Trial of atenolol and chlorthalidone for hypertension in black South Africans

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Summary and conclusions

Twenty-four black patients (Zulus) with hypertension participated in a double-blind, placebo-controlled cross-over trial of the efficacy of a beta-blocking agent (atenolol) 100 mg once daily as compared with chlorthalidone 25 mg once daily. The two drugs were also given combined at these doses and the effects compared with those of the drugs given alone.

Atenolol as sole treatment had no appreciable effect on blood pressure as compared with placebo. Chlorthalidone produced a small decrease, but this was not statistically significant. Combining the two drugs, however, produced a significant reduction in blood pressure (mean lying blood pressure $p < 0.001$; mean standing blood pressure $p < 0.0002$).

These findings suggest that beta-blockers should not be regarded as baseline treatment of hypertension in blacks.

Introduction

Beta-blockers are effective hypotensive agents in Caucasians. In a double-blind cross-over trial on 18 hypertensive Jamaicans, however, Humphreys and Delvin found no significant difference between propranolol and an inert placebo.[2] This was not confirmed by Grell in an open study of the drug.[3] I reported control of blood pressure with propranolol in eight out of 12 Indians and only four out of 13 black hypertensive patients.[4] The fall in blood pressure in the Indians as compared with the blacks was statistically significant ($p < 0.002$).

Evidence suggests that most blacks with hypertension have low plasma renin activities.[5] Diuretics such as chlorthalidone increase plasma renin activity. Hence I decided to study the effect of atenolol 100 mg once daily alone and in association with chlorthalidone 25 mg once daily and to compare them with chlorthalidone alone in black hypertensive patients. Chlorthalidone is long acting and is thus suitable for use with atenolol, which is given in a once-daily dose.

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Patients and methods

Twenty-four black hypertensive patients (Zulus) participated in the trial, which had a double-blind, cross-over design. The sequences for the administration of treatments comprised the 24 possible permutations of atenolol plus placebo, chlorthalidone plus placebo, atenolol plus chlorthalidone, and placebo plus placebo. Each patient was allocated to a sequence at random.

I selected for the trial only patients with mild to moderate essential hypertension (supine diastolic blood pressure (phase IV, Korotkoff sounds) 100-115 mm Hg) that did not require urgent control. Clinical and biochemical investigations were done in all cases. Criteria for exclusion were: cardiac failure, bronchial asthma, gross electrocardiographic evidence of myocardial ischaemia or heart block, myocardial infarction within the past five months, pregnancy, greatly impaired renal or hepatic function, diabetes mellitus requiring treatment, and gout. Fully informed consent was obtained from all patients.

Patients were seen at 28-day intervals. On each occasion the resting pulse rate and resting blood pressure in the lying and standing positions were recorded. Blood pressure was measured with a random-zero sphygmomanometer in the same arm on all occasions. At the first visit patients were given bottles labelled "period 1," "A" and "B," from individual packs and told to take one tablet a day from each bottle, preferably at 0700-0800. Blood pressure was usually measured between 1000 and 1200. At the end of the first month patients who still met the criteria for inclusion entered the double-blind phase of the trial (periods 2-5). The dose was one tablet from each bottle daily throughout. Tablets were counted at each visit to check compliance. At the end of each treatment period blood was taken with the patients seated for estimation of plasma renin activity (radioimmunoassay) and urea and electrolyte concentrations.

Results

Variables analysed were lying and standing systolic blood pressures, lying and standing diastolic blood pressures, and lying and standing pulse rates. Results of the Kolmogorov-Smirnov one-sample test showed that these variables could be treated as normally distributed. An analysis of variance and F test were conducted on the variables to test the difference in average effects of the four treatments. Table I

TABLE I—*Effects on blood pressure and pulse rate of various combinations of atenolol, chlorthalidone, and placebo in 24 black South Africans with hypertension. Values are means ± SEM*

	Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)			Pulse rate (beats/min)		
	Active drug	Placebo	D	Active drug	Placebo	D	Active drug	Placebo	D
Lying									
Atenolol 100 mg/day	161·5 ± 4·3	159·0 ± 4·6	+ 2·5	98·1 ± 1·9	102·5 ± 3·1	− 4·4	67·3 ± 2·0	76·2 ± 2·2	− 8·9
Chlorthalidone 25 mg/day	152·6 ± 4·6		− 6·4	96·3 ± 3·4		− 6·2	79·5 ± 2·3		+ 3·3
Atenolol 100 mg/day plus chlorthalidone 25 mg/day	145·0 ± 5·7		− 14·0	88·7 ± 2·4		− 13·8	71·7 ± 2·4		− 4·5
Standing									
Atenolol 100 mg/day	163·2 ± 5·1	161·7 ± 3·9	+ 1·5	102·4 ± 2·4	106·6 ± 3·0	− 4·2	70·2 ± 2·2	82·5 ± 2·2	− 12·3
Chlorthalidone 25 mg/day	153·3 + 4·9		− 8·4	100·8 ± 3·1		− 5·8	87·5 ± 2·8		+ 5·0
Atenolol 100 mg/day plus chlorthalidone 25 mg/day	139·4 ± 6·0		− 22·3	94·0 ± 2·7		− 12·6	74·5 ± 2·9		− 8·0

D = Difference in value between periods of treatment with active drug and placebo.

and figs 1 and 2 give the results. The mean lying and standing blood pressures of each patient during each treatment period were calculated as the diastolic pressures plus one-third of the difference between the systolic and diastolic pressures. No statistical evidence of postural hypertension was detected during any treatment period (paired t tests).

For plasma renin activity, serum sodium, potassium, chloride, and bicarbonate concentrations, and blood urea concentration a non-parametric Friedman analysis of variance was conducted to test for differences in the average effects of the four treatments. Table II shows the effects on plasma renin activity and serum potassium concentrations. There was no significant difference in serum sodium and bicarbonate and blood urea concentrations between the various treatment periods. Spearman's test for coefficient of correlation (non-parametric) showed no significant correlation between the falls in either standing, lying, or mean blood pressures in any of the treatment groups compared with placebo and the plasma renin activity. There were no appreciable side effects of atenolol or chlorthalidone.

TABLE II—*Effects of treatment on plasma renin activity and serum potassium concentrations. (Means ±SEM)*

	Plasma renin activity (μg/l/h)			Serum potassium concentration (mmol/l)		
	Active drug	Placebo	D*	Active drug	Placebo	D†
Atenolol 100 mg/day	1·5±0·3	2·7±0·9	−1·2	4·3±0·1	4·1±0·1	+0·2
Chlorthalidone 25 mg/day	4·6±1·2		+1·9	3·7±0·1		−0·4
Atenolol 100 mg/day plus chlorthalidone 25 mg/day	4·7±1·4		+2·0	3·8±0·1		−0·3

D = Difference.
*No significant difference in mean values.
†Difference in mean values; $p<0·001$.
Conversion: SI to traditional units—Serum potassium: 1 mmol/l = 1 mEq/l.

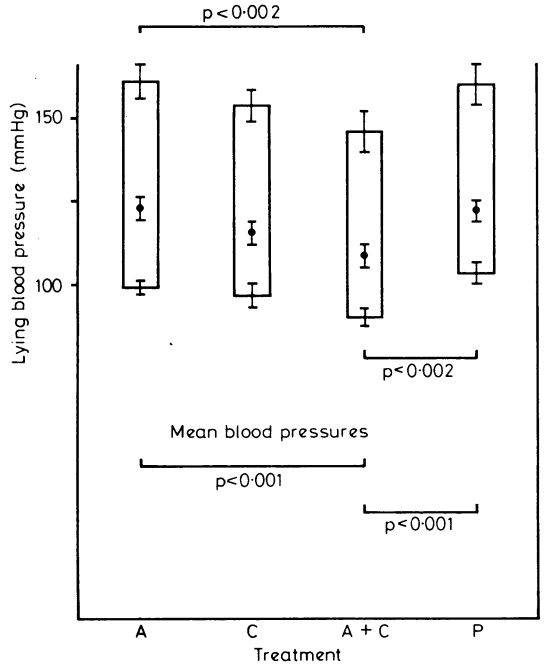

FIG 1—Lying systolic, diastolic, and mean blood pressures during treatment with atenolol (A), chlorthalidone (C), atenolol plus chlorthalidone (A+C), and placebo (P). Bars indicate ±SEM.

Comment

Blood pressure is dependent on both cardiac output and peripheral resistance; hence a beta-blocker that permits $beta_2$ vasodilatation might theoretically be expected to produce a lower blood pressure than a beta-blocker that does not. Cross-over trials of oral atenolol and non-selective beta-blockers show atenolol to be a superior antihypertensive agent.[6 7] The mode of hypotensive action on beta-blocking agents is not known, and various theories have been postulated[8].

This study showed that whereas atenolol was no better than placebo, and chlorthalidone produced a decrease in blood pressure that was not statistically significant, the combination of atenolol and chlorthalidone produced a statistically significant decrease in blood pressure in black hypertensive patients (table I; figs 1 and 2). Apparently beta-blockers act in black hypertensive patients once the excess plasma volume or sodium concentration is corrected by diuretics. A subgroup of patients with essential hypertension who failed to respond to propranolol and bendrofluazide given alone reportedly responded well to a combination of the two drugs.[9] This variant of essential hypertension may be more common in blacks than in Caucasians.

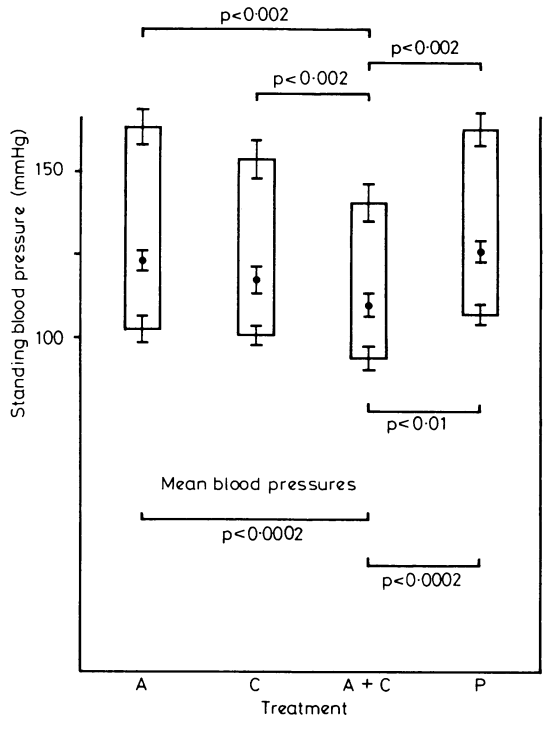

FIG 2—Standing systolic, diastolic, and mean blood pressures during treatment with atenolol (A), chlorthalidone (C), atenolol plus chlorthalidone (A+C), and placebo (P). Bars indicate ±SEM.

Therapeutic compliance was confirmed not only by counting the pills remaining at each visit but also by finding the expected changes in pulse rate and biochemical values during the various treatment periods. Lying and standing pulse rates decreased significantly (lying $p<0·005$, standing $p<0·0002$) during treatment with atenolol and atenolol combined with chlorthalidone as compared with during treatment with chlorthalidone

or placebo (table I); the serum potassium concentration showed a statistically significant decrease during treatment with chlorthalidone and chlorthalidone combined with atenolol as compared with during the atenolol or placebo period (table II); and plasma renin activity rose with chlorthalidone and decreased with atenolol, though this was not statistically significant (table II).

These findings have important implications. Beta-blockers alone are ineffective in black hypertensive patients, and thiazides rather than beta-blockers should be the baseline treatment of hypertension. When beta-blockers are used in black hypertensive patients they should initially be combined with a thiazide diuretic.

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Prevalence of urinary incontinence

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Summary and conclusions

The prevalence of urinary incontinence was investigated by determining the number of incontinent patients under the care of various health and social service agencies in two London boroughs and by a postal survey of the 22 430 people aged 5 years and over on the practice lists of 12 general practitioners in different parts of the country. The prevalence of incontinence known to the health and social service agencies was 0·2% in women and 0·1% in men aged 15-64 and 2·5% in women and 1·3% in men aged 65 and over. The postal survey, to which 89% of the people whose correct address was known replied, showed a prevalence of urinary incontinence of 8·5% in women and 1·6% in men aged 15-64 and 11·6% in women and 6·9% in men aged 65 and over. Nulliparous women had a lower prevalence than those who had had one, two, or three babies, but within the parity range of one to three there were no differences in prevalence. The prevalence was appreciably increased in women who had had four or more babies. Incontinence was moderate or severe in a fifth of those who reported it in the postal survey, of whom less than a third were receiving health or social services for the condition.

Incontinence is a common symptom, and many unrecognised cases appear to exist. There may be considerable scope for improving its management.

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Introduction

Although interest is growing in the investigation, treatment, and management of incontinence, its prevalence in the general population has so far been based on estimates made in selected groups of people of different ages.[1-11] We therefore studied the prevalence of urinary incontinence in those aged 5 and over in different areas in England and Wales.

Methods

We considered incontinence as "recognised" or "unrecognised." Those with recognised incontinence were patients known to the various health and social service agencies participating in their management. Unrecognised incontinence referred to those identified by a study in the general population. Our definition of "regular" urinary incontinence was involuntary excretion or leakage of urine in inappropriate places or at inappropriate times twice or more a month, regardless of the quantity of urine lost.

RECOGNISED INCONTINENCE

This part of the study was carried out in the London boroughs and health districts of Brent and Harrow. The relevant agencies were provided with the survey definition of incontinence and asked to provide the age, sex, address, and details of the type of incontinence (urine or faeces, or both) in the patients under their care. We received notifications from each agency for a year between 1976 and 1979, not all agencies coming into the study at the same time. The sources concerned included community nurses, old people's homes, geriatric wards of two district general hospitals, long-stay geriatric wards, psychiatric wards, hospitals and homes for the mentally handicapped, day centres, the Multiple Sclerosis Society, Spina Bifida Society, ordinary and special schools, and the pad and laundry services. We confined this study of recognised incontinence to people aged 15 and over. As the London boroughs of Brent and Harrow are not coterminus with the health districts we used population estimates for both to define a total borough and health district population,[12] which we used to calculate the prevalence of recognised incontinence in different age and sex groups.