was to assess the efficacy, safety and tolerability of Perindopril/ Indapamide (2mg/0.625mg) combination in adult Indian patients of mild to moderate hypertension.

Methodology

A prospective, multicentric (4 centres), open-label study was conducted. It had a placebo run-in period of 2 weeks followed by drug treatment [Perindopril/ Indapamide (2mg/ 0.625mg) once daily] for 8 weeks. Supine BP was

assessed at the end of every 2 weeks. Tolerability and safety was assessed by physical examination, laboratory parameters and evaluation of adverse events.

Results

There was a significant fall in the systolic and the diastolic BP starting from the second week as compared to the baseline. Mean Systolic Blood Pressure had a reduction of 15.0 % and 17.2 % at the end of 6th and 8th week respectively. Mean Diastolic Blood Pressure had a reduction of 11.0 % and 14.1 % at the end of 6th and 8th week respectively. The drug was well tolerated. The laboratory values were within normal limits.

Conclusion

Perindopril - Indapamide (2mg/0.625mg) combination once daily has a significant therapeutic effect and a good tolerability profile in patients with mild to moderate hypertension.

Keywords

Perindopril, Indapamide, efficacy, safety, hypertension

Introduction

The goal of antihypertensive treatment is to maximize therapeutic efficacy without significant side effects. The accepted approach is to initiate treatment with a low dose of a single drug and titrate its dose upwards as needed to achieve a better therapeutic effect. However this approach may not necessarily lead to higher efficacy, since most drugs reach an early plateau phase of their dose response effect, and further increase in dose leads to higher incidence and severity of side effects. Recent studies have shown that monotherapy for hypertension was successful in only 50% to 60% of the cases¹. This is because hypertension is a multifactorial disease with more than one pathophysiological mechanisms operating and thus cannot be effectively controlled by one drug.

The administration of a single drug sets in motion several counter regulatory mechanisms that can interfere with its effectiveness. The rationale for combining drugs is to counterbalance these regulatory mechanisms and thus increase their antihypertensive efficacy. Drug combinations have the following advantages: they allow the use of lower doses of the component drugs, decrease the incidence and magnitude of clinical and metabolic side effects, often have a longer duration of action than the individual drugs, are often suitable for once daily administration, increase patient compliance and frequently lower the cost of care^{2,3,4}.

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)⁵ and WHO- International Society of Hypertension (WHO/ISH)⁶ guidelines for the management of hypertension suggest that low dose combinations of antihypertensive drugs can be used as first line drugs in patients with hypertension.

A fixed low dose combination of the ACE inhibitor Perindopril 2mg and the non- thiazide diuretic Indapamide

0.625mg has been developed which meets the requirements of these guidelines. The aim of this study was to assess the efficacy, safety and tolerability of this combination in adult Indian patients of mild to moderate hypertension.

Materials And Methods

A Prospective, Multicentric (4 centres), Open-label, Phase III study was conducted.

Men and women between 18 and 75 years of age with mild-to-moderate hypertension, defined as diastolic blood pressure (DBP) >95 mm Hg and < 114 mmHg and systolic blood pressure (SBP) >140 mmHg and <200 mm Hg. were included in the study.

Excluded were women of child-bearing potential, patients with known or suspected secondary hypertension, hepatic or renal disease, cardiovascular disease or arrhythmias, uncontrolled or insulin-dependent diabetes mellitus, sodium depletion, hyperkalaemia, chronic use of oral anticoagulants, digoxin, or salt substitutes containing potassium chloride, use of short-acting nitrates or lithium, neuroleptics, or antidepressants, unstable high doses of NSAIDs or aspirin, or anyone receiving any investigational therapy within 1 month before the study. Patients receiving more than two antihypertensive medications at screening were also excluded as they were considered more likely to have severe hypertension.

This protocol was submitted to and approved by the Ethics Committee of each participating centre. At the initial evaluation (visit 1) each patient received a detailed explanation of the objectives and procedures of this study. They were asked to sign an informed consent to participate before any procedure was done.

The total duration of study was 10 weeks. It consisted of a placebo run-in period in which the placebo was given in the morning for 2 weeks to confirm blood pressure levels and to allow assessment of treatment compliance. That was followed by an 8-week period when all patients received 1 tablet of Perindopril/ Indapamide (2mg/0.625mg) once a day in the morning. Supine systolic and diastolic blood pressures of the patients were assessed at the end of 2 weeks of drug treatment. Patients were evaluated every 2 weeks for 6 more weeks.

Treatment efficacy was observed by measuring blood pressure by cuff sphygmomanometer. Laboratory safety

assessments were performed at the end of the run-in period and at the end of the study. The assessed parameters were haematology (count of red blood cells, white blood cells, differential and platelets), creatinine, sodium, potassium, AST/SGOT (serum glutamic-oxaloacetic transaminase), ALT/SGPT (serum glutamic-pyruvic transaminase), ECG (electrocardiogram). Any adverse event was recorded in the Case Record Form.

Statistical analysis was done using the ANOVA test and student's 't' test.

Results

Parameters		
No. of patients		123
Age (yrs)	Mean	51.87
	SD	12.04
	Range	28-74 yrs.
Weight (kg)	Mean	58.41
	SD	10.88
	Range	45-93 kg
Sex (%)	Male	70 (56.9)
	Female	53 (43.1)
Habits	Smoking	16 (13.0)
	Alcohol	08 (6.5)

A total of 130 patients were included in the study. Seven patients lost to follow up. A total of 123 patients were included in the final analysis. The age of the patients was ranging from 28-74 years with average age 51.87 years. Mean weight of the patients was 58.41 kg and 56.9 % of total cases were male and very few cases were smokers.

Above data shows that mean systolic blood pressure was 158.71mmHg at basal. After the treatment mean Systolic Blood Pressure had a fall of 6.6 % at the end of 2nd week which was significant. Mean Systolic Blood Pressure had a reduction of 15.0 % and 17.2 % at the end of 6th and 8th week respectively.

Table 2
Changes in Systolic and Diastolic Blood Pressure after the Treatment

Duration In Weeks	Mean SBP (mmHg) ($\bar{X} \pm SD$)	Mean DBP (mmHg) ($\bar{X} \pm SD$)
Basal	158.71 \pm 15.82	100.37 \pm 11.46
2	* 148.48 \pm 14.11	*97.4 \pm 9.11
4	* 139.67 \pm 11.84	* 92.81 \pm 7.94
6	*135.4 \pm 9.87	*89.4 \pm 6.99
8	*131.5 \pm 11.37	*86.31 \pm 8.12
By ANOVA		* P < 0.05 Significant

The mean diastolic blood pressure was 100.37mmHg at basal. After the treatment mean Diastolic Blood Pressure had a fall of 3.0% at the end of 2nd week which was significant. Mean diastolic Blood Pressure had a reduction of 11.0 % and 14.1 % at the end of 6th and 8th week respectively.

10.6% of total cases had adverse effects during the treatment. Out of these maximum were dry cough and headache followed by giddiness, diarrhoea and palpitation in two patients. The intensity of adverse events were mild to moderate.

There was no significant change in laboratory parameters at the end of treatment.

Discussion

The combination of the ACE inhibitor Perindopril and the non thiazide diuretic, Indapamide fulfil the criteria for appropriate antihypertensive therapy as described in the JNC VI guidelines⁵. The ACE inhibitors lower blood pressure through several mechanisms: inhibition of conversion of angiotensin I to angiotensin II, a potent vasoconstrictor peptide ; suppression of aldosterone release from the adrenal glands; inhibition of kinin degradation through inhibition of kininase II; inhibition of central sympathetic nervous system. A combination of Perindopril with Indapamide is a logical one, because the ACE inhibitor will enhance the natriuretic effect of the diuretic and will also block the renin stimulation and potassium loss from the diuretic. The combined formulation demonstrates bioequivalence with its individual components⁷. The choice of the low dose combination

Perindopril (2mg) and Indapamide (0.625 mg) used in this study is based on various dosage finding studies⁸.

A total of 123 patients with mild to moderate hypertension as per the JNC VI guidelines⁵ were enrolled in the study. There was a significant fall in the systolic and the diastolic BP starting from the second week as compared to the baseline. Mean Systolic Blood Pressure had a reduction of 15.0 % and 17.2 % at the end of 6th and 8th week respectively. Mean diastolic Blood Pressure had a reduction of 11.0 % and 14.1 % at the end of 6th and 8th week respectively.

Similar efficacy was seen in a long term study, among 35 patients who achieved blood pressure normalization with the fixed dose combination and 79.8% sustained their normalization over 1 year⁹. Therapeutic trials based on cardiovascular mortality have shown that that reduction of systolic pressure requires normalization of both large artery stiffness and wave reflections which are satisfactorily achieved with low dose Perindopril-Indapamide combination¹⁰.

Perindopril-Indapamide combination has nitric oxide enhancing properties¹¹. It has shown to attenuate Left Ventricular hypertrophy¹², and has renoprotective action¹³. It has shown to be highly efficacious in the elderly¹⁴ and patients with mild to severe renal failure¹⁵. It has a better efficacy as compared to Losartan¹⁶, Atenolol¹⁰, and Irbesartan¹⁷. The effect of Perindopril- Indapamide in the prevention of stroke has been well documented in the PROGRESS trial¹⁸.

Perindopril-Indapamide combination was very well tolerated. The common side effects were dry cough and headache which were mild in nature. There was no patient dropout in the study due to adverse events. There was no report of any serious adverse event. No significant laboratory changes could be detected, which indicates a good safety profile. Similar findings are reported in other studies¹⁹.

In conclusion the present study has confirmed that Perindopril- Indapamide (2mg/0.625mg) combination once daily has a significant therapeutic effect and a good tolerability profile in patients with mild to moderate hypertension.

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