A COMPARATIVE STUDY OF ISRADIPINE AND NIFEDIPINE IN THE MONOTHERAPY OF MILD TO MODERATE HYPERTENSION IN THE GHANAIAN

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SUMMARY

Clinical experience with the new dihydropyridine calcium antagonist, isradipine, is reported. Isradipine was compared with nifedipine in a multicentre open, parallel group, clinical therapeutic trial involving 70 patients with mild to moderate hypertension. A four week placebo washout period was followed by a 12 week active treatment period during which patients were randomized to receive either 2.5 mg isradipine twice daily (n = 40) or 10 mg nifedipine three times daily (n = 30). Isradipine significantly reduced sitting systolic/diastolic blood pressures from 176.7±21.0/106.7±7.0mmHg to 142.9±15/93.1±7.7mmHg ($p< 0.001$) at the end of 12 weeks. Similarly, nifedipine reduced sitting systolic/diastolic blood pressures from 170.2±19.5/106.2±7.4mmHg to 139.1±9.7/92.1±7.8 mmHg ($p< 0.001$). Normalisation (diastolic<90 mmHg) rates were 67% and 60% for isradipine and nifedipine respectively while good response (diastolic fall > 10mmHg) rate was over 85% on either drug. Heart rate did not significantly change with either treatment. Three (3) patients taking isradipine experienced headache and 7 patients taking nifedipine had drug related adverse effects (5 had headache, 1 insomnia and 1 first dose hypotension). Therapy was withdrawn in 4 patients taking nifedipine and 1 taking isradipine. It is concluded that isradipine is comparable to nifedipine and is an effective and well tolerated antihypertensive agent in the Ghanaian.

Key Words: Isradipine, Nifedipine, hypertension, efficacy, tolerability.

INTRODUCTION

Effective management of hypertension of people of African descent is a multifaceted and challenging problem. While the drug treatment of hypertension

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of people of African descent is generally the same as for Caucasians, there are certain important differences which influence the scientific consideration of the choice of drug in specific cases. Fro example, hypertension in patients of African descent as a whole is less responsive to B-blockers and angiotensin converting enzyme inhibitors[1,2,3]. On the other hand, calcium antagonists have been shown to be equally effective in lowering blood pressure in people of African descent and Caucasians, and have been found useful in first line monotherapy[1-4].

The calcium antagonist, nifedipine, has been on the Ghanaian and African market for a long time. It has been shown to be equally effective as thiazide diuretics and more effective than propranolol and methyldopa[5]. Recently, the newer calcium antagonist, isradipine has been introduced to clinical use in Ghana. It is of the same class as nifedipine, a dihydropyridine. Reports of the clinical use of isradipine outside of Africa have shown its favourable efficacy and safety profile[6,7]. However, there has been no record of its use in Ghana. This article therefore summarizes the first clinical experience of the use of isradipine in the treatment of mild to moderate hypertension in Ghana. The efficacy and safety of this new agent, isradipine, was compared to those of the established agent, nifedipine, in a multicentre, open, parallel group, clinical-therapeutic trial in which both drugs were administered as first line monotherapeutic agents.

CLINICAL MATERIAL AND METHODS

Patients 25 to 70 years with mild to moderate hypertension (untreated diastolic blood pressure (DBP) consistently between 95 and 114 mm Hg) were recruited into the study. The following rendered a patient ineligible for entry into the trial:

- severe, secondary or malignant hypertension;
- labile hypertension;
- uncontrolled congestive heart failure;
- gastro-intestinal, genito-urinary or hepatic diseases which may interfere with the absorption, metabolism or excretion of the study drugs;
- a history of alcoholism or drug abuse within the last 2 years;
- pregnancy or lactation;
- abnormal kidney function test;
- patients on the following drugs which may interfere with valuation of the study:
    * Monoamine oxidase (MAO) inhibitors
    * Tricyclic antidepressants
    * Psychotropic drugs
    * long acting nitrates
    * antacids with high sodium content.

Diagnosis of essential hypertension was made on patients' history , and physical examination with laboratory support and confirmed at the end of placebo washout period. After withdrawal of any previous anti-hypertensive therapy, patients completed a 4 week placebo (Vitamin C 25 mg twice daily) washout period. At the end of this period patients whose sitting diastolic blood pressure (DBP) was consistently between 95 and 144 mmHg on at least two consecutive occasions were randomly assigned to receive either isradipine 2.5 mg twice or nifedipine 10 mg three times daily for 12 weeks.

Patients were seen and evaluated at 2 weekly intervals during the placebo washout period and at 4 weekly intervals during the active treatment period. At each visit sitting and standing blood pressure (BP) and heart rate were measured. On each occasion, systolic and diastolic (korotkov phase v) were three times at two minutes interval and the readings averaged as recommended by the American Heart Association[8]. ECG and blood tests, including full blood count, lipid profile, blood urea and electrolytes, creatinine, and liver function tests were performed at the beginning and at the end of the active

treatment period. Adverse events related to the drugs were documented from spontaneous communication and standardized questioning. Safety was assessed by examination of reported adverse events. All patient gave informed consent before taking part in the study. The homogeneity of treatment groups with respect to age, weight, and entry blood pressure was assessed by analysis of variance. Statistical analysis of the response to each drug treatment from baseline and between the two groups were done using a two tailed Student's t-test. The significance of the difference was expressed as a p-value. A p-alue of < 0.05 was considered statistically significant.

RESULTS

Following the initial placebo washout period, seventy patients were eligible to enter the active treatment period. The baseline characteristics of the patients are shown in Table 1. There were no significant differences between the two groups of patients. All patients had normal full blood count, renal and hepatic function and lipid profile. Three patients in the isradipine group and two in the nifedipine group had mild left ventricular hypertrophy on ECG. Drug treatment with either drug did not change these patient characteristics.

The effect of treatment of sitting and standing BP are shown in Tables 2 and 3, respectively. Both drugs significantly ($p < 0.001$) decreased sitting and standing systolic and diastolic BP within four weeks of their administration and these were maintained for the twelve weeks of the study. Isradipine caused a mean fall in sitting SBP and DBP of 33.8±5.6 and 13.6±2.9 mmHg respectively over the 12 weeks. Similarly, nifedipine reduced sitting SBP and DBP by an average of 31.1±6.8 and 14.1±4.2 mmHg, respectively. These effects of isradipine and nifedipine were not significantly different. Standing blood pressure was reduced to the same extent as the sitting blood pressure by both drugs. Normalization defined as reduction of sitting DBP to 90mmHg or less was achieved in 67% and 60% of patients treated with isradipine and nifedipine respectively. Good response to treatment defined as fall of sitting DBP by ≥ 10mmHg was achieved in over 85% of patients on either drug.

Table 1. Baseline Characteristics of Study Patients

	Isradipine (n = 40)	Nifedipine (n = 30)
Age (years)	54.2 ± 10.2	58.6 ± 11.5
Gender (%)		
Male	(16) 40%	(12) 40%
Female	(24) 60%	(18) 60%
Body Weight (kg)	75.6 ± 9.1	73.3 ± 10.1

Values are expressed as mean ± SD

Table 2. Effect of Treatment with Isradipine and Nifedipine on Sitting Blood Pressure in mmHg

		Isradipine	Nifedipine
Week 0	SBP	176.7 ± 21.1	170.2 ± 19.5
	DBP	106.7 ± 7.4	106.7 ± 7.4
Week 12	SBP	142.9 ± 15	139.1 ± 9.7
	DBP	93.1 ± 7.7	92.1 ± 7.8

Table 3. Effect of Treatment with Isradipine and Nifedipine on Standing Blood Pressure in mmHg

Active Treatment		Isradipine	Nifedipine
Week 0	SBP	182.2 ± 23.1	176.1 ± 20.5
	DBP	115.6 ± 9.2	110.2 ± 9.4
Week 12	SBP	147.4 ± 19.8	143.2 ± 10.1
	DBP	101.9 ± 8.8	95.9 ± 7.9

SBP = Systolic Blood Pressure
DBP = Diastolic Blood Pressure

There were insignificant variations in heart rate in both groups and no evidence of reflex tachycardia.

Adverse Events

For the whole study ten patients reported adverse events. Three (3) patients had headache on isradipine; 2 of them mild transient headache which did not lead to withdrawal of the drug; but in the 3rd patient headache was severe and it led to withdrawal of isradipine.

Of the 7 patients who reported adverse events with nifedipine, 3 had severe headache which necessitated withdrawal of nifedipine, had mild transient headache and were able to continue treatment, one patient reported severe insomnia three-days after taking the drug because of which she stopped taking the drug; one patient had symptomatic severe first dose hypostatic effect (BP fell from 210/110 to 130/80) however the drug was not withdrawn.

DISCUSSION

Calcium antagonists are the preferred drugs in hypertensive patients with gout, angina, and probably diabetes. They may probably be preferred in patients with end organ damage such as left ventricular hypertrophy, renal impairment and stroke, which are common in patients of African descent[1,2]. The results of this study showed that isradipine, a new dihydropyridine, is as effective and safe as an antihypertensive as nifedipine, in the first line monotherapy of mild to moderate hypertension. It lowered blood pressure to the same extent as nifedipine. However, there were fewer adverse events reported with isradipine than with nifedipine. One out of 40 was withdrawn in the isradipine group while 4 out of 30 patients were withdrawn from the nifedipine group because of adverse events. However, the number of patients involved in the study was too small to establish any significant differences. The methodology also lacks the advantage of a double-blind placebo controlled study.

The results of this study is similar to those reported in the literature. Double blind placebo-controlled comparative studies of isradipine and nifedipine showed that the two drugs were comparable in reducing blood pressure [4,9]. However, in the long term isradipine was superior to nifedipine and the incidence of side effects was significantly lower with isradipine than nifedipine [4,9].

The achievement in this study of DBP normalization rate of over 60%, and good response rate of over 85% indicated that either drug can be as a first line monotherapeutic agent for the Ghanaian with moderate hypertension.

Since nifedipine has been shown to be more effective than propranolol in the African[5], it could be extrapolated from the results of this study that isradipine would also be more efficacious than propranolol. While the present study did not address this issue, results form other centres have clearly demonstrated this to be the case [6,7,10]. The hypertensive efficacy of isradipine was reported to be at least similar to that of hydrochlorothiazide, but superior to that of propranolol and prazosin [5-7,10].

Further, in controlled, double blind, clinical trials, isradipine has been found to be an effective first line monotherapeutic antihypertensive drug, regardless of the age or race of the patients and without metabolic adverse effects[5-7,10]. Thus, isradipine is equally effective in people of African descent as in Caucasians.

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