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Effect of Slow-Release Indapamide and Perindopril Compared With Amlodipine on 24-Hour Blood Pressure and Left Ventricular Mass in Hypertensive Patients of African Ancestry

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Background: In the treatment of hypertension in subjects of African origins, although hydrochlorothiazide (HCTZ) is not as effective as calcium channel blockers, indapamide is superior to HCTZ. In the present study we therefore compared the effects of slow release (SR) indapamide with the calcium channel blocker amlodipine, when used as initial therapy, on blood pressure (BP) and left ventricular mass (LVM) during 6 months of treatment in this group.

Methods: Patients with a mean daytime ambulatory diastolic BP ≥90 mm Hg and ≤110 mm Hg (n = 125, aged 53 ± 11 years, 68% women) were randomized to receive open-label 1.5 mg of indapamide SR or 5 mg of amlodipine. If daytime ambulatory diastolic BP at 1 month was ≥90 mm Hg, 4 mg of perindopril was added to indapamide SR or the dose of amlodipine was increased to 10 mg.

Results: After 1 month of therapy, there was an equivalent decline in systolic and diastolic BP in both groups ($P < .0001$). In the indapamide-treated group (n = 62) the daytime BP decreased from 153 ± 12/101 ± 6 mm Hg to 138 ± 15/92 ± 10 mm Hg and for amlodipine (n = 58), it decreased from 152 ± 13/99 ± 5 mm Hg to 138 ± 12/91 ± 8 mm Hg. At 6 months daytime ambulatory BP decreased to 130 ± 15/86 ± 8 mm Hg and to 129 ± 11/85 ± 5 mm Hg for the indapamide SR (n = 42) and amlodipine (n = 44) treatment groups, respectively. Both groups showed equivalent regression of LVM index and relative wall thickness.

Conclusions: These data suggest that in hypertensive patients of African ancestry initiating therapy with 1.5 mg of indapamide SR and then adding 4 mg of perindopril is equally as effective as amlodipine therapy at reducing BP, and modifying target organ damage. Am J Hypertens 2004;17:428–432 © 2004 American Journal of Hypertension, Ltd.

Key Words: Ambulatory blood pressure monitoring, blacks, antihypertensive agents, indapamide.

Both the South African Hypertension and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) guidelines recommend thiazide diuretics as initial therapy for the treatment of uncomplicated hypertension.[1,2] However, in a multiarm combination trial, a dihydropyridine calcium channel blocker (CCB), when used as monotherapy was shown to be more efficacious than other classes of antihypertensive agents including low dose hydrochlorothiazide (HCTZ) (12.5 to 25 mg daily) as determined from 24-h ambulatory blood pressure monitoring (ABPM) in patients of African ancestry.[3] Nevertheless using 24-h ABPM to assess efficacy, we have recently demonstrated[4] that monotherapy with indapamide at a dose of 2.5 mg daily was superior to low dose HCTZ (12.5 mg daily)[5] in the management of hypertension in patients of African origins with mild-to-moderate hypertension. Whether indapamide used as initial therapy mediates equivalent antihypertensive and beneficial target organ effects when compared to dihydro-

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pyridine CCB therapy has not been evaluated. Therefore, in the present study we compared the effect of slow-release (SR) indapamide at a dose of 1.5 mg once daily to that of the dihydropyridine CCB amlodipine at a dose of 5 mg daily, on ambulatory BP in patients of African ancestry with mild-to-moderate hypertension. We also evaluated whether these initial therapeutic approaches were comparable when assessing subsequent ambulatory BP control and regression of left ventricular mass (LVM) after the addition of further therapy (an angiotensin-converting enzyme inhibitor to the indapamide-treated group and an additional 5 mg of amlodipine to the CCB-treated group) to patients who had not achieved BP target.

Methods

Study Population

This was a single-center, open-label, randomized, prospective study, conducted at Chris Hani Baragwanath Hospital, from 2001 through 2002. The protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Men and women, aged 21 to 70 years, without significant concomitant cardiovascular or noncardiovascular disease were recruited. Women of reproductive age had to consent to adequate contraception. All patients gave written informed consent before inclusion into the study.

BP Measurements

Patients were initially screened using a Dinamap 1846 SX vital signs monitor (Critikon Inc, Tampa, FL).[6] Eligible patients were enrolled in a wash-out placebo run-in phase of 2 weeks. Thereafter, a 24-h ABPM was performed using SpaceLabs 90207 oscillometric monitor (SpaceLabs Inc, Redmond, WA), programmed to obtain readings every 15 min from 6 AM to 6 PM and every 20 min from 6 PM to 6 AM.[7] If the mean daytime ambulatory diastolic BP was ≥90 mm Hg and ≤114 mm Hg, patients were randomized to one of two treatment arms: indapamide SR (1.5 mg once daily; Natrilix SR, Servier Lab, Neuilly-sur-Seine, France), or amlodipine (5 mg once daily; Norvasc, Pfizer, New York, NY). Patients were excluded if their compliance during the placebo run-in phase was poor (<80% or >120% of the expected tablet count).

After 1 month of therapy, if BP target was not achieved (daytime ambulatory diastolic BP ≥85 mm Hg), 4 mg/d perindopril (Coversyl, Servier Lab) was added to the diuretic-treated group, or amlodipine was increased to 10 mg in the CCB-treated group. Thereafter, patients continued on the same therapy for another 5 months with visits at monthly intervals. After 2 months if a mean daytime ambulatory diastolic BP of <100 mm Hg and a decrease in the mean daytime ambulatory diastolic BP of ≥10 mm Hg were not achieved, the patients were withdrawn from the study. Throughout the study, patients who experienced any serious adverse events or had a daytime ambulatory systolic BP >180 mm Hg and a daytime ambulatory diastolic BP >110 mm Hg were also withdrawn.

Echocardiography

Two-dimensional targeted M-mode echocardiograms were obtained with a Hewlett-Packard Sonos 2500 (Hewlett-Packard Co., Palo Alto, CA) system using a 2.5-MHz transducer at the end of the 2-week washout phase, and after 2 and 6 months of therapy. The echocardiograms were analyzed according to the American Society of Echocardiography recommendations.[8] The LVM index (LVMI) was derived according to an anatomically validated regression method that corrects LVM estimates obtained from the recommended measurements.[9] Replicated measurements of LVMI showed that the inter- and intraobserver coefficients of variation were 12.4% and 11.4%, respectively.

Statistical Analysis

Database management and statistical analysis were performed with SAS software, version 8.2 (SAS Institute Inc., Cary, NC). Between and within-group differences in continuous measurements were tested with multiple repeated measures analysis of variance, adjusting for baseline BP values. Proportions were compared using the χ^2 test or Fisher's exact test when necessary.

Results

Of the 283 patients screened for the study, 125 were randomized. Sixty-one patients received amlodipine (5 mg/d) and 64 patients received indapamide SR (1.5 mg/d) as initial treatment. The baseline study groups were mostly women with a high mean body mass index (BMI) (Table 1). There were no statistical differences between baseline characteristics, except for the daytime ambulatory diastolic BP between the two groups (Table 1). From the cohort 44 patients in the amlodipine-treated group and 42 patients in the indapamide SR-treated group completed 6 months of treatment. Thirteen patients were withdrawn and 4 defaulted in the amlodipine-treated group, and 17 were withdrawn and 5 patients defaulted in the indapamide SR-treated group. Major adverse events requiring withdrawal were: angioneurotic edema (1 patient) due to perindopril, severe dizziness (1 patient) due to indapamide SR; and pedal edema (6 patients) and generalized edema (1 patient) in the amlodipine-treated group. Nonserious adverse events included dry cough in 3 patients in the idapamide–perindopril-treated group and 1 patient in the amlodipine-treated group.

BP

The reduction in BP was similar in both groups (Table 2). The decline in ambulatory daytime systolic BP/diastolic

Table 1. Baseline demographic characteristics

	Amlodipine (*n* = 61)	Indapamide SR (*n* = 64)
Age (yr)	53.7 ± 10.5	51.6 ± 10.7
Sex (F/M%)	43 (71)	42 (66)
Body weight (kg)	78.9 ± 14.6	77.8 ± 16.2
Body mass index (kg/m^2)	30.8 ± 6.5	29.9 ± 6.8
Serum cholesterol (mmol/L)	5.1 ± 1.0	5.2 ± 1.2
Serum glucose (mmol/L)	5.1 ± 1.6	5.3 ± 2.7
Serum creatinine (μmol/L)	80 ± 18	84 ± 18
Serum potassium (mmol/L)	3.7 ± 0.7	3.7 ± 0.9
BP (mm Hg)/HR (beats/min)		
Dinamap SBP/DBP	151 ± 16/94 ± 8	153 ± 14/95 ± 8
Dinamap HR	74 ± 10	74 ± 11
24-h SBP/DBP	148 ± 14/94 ± 6	148 ± 12/95 ± 6
Daytime SBP/DBP	152 ± 13/99 ± 5	153 ± 12/101 ± 6*
Daytime HR	79 ± 10	80 ± 12
Nighttime SBP/DBP	144 ± 16/89 ± 7	143 ± 15/90 ± 8

* $P = .03$ (daytime diastolic BP between the two groups).
BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

BP profiles was 14 ± 16/7 ± 8 mm Hg for the amlodipine-treated group and 14 ± 15/8 ± 10 mm Hg in the indapamide SR-treated group at 1 month (Table 2). At 1 month BP control rates were similar in both groups. Using a target daytime ambulatory diastolic BP <85 mm Hg, 16% (9 of 58 patients) and 23% (14 of 62 patients) control rates were achieved with amlodipine and indapamide SR, respectively. The daytime ambulatory systolic BP was <140 mm Hg in 55% of patients (32 of 58 patients) in the amlodipine-treated group and 61% of patients (38 of 62 patients) in the indapamide SR-treated group. The daytime ambulatory systolic and diastolic BP was <140/85 mm Hg in 16% of patients (9 of 58 patients) in the amlodipine-treated group and 21% of patients (13 of 62 patients) in the indapamide SR-treated group.

At 6 months, the decrease in BP and absolute BP values achieved were similar between the groups (Table 2). Although the baseline daytime ambulatory diastolic BP was slightly higher in the indapamide SR-treated group, at the end of the study, the indapamide SR-treated group achieved BP control (daytime ambulatory diastolic BP <85 mm Hg) in 52% of patients (22 of 42 patients), which was similar to that in the amlodipine-treated group, where BP control was achieved in 52% of patients (23 of 44 patients). In those patients who remained on initial therapy, in the indapamide SR-treated group only 3 (7%) patients and in the amlodipine-treated group only 4 (9%) patients remained controlled. After 6 months of therapy the daytime ambulatory systolic BP was <140 mm Hg in 86% of patients (38 of 44 patients) in the amlodipine-treated group and 76% of patients (32 of 42 patients) in the indapamide SR-treated group. The daytime ambulatory systolic and diastolic BP was <140/85 mm Hg in 52% of patients (23 of 44 patients) in the amlodipine-treated group

Table 2. Conventional, Dinamap, and ambulatory BP at baseline, 1 month, and at 6 months of the study

SBP/DBP (mm Hg)	Baseline	1 month	6 months
Amlodipine	*n* = 61	*n* = 58	*n* = 44
Office†	153 ± 15/97 ± 8	138 ± 15/90 ± 8*	127 ± 13/81 ± 8*
Dinamap	151 ± 16/94 ± 8	136 ± 14/87 ± 8*	124 ± 15/79 ± 7*
24-h	148 ± 14/94 ± 6	134 ± 12/86 ± 8*	126 ± 11/81 ± 6*
Daytime	152 ± 13/99 ± 5	138 ± 12/91 ± 8*	129 ± 11/85 ± 5*
Nighttime	144 ± 16/89 ± 7	129 ± 13/81 ± 8*	124 ± 12/77 ± 7*
Indapamide SR	*n* = 64	*n* = 62	*n* = 42
Office†	153 ± 14/97 ± 7*	135 ± 15/88 ± 8*	128 ± 14/85 ± 8*
Dinamap	153 ± 14/95 ± 7*	135 ± 18/86 ± 12*	127 ± 18/81 ± 10*
24-Hour	148 ± 12/95 ± 6*	134 ± 15/87 ± 9*	126 ± 16/81 ± 8*
Daytime	153 ± 12/101 ± 6*	138 ± 15/92 ± 10*	130 ± 15/86 ± 8*
Nighttime	143 ± 15/90 ± 8*	130 ± 15/83 ± 9*	123 ± 17/77 ± 9*

Abbreviations as in Table 1.
* $P < .0001$ (between baseline and 1 month/6 months).
† Blood pressure was measured according to the recommendation of the American Heart Association.

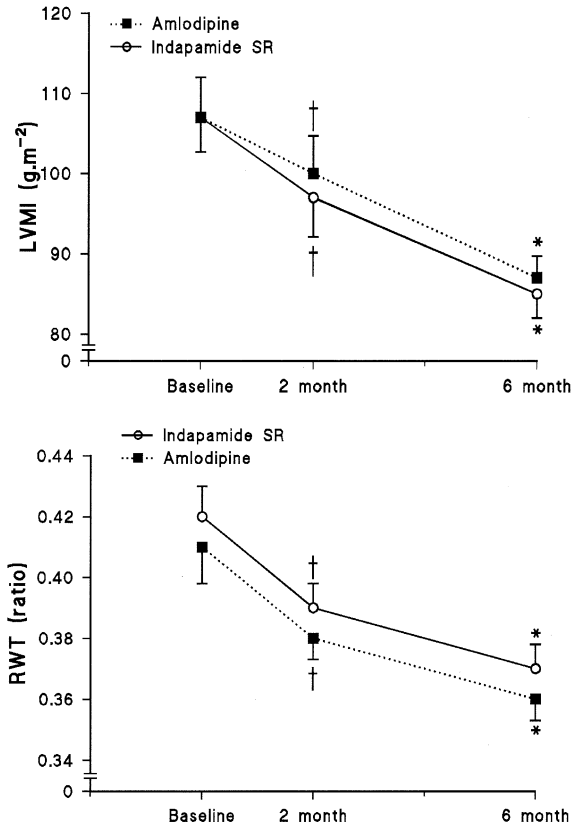

FIG. 1. Left ventricular mass index (LVMI) (**top**) and relative wall thickness (RWT) (**bottom**) reduction after 2 and 6 months of therapy. †$P < .0001$ (2 months versus baseline); *$P < .001$ (6 months *v* 2 months).

and 52% of patients (22 of 42 patients) in the indapamide SR-treated group.

Left Ventricular Mass

The decline in systolic BP was associated with regression of LVMI after 2 and 6 months of therapy (Fig. 1). This regression was achieved by a reduction in posterior ventricular and interventricular septal wall thickness and not by a decrease in LV end-diastolic diameter (Table 3). Furthermore, we showed reversal of LV concentric remodeling as evidenced by a reduction in relative wall thickness (RWT). The reduction in LVMI and in RWT was similar in both groups after 2 and 6 months of therapy (Fig. 1).

Biochemistry

No changes in biochemical parameters were noted with treatment except for a similar decrease in cholesterol concentrations in both groups (data not shown) after atorvastatin administration to four patients in the indapamide SR-treated group and to seven patients in the amlodipine-treated group. Potassium supplementation was required in two patients in each group.

Discussion

The major findings of this study are that in patients of African ancestry with mild-to-moderate hypertension: 1) monotherapy with indapamide SR (1.5 mg/d) decreases ambulatory and office BP to a similar extent as compared to amlodipine (5 mg/d) after 1 month of therapy; 2) the combination of indapamide SR (1.5 mg) and perindopril (4 mg/d) was equally as effective as amlodipine (10 mg/d) at lowering BP after 6 months of therapy, and 3) the decline in BP after therapy was associated with continued regression of LVMI and a decrease in RWT to an equivalent extent in both treatment groups.

The present study is the first to compare the efficacy of the SR indapamide (thiazide diuretic) to that of the dihydropyridine CCB, amlodipine, on ambulatory BP in subjects of African ancestry with mild-to-moderate hypertension. Equivalent efficacy was achieved. This is in contrast to the greater antihypertensive efficacy of CCB (including dihydropyridines) agents as compared to low dose HCTZ (12.5 to 25 mg daily) used in this ethnic

Table 3. Echocardiographic data at baseline after 2 and at 6 months of treatment

	Baseline	2 months	6 months
Amlodipine (n = 36)			
24-h SBP/DBP (mm Hg)	147 ± 12/93 ± 6	126 ± 9/82 ± 5†	125 ± 10/80 ± 5
LVEDD (mm)	49.1 ± 5.2	49.9 ± 4.6	48.8 ± 3.5
PWED (mm)	10.0 ± 1.2	9.4 ± 1.0†	8.7 ± 0.8*
IVSD (mm)	10.5 ± 1.6	9.8 ± 1.3†	9.1 ± 0.9*
LVM (g)	191 ± 54	178 ± 49†	154 ± 27*
Indapamide SR (n = 37)			
24-h SBP/DBP (mm Hg)	147 ± 13/94 ± 6	128 ± 11/82 ± 6†	128 ± 16/82 ± 9
LVEDD (mm)	49.0 ± 4.3	48.8 ± 4.1	48.4 ± 3.5
PWED (mm)	10.3 ± 1.4	9.5 ± 1.2†	8.9 ± 1.1*
IVSD (mm)	11.1 ± 1.8	10.0 ± 1.4†	9.4 ± 1.2*
LVM (g)	200 ± 54	176 ± 49†	158 ± 37*

* $P < .001$ (2 to 6 months) † $P < .0001$ (baseline to 2 months).

LVEDD = left ventricular end diastolic diameter; PWED = posterior ventricular wall thickness; IVS = inter-ventricular septal wall thickness; LVM = left ventricular mass; other abbreviations as in Table 1.

group. The data in the present study are consistent with the comparable efficacy of indapamide SR (1.5 mg) with amlodipine (5 mg) at reducing systolic BP in elderly patients of mainly European ancestry with isolated systolic hypertension.[10]

In the present study, initial monotherapy failed to achieve control of BP to accepted therapeutic targets as determined by ABPM in the majority of patients. Similar findings were noted in the Antihypertensive and Lipid Lowering to prevent Heart Attack Trial (ALLHAT),[11] in which 35% of patients were of African ancestry and the initial office BP values in untreated patients in the diuretic (chlorthalidone) and the CCB (amlodipine) treatment arms were 156/89 mm Hg and 157/90 mm Hg, respectively (as compared to a baseline office BP in the present study of 153/97 mm Hg). In the ALLHAT, although the dose of chlorthalidone was uptitrated to 25 mg daily and the dose of amlodipine was increased to 10 mg daily, 63% of the patients required the addition of a β-blocker, atenolol, to achieve an office target BP of $<$140/90 mm Hg.

In the present study the equivalent effect on BP, using both therapeutic approaches, was associated with similar reductions in LVMI and RWT. The significant reduction of RWT in both treatment groups underscores the favorable effect of antihypertensive therapy on LV remodeling.

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