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Comparison of nifedipine and propranolol as second line agent for hypertension in black Kenyans

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Nifedipine is reported to be particularly effective as an antihypertensive agent in low renin hypertension.¹ Because of the predominance of low renin hypertension among black Kenyan patients we compared the efficacy of propranolol plus diuretic, a standard treatment in Africa,² with nifedipine plus diuretic in Kenyan patients whose blood pressure was not controlled by diuretic treatment.

Patients, methods, and results

Thirty seven black Kenyans aged 30-69 attending a hospital clinic for hypertension were admitted to this double blind crossover trial. All treatment was withdrawn for a minimum of two weeks, after which inclusion in the trial depended on a diastolic blood pressure >105 mm Hg. This was followed by four weeks of treatment with a diuretic (hydrochlorothiazide 25 mg once daily), when those whose diastolic blood pressure fell below 90 mm Hg were withdrawn from the trial. Patients were then randomly allocated, in balanced blocks of four, to six weeks' treatment with either diuretic plus slow release nifedipine 20 mg twice daily or diuretic plus propranolol 80 mg twice daily. After another four weeks of treatment with diuretic alone the study treatments were crossed over.

Blood pressure was measured with a random zero sphygmomanometer by one of three observers whose technique had been standardised beforehand. At each visit blood pressure was recorded twice after five minutes' lying down, a radial pulse being measured between readings, and blood pressure and radial pulse were recorded after two minutes' standing. Patients were seen every two weeks throughout the trial. At the

start of the trial and at the end of each stage patients were weighed and full biochemical blood screens, including plasma renin activity, were carried out. Plasma renin activity was estimated (after standardised sampling) by radioimmunoassay of angiotensin I generated by incubating plasma for four hours. Results were analysed with Student's *t* test for paired data and Hills and Armitage's method for analysing data from crossover trials.³

Five patients were withdrawn after responding to diuretic treatment alone. Another patient withdrew because of work commitments, and two were withdrawn while taking propranolol (one patient's diastolic blood pressure rose above 125 mm Hg and one had symptoms suggesting heart failure). Of the 29 remaining patients, 16 initially took nifedipine plus diuretic. This combination produced significantly lower systolic and diastolic blood pressures than propranolol plus diuretic (*p* < 0.05) (table). Both combinations of drugs significantly reduced blood pressure compared with diuretic alone (*p* < 0.05).

There were no significant changes in the patients' mean weight and serum creatinine and sodium concentrations throughout the trial. Serum uric acid and blood urea concentrations rose and serum potassium fell significantly during diuretic treatment, suggesting good compliance (confirmed by pill counts and the changes in pulse rates). Plasma renin activity was low and changed with treatment (table). Twenty two patients' lying mean arterial blood pressure and 19 patients' standing mean arterial blood pressure fell more with nifedipine than with propranolol. Although those whose blood pressure fell more when nifedipine was added to diuretic had a lower mean plasma renin activity (0.47 (SD 0.60) nmol/l/h), these differences were not significant (*t* test). One patient was withdrawn because of side effects (see above), but, otherwise, side effects were few. No patients complained of severe headaches or flushing while taking nifedipine.

Comment

Both diuretics and calcium antagonists are effective and superior to β blockers in treating black hypertensive patients.⁴ We have previously shown diuretics plus nifedipine to be an effective combination for black

Mean (95% confidence interval) lying and standing blood pressure and pulse rate and median (range) plasma renin activity in 29 patients at each stage of trial

	Lying			Standing			Plasma renin activity (nmol/l/h)
	Blood pressure (mm Hg)		Pulse rate (beats/min)	Blood pressure (mm Hg)		Pulse rate (beats/min)	
	Systolic	Diastolic		Systolic	Diastolic		
1 Before treatment	180 (169 to 191)	114 (109 to 119)	70 (66 to 74)	175 (165 to 184)	122 (116 to 127)	79 (74 to 83)	0.02 (0.1-48)
2 After diuretic alone	167 (156 to 178)	106 (101 to 110)	73 (69 to 77)	163 (154 to 173)	112 (107 to 117)	83 (78 to 88)	0.29 (0.2-65)
3 After diuretic + propranolol	150 (140 to 159)	95 (91 to 99)	61 (57 to 65)	145 (135 to 156)	100 (96 to 104)	66 (61 to 70)	0.23 (0.6-15)
4 After diuretic + nifedipine	141 (135 to 147)	91 (87 to 95)	77 (72 to 82)	135 (129 to 141)	94 (89 to 99)	90 (84 to 95)	0.58 (0.76-9)
5 Difference between 3 and 4 averaged over periods	8.2* (0.6 to 15.8)	4.1* (0.2 to 8.0)	-15.9** (-20.4 to -11.4)	9.9* (0.5 to 19.3)	6.0* (0.3 to 11.7)	24.6*** (18.7 to 30.5)	0.66†

p* < 0.05, *p* < 0.01, ****p* < 0.001 (*z* test).³

†*p* < 0.01 for difference between medians (Mann-Whitney rank sum test).

hypertensive patients.⁵ In this study nifedipine plus diuretic lowered blood pressure more effectively than propranolol plus diuretic, which has previously been shown to be effective in black hypertensive patients.² Although comparisons of fixed doses of drugs have limitations, the doses of propranolol and nifedipine used were in the middle of their therapeutic ranges. Experience in Kenyan hypertension clinics confirms reports that black hypertensive patients have lower plasma renin activities than white patients. Perhaps because of this, we found nifedipine plus diuretic to be an excellent combination for treating hypertension among black Kenyan patients.

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Cancer mortality and atenolol treatment

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In the Medical Research Council's randomised trial of elderly hypertensive patients, men receiving atenolol had a higher death rate from cancer than those receiving diuretic or placebo.¹ This was not observed in women receiving atenolol, whose mortality was similar to those receiving diuretic and lower than those receiving placebo. The extra cancer deaths were apparently from lung cancer. A randomised trial of elderly hypertensive patients in primary care reported a non-significant excess of fatal cancers of the bronchus in the group given atenolol compared with the control group (an excess risk of 1.89, 95% confidence interval 0.88 to 4.08).² We therefore examined the relation between atenolol treatment and cancer in a large study of hypertensive patients.

Methods and results

The Department of Health hypertension care computing project is a longitudinal study of patients who attended one of five hospital hypertension clinics (95%) or four general practices (5%) in the United Kingdom during 1971-86, with continuing mortality follow up.^{3,4} Our analyses are based on deaths until 31 October 1990. Patients were placed in mutually exclusive groups according to type of antihypertensive treatment: any record of atenolol treatment irrespective of other concomitant treatments; any record of another β blocker irrespective of other concomitant treatments except atenolol; any record of methyldopa treatment irrespective of concomitant treatments

except any β blocker; or any record of diuretic treatment irrespective of other concomitant treatments except any β blocker or methyldopa.

Patient years of observation were measured from the first date of a prescription up to the patient's death or 31 October 1990. Mortalities from cancer (cancer given as the underlying cause of death) were calculated for each treatment and were adjusted for age by the direct method. We compared the risks between treatments with the Cox proportional hazards model, adjusting for age and smoking. We performed a nested case-control study of deaths from lung cancer, matching 79 cases (58 men and 21 women: 68 with lung cancer given as the underlying cause of death and 11 with any mention of lung cancer on the death certificate) with 154 controls. We also calculated standardised mortality ratios for all hypertensive patients.

There was no evidence for an adverse relation between atenolol and all cancers or lung cancer (table). Adjustment of the relative risks for smoking made little difference. Women taking atenolol appeared to be at lower risk of lung cancer, but the number of deaths was small and confidence intervals wide. There was no evidence that treatment had different effects on men and women. Blood pressure (whether treated or untreated, systolic or diastolic) showed no relation with deaths from all cancers or lung cancer.

A conditional multiple logistic regression analysis of our case-control study gave a relative risk from smoking of 4.2 (95% confidence interval 1.9 to 9.0, $p < 0.0004$) and from atenolol treatment of 0.9 (0.4 to 2.1, $p = 0.7$). The only excess standardised mortality ratio was for renal cancer (ICD codes 1890-9) with a value of 196 (107 to 328, $p = 0.03$) for men and women combined.

Comment

We found no evidence to support previous suggestions of an excess of cancer in men treated with

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Death rates adjusted for age and relative risks from cancer for different antihypertensive treatments

			Deaths from all cancers		Deaths from lung cancer		Relative risk (95% confidence interval) compared to atenolol				All other treatments combined	
Treatment	Mean (SD) age	Patient years of observation	Total	No/1000 patient years	Total	No/1000 patient years	All cancers	All cancers adjusted for smoking	Lung cancer	Lung cancer adjusted for smoking	All cancers	Lung cancer
Men												
Atenolol (n=2313)	52 (11)	17 409	85	5.6	20	1.3	1.0	1.0	1.0	1.0	0.9 (0.7 to 1.3)	1.2 (0.7 to 2.3)
Other β blockers (n=706)	52 (11)	8 660	42	4.6	10	1.3	0.8 (0.5 to 1.2)	0.8 (0.5 to 1.2)	1.1 (0.5 to 2.3)	1.1 (0.5 to 2.4)		
Methyldopa (n=316)	57 (11)	3 335	35	7.3	8	1.7	1.5 (1.0 to 2.2)	1.4 (0.9 to 2.2)	1.7 (0.7 to 4.0)	1.6 (0.6 to 3.9)		
Diuretic (n=570)	54 (12)	5 231	32	5.5	11	1.9	1.0 (0.7 to 1.5)	1.0 (0.6 to 1.5)	1.5 (0.7 to 3.2)	1.6 (0.7 to 3.5)		
Women												
Atenolol (n=2199)	53 (13)	17 350	57	3.7	5	0.4	1.0	1.0	1.0	1.0	0.9 (0.7 to 1.4)	2.5 (0.8 to 7.9)
Other β blockers (n=797)	53 (13)	9 420	42	4.4	6	0.6	1.0 (0.7 to 1.6)	1.0 (0.6 to 1.6)	2.7 (0.8 to 9.0)	3.0 (0.8 to 10.7)		
Methyldopa (n=383)	57 (13)	4 765	24	4.1	5	1.0	0.9 (0.5 to 1.6)	1.1 (0.6 to 1.9)	2.8 (0.7 to 10.8)	3.6 (0.9 to 15.2)		
Diuretic (n=755)	55 (14)	7 286	27	3.5	4	0.6	0.9 (0.6 to 1.4)	0.8 (0.5 to 1.3)	1.4 (0.4 to 5.5)	1.3 (0.3 to 6.0)		