COMPARISON OF INDAPAMIDE AND LOW-DOSE HYDROCHLOROTHIAZIDE MONOTHERAPY IN BLACK PATIENTS WITH MILD TO MODERATE HYPERTENSION

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Objectives. To assess, using ambulatory blood pressure monitoring (ABPM), the antihypertensive efficacy of hydrochlorothiazide 12.5 mg and indapamide 2.5 mg given as a monotherapy over 3 months to black patients with mild to moderate essential hypertension.

Design. Single-centre, prospective, randomised open pilot study in three phases: (*i*) 1-week drug-free washout period; (*ii*) 2-week placebo run-in phase; and (*iii*) 3-month prospective open-label active treatment period.

Results. Forty-two black patients with mean daytime diastolic BP (DBP) ≥ 90 mmHg and ≤ 115 mmHg (mean age 57 ± 11 years, 28 women/14 men) were enrolled into the study. Overall, a profound and sustained BP reduction was achieved with indapamide at 3 months ($N = 20$). The 24-hour BP decreased from 150 ± 17/94 ± 6 mmHg to 130 ± 19/82 ± 9 mmHg ($P < 0.0001$ for systolic BP (SBP) and DBP at 3 months versus baseline); the mean daytime BP decreased from 155 ± 15/98 ± 6 mmHg to 134 ± 18/87 ± 10 mmHg ($P < 0.0001$ for SBP and DBP at 3 months versus baseline). The overall control (mean daytime DBP < 90 mmHg) and response (decrease in daytime DBP ≥ 10 mmHg) rates achieved with indapamide were 10/20 (50%) and 13/20 (65%), respectively. In contrast, monotherapy with hydrochlorothiazide resulted in more modest BP reduction and control and response rates at 3 months ($N = 22$). The 24-hour BP decreased from 147 ± 14/94 ± 7 mmHg to 139 ± 19/88 ± 2 mmHg ($P < 0.05$ for DBP at 3 months versus baseline, P = NS for SBP); the mean daytime BP decreased from 151 ± 14/98 ± 5 mmHg to 144 ± 16/93 ± 10 mmHg ($P < 0.05$ for DBP at 3 months versus baseline, P = NS for SBP). The corresponding control and response rates were 7/22 (32%) and 8/22 (36%). Both hydrochlorothiazide and indapamide caused significant hypokalaemia.

Conclusions. Monotherapy with indapamide is associated with greater BP reduction and control and response rates than monotherapy with low-dose hydrochlorothiazide and may be an appropriate choice of antihypertensive diuretic therapy in black South African patients with mild to moderate hypertension.

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Low-dose thiazide diuretics are widely recommended as first-line antihypertensive therapy in mild to moderate hypertension.[1,2] It has been shown, using ambulatory blood pressure (BP) monitoring (ABPM), that their short-term (3 months) BP-lowering effect as monotherapy in black South African hypertensives is modest.[3] However, their long-term efficacy in this population is not well established. Also, the role of other diuretics such as indapamide as first-line agents in the management of mild to moderate hypertension in such patients is not well documented.

In the present study, using ABPM in 42 mild to moderate black South African hypertensive patients, we assessed the antihypertensive efficacy of low-dose hydrochlorothiazide 12.5 mg daily (Dichlotride, Merck Sharpe & Dohme) and indapamide 2.5 mg daily (Natrilix, Servier Laboratories), given once daily as monotherapy over 3 months.

METHODS

Patient population

Included in the study were black patients with mild to moderate hypertension who met two entry BP criteria, namely an average sitting DBP ≥ 95 and < 115 mmHg, measured as a mean of 10 readings over a 30-minute period using a Dinamap device (Critikon 1846 SX Vital Signs Monitor), and a mean daytime ambulatory DBP ≥ 90 mmHg and < 115 mmHg. The BP measurements were, therefore, free of observer bias. Eligible patients of either sex with essential mild to moderate hypertension (either newly diagnosed or not adequately controlled previously) were entered into the study after a 1-week washout period (for patients not controlled on their current therapy), followed by a 2-week placebo run-in phase; they were then randomised to 3 months' therapy with active medication. Laboratory tests and 24-hour electrocardiogram (ECG) Holter monitoring were performed at baseline and 3 months to assess the safety of the study medications and their effect on the incidence of arrhythmia.

Exclusion criteria were as follows: pregnant or lactating women, DBP ≥ 115 mmHg, SBP > 200 mmHg, secondary

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hypertension, myocardial infarction or cerebrovascular insufficiency within the 3 months preceding enrolment, cardiac arrhythmias, insulin-dependent diabetes mellitus, clinically significant alteration in renal or liver function, electrolyte abnormalities, hyperuricaemia, clinically significant depression 6 months before enrolment, history of alcohol or drug abuse, unco-operative or antagonistic personality, or previous history of intolerance to any of the study drugs.

All patients gave written informed consent before enrolment. The trial protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand and the Pharmacy and Therapeutics Committee of Chris Hani-Baragwanath Hospital, Johannesburg.

Study design

This single-centre, prospective, randomised, open pilot study included three phases: (*i*) a 1-week drug-free wash-out period; (*ii*) a 2-week placebo run-in phase to identify placebo responders; and (*iii*) a 3-month prospective open-label active treatment period. All eligible patients were randomised 1:1 to either hydrochlorothiazide 12.5 mg daily or indapamide 2.5 mg daily, for 3 months. Twenty-four-hour ABPM was performed at baseline and after 3 months of diuretic therapy.

Compliance assessment by tablet count was performed at each monthly visit. All patients showed good compliance with the therapy (80 - 120%) throughout the study.

BP measurement

Office BP was measured following the recommendations of the American Heart Association.[4]

By using the Dinamap Critikon 1846 SX vital signs monitor, BP was measured every 3 minutes for up to 30 minutes. The monitors were calibrated against mercury sphygmomanometers, with a maximum acceptable difference of ± 5 mmHg at 200 mmHg.[5] The reason for using the Dinamap as a screening device was to eliminate observer bias and white-coat hypertension as much as possible.

Twenty-four-hour ABPM was performed using SpaceLabs 90207 oscilliometric BP monitors calibrated against a mercury sphygmomanometer before use in each patient, with monitor readings being within 3 mmHg or 2% of the manometer readings, whichever was greater.[6] Monitors were programmed to read BP and heart rate (HR) every 15 minutes from 06h00 to 18h00 and every 20 minutes from 18h00 to 06h00. Mean daytime (06h00 - 18h00) and night-time (18h00 - 06h00) BP and HR were calculated.

Trough and peak ratio measurement using ABPM

The average of two consecutive hours of maximum BP lowering during the day was defined as peak effect. The average of the last 2 hours of the 24-hour period was defined as trough effect. Only responding patients were included in the trough-to-peak analysis (reduction in mean daytime DBP ≥ 10 mmHg).

Microalbumin excretion rate

Twenty-four-hour urine samples were collected at baseline and at the end of study and sent to the laboratory for microalbumin measurement. Microalbuminuria was defined as a microalbumin excretion rate between 30 and 300 mg per 24 hours.

Ambulatory ECG Holter monitoring

Ambulatory ECG Holter recordings were performed over a 24-hour period using SpaceLabs 90205 portable tape recorders. The complete 24-hour record was printed with a Spacelabs FT 3000 full-disclosure unit. The printouts were analysed by an experienced technologist, who was blinded to the results of other investigations or the patient's treatment. Patients were categorised according to the maximum absolute number of ventricular extrasystoles in any single hour during the 24-hour monitoring. The occurrence at any stage of multifocal ventricular premature beats (VPBs), ventricular couplets or ventricular tachycardia was also documented.

Statistical analysis

Results are presented as mean ± standard deviation (SD). Continuous data were analysed using the Student's *t*-test, ANOVA and MANOVA tests. When no proof of normality was available, non-parametric tests, i.e. Wilcoxon's matched pairs signed-rank test and the Kruskal-Wallis and Friedman tests, were used for between- and within-group comparisons. A *P*-value of < 0.05 was considered significant for all statistical tests.

RESULTS

Table I summarises the baseline demographic characteristics for the study population. The patients were mostly female with a high body mass index. It is important to note that 9/42 patients (21%) had non-insulin-dependent diabetes mellitus and 6/42 patients (14%) had microalbuminuria. No patients had been taking reserpine as part of medication before this study.

Table II shows the BP-lowering effect of both diuretics, using 24-hour ABPM and Dinamap. Monotherapy with indapamide was associated with significant reduction in Dinamap SBP and DBP (25 and 11 mmHg, respectively), with no clinically apparent effect on the HR. The BP response, measured by 24-hour ABPM, is consistent with the above observation, with reduction of SBP and DBP of 20 and 12 mmHg, respectively. In contrast, the antihypertensive effect of hydrochlorothiazide was more modest ($P = 0.05$ for indapamide versus hydrochlorothiazide at 3 months). The reduction in 24-hour SBP achieved with hydrochlorothiazide (8 mmHg) was not significant, but the DBP reduction (6 mmHg) reached statistical significance.

The above differences in overall BP-lowering effect between low-dose hydrochlorothiazide and indapamide are reflected in

Table I. Demographic data

	All patients (N = 42)	Hydrochlorothiazide (N = 22)	Indapamide (N = 20)
Age (yrs)	57 (11)*	55 (12)*	59 (8)*
Male/female (N)	14/28	8/14	6/14
BMI (kg/m²)	31 (8)*	30 (9)*	30 (8)*
Hypertension duration (yrs)	5.5 (5.8)*	4.9 (5.0)*	5.2 (5.9)*
Newly diagnosed (N (%))	7 (17)	4	3
Previously treated with hydrochlorothiazide (N (%))	12 (28.6)	5	7
Type II diabetes mellitus (N (%))	9 (21)	3	6
Microalbuminuria (N (%))	6 (14)	4	2
Smokers, > 5 cigarettes/day (N (%))	8 (19)	4	4
Alcohol use, 1 - 7 drinks/week (N (%))	6 (14)	3	3

* Mean and standard deviation.
BMI = body mass index.

the control (mean daytime DBP < 90 mmHg) and response (reduction in mean daytime DBP ≥ 10 mmHg) rates as shown in Table III. The response rate was 8/22 (36%) for hydrochlorothiazide and 13/20 (65%) for indapamide (P < 0.01 indapamide versus hydrochlorothiazide). The corresponding control rates for hydrochlorothiazide and indapamide were 7/22 (32%) and 10/20 (50%), respectively (P < 0.01 indapamide versus hydrochlorothiazide). Furthermore, the antihypertensive effect of hydrochlorothiazide and indapamide was sustained over the 24-hour period (Figs 1 and 2), with good trough-to-peak ratios for both SBP and DBP in responding patients.

Table IV documents the effect of the different diuretic therapies on biochemical parameters, showing significant decrease in potassium level for both groups. No other significant biochemical abnormalities were detected. Neither of the study medications had an effect on the microalbumin excretion rate.

The incidence of ventricular arrhythmic events is shown in Table V. None of the study drugs had any effect on the incidence of arrhythmic events. No sustained ventricular tachycardia was observed at baseline and end of treatment.

Discussion

The major findings of this study are: (*i*) monotherapy with indapamide was associated with significantly greater reduction

Table II. Blood pressure and heart rate at baseline and after 3 months of diuretic monotherapy (mean values and standard deviation)

	Hydrochlorothiazide (12.5 mg/d, N = 22)		Indapamide (2.5 mg/d, N = 20)	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Dinamap BP (mmHg)				
Baseline	154 (16)	96 (8)	161 (13)	97 (9)
3 months	146 (19)	92 (10)	136 (20)*	86 (10)†
24-hour BP (mmHg)				
Baseline	147 (14)	94 (7)	150 (17)	94 (6)
3 months	139 (19)	88 (12)†	130 (19)†	82 (9)‡
Daytime BP (mmHg)				
Baseline	151 (14)	98 (5)	155 (15)	98 (6)
3 months	144 (16)	93 (10)†	134 (18)*	87 (10)‡§
Night-time BP (mmHg)				
Baseline	142 (15)	89 (9)	141 (24)	87 (7)
3 months	133 (23)	82 (15)	125 (21)†	76 (8)‡
24-hour heart rate (bpm)				
Baseline	78 (10)		76 (13)	
3 months	79 (9)		78 (14)	
Day-time heart rate (bpm)				
Baseline	82 (11)		80 (14)	
3 months	83 (10)		81 (15)	
Night-time heart rate (bpm)				
Baseline	74 (9)		72 (13)	
3 months	74 (9)		75 (14))	

* P < 0.002 at 3 months versus baseline.
† P < 0.05 at 3 months versus baseline.
‡ P < 0.0001 at 3 months versus baseline.
§ P < 0.05 indapamide versus hydrochlorothiazide at 3 months of monotherapy.
bpm = beats per minute.

Table III. Control (mean daytime DBP < 90 mmHg) and response (reduction in mean daytime DBP ≥ 10 mmHg) rates and trough-to-peak ratios in responding patients after 3 months of monotherapy with indapamide 2.5 mg daily and hydrochlorothiazide 12.5 mg daily

	Hydrochlorothiazide (*N* = 22)	Indapamide (*N* = 20)
Control rate (%)	7/22 (32%)	10/20 (50%)*
Response rate (%)	8/22 (36%)	13/20 (65%)*
Trough-to-peak ratio (%, mean (± SD))		
SBP	96 (8)	95 (8)
DBP	84 (17)	91 (9)

* $P < 0.01$ indapamide versus hydrochlorothiazide.
SD = standard deviation.

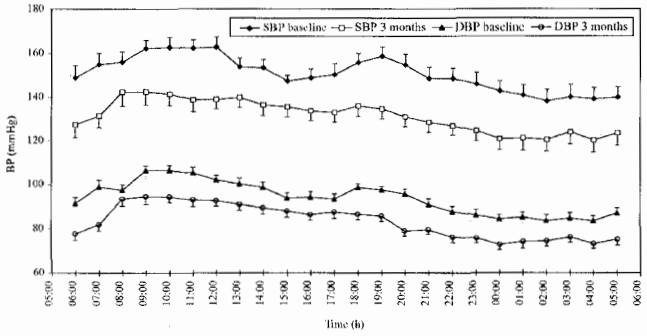

Fig. 1. Twenty-four-hour blood pressure profiles at baseline and after 3 months of therapy with indapamide 2.5 mg once daily (N = 20).

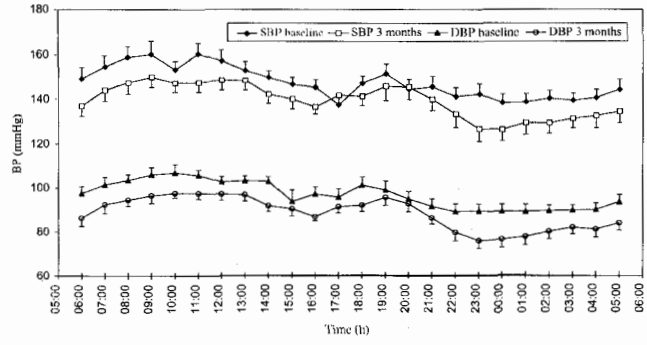

Fig. 2. Twenty-four-hour blood pressure profiles at baseline and after 3 months of therapy with hydrochlorothiazide 12.5 mg once daily (N = 22).

of SBP and DBP at 3 months compared with low-dose hydrochlorothiazide in mild to moderate black South African hypertensives; (*ii*) there was a significant decrease in serum potassium levels after 3 months of diuretic monotherapy, observed with both agents; and (*iii*) neither of the study drugs was associated with increased incidence of arrhythmias.

Low-dose thiazide diuretics have been recommended and used as first-line therapy in the management of mild to

Table IV. Changes in biochemical parameters following 3 months of diuretic monotherapy (mean values and standard deviation)

	Hydrochlorothiazide (*N* = 22)	Indapamide (*N* = 20)
Sodium (mmol/l)		
Baseline	141 (4)	141 (5)
3 months	140 (5)	139 (4)
Potassium (mmol/l)		
Baseline	4.3 (0.6)	4.2 (0.5)
3 months	3.8 (0.6)*	3.6 (0.6)†
Creatinine (µmol/l)		
Baseline	72 (14)	77 (22)
3 months	72 (12)	88 (10)
Glucose (mmol/l)		
Baseline	4.5 (0.5)	5.1 (1.6)
3 months	4.6 (0.9)	5.1 (1.1)
Total cholesterol (mmol/l)		
Baseline	5.0 (1.4)	4.9 (1.0)
3 months	5.20 (1.4)	5.1 (1.0)
LDL (mmol/l)		
Baseline	2.8 (1.2)	2.9 (1.0)
3 months	3.0 (1.3)	3.0 (1.2)
HDL (mmol/l)		
Baseline	1.5 (0.9)	1.2 (0.3)
3 months	1.4 (0.3)	1.3 (0.4)
Triglycerides (mmol/l)		
Baseline	1.6 (0.6)	1.9 (0.9)
3 months	1.7 (0.8)	2.0 (1.0)
Microalbuminuria (*N*)		
Baseline	4	2
3 months	4	4

* $P < 0.05$ at 3 months versus baseline.
† $P < 0.005$ at 3 months versus baseline.
LDL = low-density lipoprotein; HDL = high-density lipoprotein.

moderate hypertension in this population. However, their efficacy as a monotherapy is, at best, modest and many black hypertensive patients require combination antihypertensive therapy. Materson *et al.*[7,8] have shown that in young African-American patients with mild to moderate hypertension office DBP of less than 90 mmHg at 1 year was achieved in only 42% of patients, using 12.5 - 50 mg hydrochlorothiazide. Furthermore, using low-dose hydrochlorothiazide (12.5 mg), the above goal was reached in only 35% of patients. In the present study, using 24-hour ABPM, we found that a low-dose thiazide diuretic achieved BP control in 32% of the patients at 3 months, with a response rate of 36%. In comparison, therapy with indapamide was associated with greater BP reduction and higher control (50%) and response (65%) rates. Furthermore, the BP reduction achieved with indapamide was greater than that achieved with hydrochlorothiazide ($P = 0.05$ indapamide versus hydrochlorothiazide at 3 months). Our decision to use hydrochlorothiazide 12.5 mg rather than 25 mg daily is justified by the findings of Skoularigis *et al.*[3] in a similar group of patients, who showed that the increase in the hydrochloro-

Table V. Incidence of ventricular arrhythmia events at baseline, 3 months, and at end of study (number of patients)

	Hydrochlorothiazide (*N* = 15)	Indapamide (*N* = 15)
VPB < 10/hour		
Baseline	12	13
3 months	2	12
VPB 10 - 30/hour		
Baseline	9	1
3 months	3	3
VPB > 30/hour		
Baseline	8	1
3 months	0	2
Couplets		
Baseline	0	0
3 months	0	0
Non-sustained VT		
Baseline	0	0
3 months	1	1

VPB = ventricular premature beats; VT = ventricular tachycardia.

thiazide dose from 12.5 to 25 mg daily did not have any additional significant effect on BP, but worsened the hypokalaemia. Therefore, based on these results, indapamide may be an appropriate choice of antihypertensive diuretic therapy in black South African patients with mild to moderate hypertension. Both study medications were well tolerated, with no serious adverse events or deaths observed. However, serum potassium levels should be monitored throughout therapy with both diuretics and potassium supplementation should be given where necessary.

We have referred to black patients as this was our study population at Chris Hani-Baragwanath Hospital. Patients of African descent respond differently to Caucasians when given antihypertensive medication, and this is well documented in the literature. As black patients suffer more from the effects of hypertension — end-stage renal failure, heart failure, etc. — it is important to determine causes and optimal treatment in this high-risk group both in South Africa and other populations elsewhere (e.g. African-Americans).

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DIABETES IN RURAL SOUTH AFRICA — AN ASSESSMENT OF CARE AND COMPLICATIONS

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Objectives. To describe the diabetic population under care of the public health sector in a district in rural KwaZulu-Natal, to assess the nature of their care, their glycaemic control and the extent of their complications.

Subjects and methods. Two hundred and fifty-three diabetic patients consecutively attending clinics for review were interviewed and examined, and where available a 12-month retrospective review of clinical records was performed. Random blood glucose, haemoglobin A_{1c} (HbA_{1c}) and urine albumin/creatinine ratio were assayed.

Results. Acceptable glycaemic control (HbA_{1c} < 2% above normal population range) was found in only 15.7% of subjects (95% confidence interval (CI): 11.4 - 20.8%). Mean HbA_{1c} was 11.3%. The prevalence of hypertension (blood pressure ≥ 160/95 mmHg and/or prescribed antihypertensive medication) was 65.4% (CI: 59.0 - 71.1%). Of 129 patients who were prescribed antihypertensives, 14.0% (CI: 8.5 - 21.2%) were normotensive (< 140/90 mmHg). Severe obesity was present in 36.5% (CI: 30.4 - 42.9%). Rates of attendance for review and compliance with diabetic medications were high. Blood glucose monitoring was not regularly performed and medications were rarely modified. Complications were common and mostly undiagnosed. Retinopathy of any grade was found in 40.3% of patients (CI: 33.2 - 50.9%) and was severe enough to warrant laser photocoagulation in 11.1% (CI: 8.5 - 21.2%). Microalbuminuria was found in 46.4% (CI: 40.0 - 53.0%) and foot abnormalities attributable to diabetes in 6.0% (CI: 3.4 - 9.7%).

Conclusions. Care and control of diabetes in this rural community is suboptimal. There is a need for primary care staff to focus on modifying prescriptions in the face of poor blood glucose control and/or uncontrolled hypertension. Additional training and support for nursing staff and education for patients will be central to achieving this level of intervention.

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