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Evaluation of lacidipine (a calcium blocker) in the treatment of hypertension in black African people: a double-blind comparison with hydrochlorothiazide

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Summary
Diuretics and calcium blockers are particularly effective in the treatment of hypertension in Blacks, who, characteristically, have low-renin hypertension. The efficacy and tolerable of lacidipine (a calcium) blocker of the dihydropyridine class) and hydrochlorothiazide (a diuretic) were compared in a 12 week double-blind randomised parallel group study of Nigerians with essential hypertension. Lacidipine was given at a starting dose of 4 mg daily by mouth and increased to 6 mg if there was no satisfactory response at 4 weeks, and hydrochlorothiazide was stared at 25 mg daily by mouth and increased to 50 mg if necessary. Twenty-four patients (8 male) in the lacidipine group and 17 (5 male) in the hydrochlorothiazide group were evaluable at the end of the trial. In the lacidipine group, SBP was significantly reduced from 157 ± 14 mmHg to 146 ± 24 mmHg ($P < 0.00001$) and DBP from 90 ± 9 mmHG to 87 ± 15 mmHg ($P < 0.00001$) with BP normalisation rates of 67% and 79% at 4 weeks and 12 weeks, respectively. In the hydrochlorothiazide group, SBP was significantly reduced from 16.4 ± 19 mmHg to 141 ± 17 mmHg ($P < 0.00001$) and DBP from 102 ± 6 mmHG to 89 ± 7 mmHg ($P < 0.00001$) with normalisation rates of 77% and 82% at 4 weeks and 12 weeks respectively. The groups did not differ in BP reduction nor normalisation rates. There were no reported side effects.

Keywords: *Hypertension, calcium blockers, diuretics, Nigerians.*

Résumé
Les composés diuretiques et bloqueurs de calcium sont particulierement effectif dans le traitement de l''ypertension chez les gens de race noire, qui ont de manière characteristique une faible hypertension – renin. L'efficacité et la tolerabilité de la lacidipine (un bloqueur de calcium de la class de la dihydropyridine) et de l'hydrochlorothiacide (un diuretique) ont été comparés dans une étude au hazard doublement aveugle et parallele pendant 12 semaines chez des Nigerians ayant une hypertension essentielle. La lacidipine était donné à une dose commencente de 4mg/jour par voie orale et accurt à 6mg si il n'yavait pas response satisfaisante après 4 semaines. L'hydro-chlorothiazide avait été donné à une dose commencente de 25mg/jour par voie orale et augmenté à 50mg si trouvé necessaire. Vingt-quatre patients (don't 8 hommes) dans le groupe de traitement à l'hydrochlorothiazide avaient été evalués à la fin de l'étude. Dans les groupes de traitement à la lacidipine, la SBP avait été rediute significativement de 157 ± 14mmHg ($P < 0.0001$) à 146 ± 24mmHg ($P > 0.00001$) et la DBP de 90 ± 90mmHg à 87 ± 15mmHg ($P < 0.00001$) avec un taux de normalisation de la Pression arterielle de 67% à 79% à 4 et 12 semaines respectivement. Dans le groupe à hydrochlorothiazide, la SBP était reduite de manière significative de 164 ± 19mmHg à 141 ± 17mmHg ($P < 0.00001$) et la DBP de 102 ± 6mmHg à 89 ± 7mmHg ($P < 0.0001$) avec un taux de normalisation de 77 à 82% à 4 et 12 semaines respectivement. Les groupes n'ont pas eu de difference dans la les taux de reduction ou de normalisation de la pression sanguine. Il n'y avait pas u de cas rapportés d'effects secondaires.

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Introduction

Lacidipine is a newly introduced calcium channel blocker of the 1,4-dihydropyridine class. It has been shown to act by selective action on the peripheral vasculature to reduce peripheral vascular resistance and therefore blood pressure. In clinical trials, the drug was found to be well tolerated even when used for up to 9 months either as montherapy or in combination with other drugs [1]. The trials have also shown that its antihypertensive effects are noticeable within 24 hours of administration. In addition, the drug has been shown not to have cardio-depressant activity and can therefore be used in patients with mild myocardial damage. With a half-life of about 8 hours, It can be suitably given in a daily dosage [2].

Previous studies have demonstrated the effectiveness and tolerability of calcium blockers in Nigerian hypertensives [3,4] a group with characteristically low plasma renin activity [5] in whom diuretics are also expected to be effective. At least one report [6] has emerged from Nigeria showing equal efficacy of a calcium blocker, amlodipine, with a thiazide diuretic in the treatment of hypertension. It is of both theoretical and practical value to compare the efficacy and tolerability of lacidipine with a thiazide, hydro-chlorothiazide, in Nigerian hypertensives.

Methods

The study was carried out at the University College Hospital, Ibadan. Patients were recruited into the study if they had mild to moderate essential hypertension. (DBP ≥ 95 mmHg but < 115 mmHg) in the sitting position, and SBP not exceeding 200 mmHg. Ethical clearance was obtained from the hospital ethical committee and informed consent was obtained from the patients. Patients who were already receiving anti-hypertensive treatment, but were considered suitable for the study, had their medication withdrawn to allow for a run-in period of 4 weeks during which they were placed on placebo. At the end of the run-in period, they were reassessed to confirm that their sitting DBP satisfied the criteria set out above. The BP was taken 3 times at each visit and the means used for analysis. A complete physical examination was also carried out and the blood

biochemistry was checked. Patients with history of stroke, heart failure, renal failure, hepatic disease and secondary hypertension were excluded.

The design was a double-blind, parallel group study. Patients were randomised to either lacidipine 4 mg orally, daily, or hydrochlorothiazide 25 mg orally, daily, for 12 weeks. They underwent an initial 4-week titration after which they were reassessed to see if their sitting DBP had dropped to below 90 mmHg or by 15 mmHG of the entry value; if not, the doses were increased to lacidipine 6 mg daily or hydrochlorothiazide 50 mg daily for the remaining 8 weeks.

The physical examination and the blood biochemistry were repeated at the end of the study.

Statistics: Categorical variable were examined by Fisher's exact tests. Comparison of means was by 2 way analysis of variance for repeated measures for drug and time effects and interactions. Significant terms were further analysed by Scheffe's test significance was at $P < 0.05$.

Results

Sixty-two hypertensive patients were recruited. Thirty patients were randomised to receive lacidipine and 32 to hydrochlorothiazide. Only those who completed all six visits were evaluable. Twenty-four patients (8 males) in the lacidipine group and 17 patients (5 males) in the hydrochlorothiazide group were evaluable at the end of the trial, the others having dropped out. The reasons for dropping out were non-medical and were related to inability to keep appointments. The baseline data on the groups is shown in Table 1.

Table 1: Baseline data on the lacidipine and hydrochlorothiazide groups

	Lacidipine (n = 24)	Hydrochlorothiazide (n = 17)
Male/Female	8/16	5/12
Age (years)	52.5 ± 14.4	53.2 ± 17.6
Weight (kg)	53.3 ± 23.2	47.3 ± 33.5
SBP (mmHg)	153.5 ± 13.1	162.5 ± 21.0
DBP (mmHg)	100.1 ± 4.4	101.2 ± 6.1

Visits 1 to 6 are explained in Table 2. Treatment was started at visit 3. At visit 4 the sitting DBP of 16 patients on lacidipine (67%) and 13 on hydrochlorothiazide (77%) had dropped to below 90 mmHg ($p = 0.75$), and at visit 6 the numbers were 19 (79%) and 14 (82%), respectively ($p = 1.13$). The changes in BP are shown in Table 2. There were significant falls in the sitting and standing DBP in each drug group.

There were significant differences in the SBP from visits 3 to 6 in both drug groups ($P < 0.00001$) with no significant difference between the drug groups. Similarly, there were significant differences in the DBP ($P < 0.0001$) with no differences between the groups. There were no drug by time interactions. Further analysis showed significant differences in SBP between visits 3 and 4, 3 and 5, 3 and 6 ($P < 0.0005$), 3 and 5 ($P < 0.005$), 3 and 6 ($p < 0.0005$), and 4 and 6 ($P < 0.01$). There were no side effects reported.

Table 2: Blood pressure changes during treatment with lacidipine and hydrochlorothiazide

Visit	1	2	3	4	5	6
Week	-4	-2	0	4	8	12
Lacidipine						
n	30		24	24	24	24
SBP (sitting)	149 ± 19	158 ± 15	157 ± 14	143 ± 22	144 ± 19	146 ± 24
SBP (standing)	152 ± 18	160 ± 17	159 ± 15	147 ± 22	145 ± 30	146 ± 22
DBP (sitting)	91 ± 8	98 ± 6	101 ± 5	90 ± 9	89 ± 10	87 ± 15
DBP (standing)	100 ± 7	104 ± 8	106 ± 6	96 ± 10	95 ± 11	93 ± 10
Pulse	80 ± 12	78 ± 11	81 ± 12	80 ± 11	81 ± 12	83 ± 10
Hydrochlorothiazide						
n	32		17	24	24	24
SBP (sitting)	153 ± 18	159 ± 21	164 ± 19	149 ± 21	147 ± 18	141 ± 17
SBP (standing)	155 ± 19	161 ± 23	166 ± 21	150 ± 19	152 ± 16	145 ± 14
DBP (sitting)	90 ± 9	97 ± 8	102 ± 6	94 ± 9	92 ± 10	89 ± 7
DBP (standing)	100 ± 9	104 ± 11	106 ± 7	99 ± 11	98 ± 11	92 ± 8
Pulse	80 ± 11	82 ± 9	79 ± 10	80 ± 10	80 ± 7	80 ± 10

Discussion

For many years, diuretics had formed the cornerstone of drug therapy of hypertension, especially Blacks [7].

The introduction of the calcium antagonists offered an alternative choice without the metabolic side effect of diuretics. This study has again show that diuretics (hydrochlorothiazide) and calcium blockers (lacidipine) are equally effective in Blacks.

Twenty-four patients in the lacidipine group and 17 in the hydrochlorothiazide group completed the study. Lacidipine was given at the standard initial dose of 4 mg, which had been employed in another study in Nigerians, and increased to 6 mg where applicable [8]. Similarly, hydrochlorothiazide was given at an initial dose of 25 mg and increased to 50 mg daily as in another previous study in Nigerians [6]. The effectiveness of these doses was reflected in the 67% and 77% control rates with lacidipine and hydrochlorothiazide, respectively, at 4 weeks and 79% and 82% at 12 weeks. The control, or normalisation, rate with lacidipine obtained in this study is similar to the 78% rate with lacidipine [8] and the 75% with isradipine [4] in other studies in Nigerians, but less than the virtually 100% normalisation rates have been obtained in the various studies with calcium blockers. This restates the current

thinking that calcium blockers could be employed as first line agents, and as monotherapy in the treatment of hypertension in Blacks.

Drawbacks to the use of calcium blockers would include the side effects of palpitations, headaches, nocturia [4] although none were reported in this study. Calcium blockers are likely to be more expensive than diureics, and this may limit their wide use in Nigeria and in much of the developing world.

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