Comparison of the antihypertensive effect of enalapril and propranolol in black South Africans

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Summary
Angiotensin-converting enzyme (ACE) inhibitors are useful antihypertensive agents. Enalapril maleate is a new ACE inhibitor with actions similar to those of captopril but with fewer side-effects. A study was conducted on 19 black South Africans with mild or moderate essential hypertension; enalapril was compared with propranolol as monotherapy or together with hydrochlorothiazide in a 1-year randomized, double-blind, parallel study. Neither enalapril nor propranolol alone produced consistent, significant reductions in blood pressure. There were no significant differences between the blood pressure responses to enalapril and to propranolol (either with or without hydrochlorothiazide). It is concluded that neither enalapril nor propranolol is effective as monotherapy in the treatment of hypertension in South African blacks, but that both require the addition of a thiazide diuretic.


During the last few years the side-effects and long-term metabolic consequences of thiazide diuretics and β-blockers have come under close scrutiny, in the context of their use as first-line agents in the treatment of hypertension. Thiazide diuretics cause an increase in plasma total cholesterol, low-density lipoprotein, cholesterol and triglyceride levels.1,2 β-Blockers, in addition to their well-known side-effects of bronchoconstriction and peripheral vasoconstriction, cause increased plasma total triglyceride and very-low-density lipoprotein levels and a decrease in high-density lipoprotein levels.3 These lipid and lipoprotein alterations have been implicated as risk factors for myocardial infarction.4 Thiazide diuretics also have a diabetogenic effect,5 increase plasma uric acid levels and induce hypokalaemia, which may increase the risk of ventricular arrhythmias.6,7 These problems, real or potential, have prompted an intensive search for reasonable alternatives to β-blockers and thiazide diuretics as first-step therapy for hypertension. One group of drugs which may be suitable is the angiotensin-converting enzyme (ACE) inhibitors.

The renin-angiotensin-aldosterone system is an important mechanism in the pathogenesis of hypertension.8 Renin is released by the kidneys, mainly in response to a decrease in arterial blood pressure. Renin acts on its substrate to produce angiotensin I, which is converted to angiotensin II by the action of ACE. Angiotensin II is a very potent vasoconstrictor, and also stimulates aldosterone release, resulting in sodium retention and an increase in plasma volume and blood pressure. Therefore, inhibition of ACE and thus decreased production of angiotensin II should be useful in the management of hypertension. ACE inhibitors act primarily as vasodilators, causing a reduction in total and renal vascular resistance without significantly changing cardiac output or heart rate.9

Captopril, one of the first ACE inhibitors, is an effective antihypertensive drug, at least as good as hydrochlorothiazide or propranolol and significantly better than placebo.10 However, at the doses used in earlier clinical trials there was a high incidence of side-effects, including taste alterations, rash and pruritus, proteinuria and neutropenia. More recent studies, using much lower doses of captopril, have shown a very low incidence of these side-effects, with no loss of efficacy.11-13 Enalapril maleate (MK-421) is a new ACE inhibitor with pharmacological actions similar to those of captopril.14-16 It lacks the free sulphydryl groups to which most of the undesirable adverse reactions to captopril have been attributed.16,17 Enalapril has been reported to be effective in the lowering of blood pressure in hypertensive patients and to be relatively free of side-effects — there has been no case of neutropenia, 1 case of proteinuria, 1 case of taste disturbance and 3 cases of drug-related skin rash among 2200 patients.18-21

There is known to be a poor blood pressure response in black hypertensive patients to drugs such as β-blockers and captopril which interfere with the renin-angiotensin-aldosterone system.22-25 This may partially be explained by the finding that black hypertensives commonly have 'low-renin' hypertension26 with lower plasma renin activity than white patients.27,28 We have compared the antihypertensive efficacy of enalapril and propranolol in black patients with mild-to-moderate essential hypertension.

Methods

Twenty-six black patients with essential hypertension were randomly selected from an outpatient and a factory population. The purpose of the trial was explained to each patient and informed consent was obtained. All antihypertensive therapy was withdrawn, and the patients were given one placebo tablet twice a day for 4 weeks in order to establish basal or pretreatment blood pressures, pulse rates and laboratory data. Only those patients aged 18 - 60 years, with an average untreated supine diastolic pressure of 90 - 120 mmHg at the end of weeks 2 and 4 of the placebo period, this differing by less than 10 mmHg at each visit, entered the treatment period.

Grounds for exclusion were evidence that the hypertension was secondary to a surgically remediable condition, signs of congestive cardiac failure, papilloedema, recent (6 months) myocardial infarction, recent (1 year) cerebrovascular accident or hypertensive encephalopathy, heart block or resting heart
rate less than 54/min, bronchial asthma, chronic obstructive pulmonary disease, treatment with monoamine oxidase inhibitors, appetite suppressants, oral contraceptives or any other drug known to affect blood pressure, renal failure (blood urea level > 10 mmol/l) or hepatic disease, and a history of drug allergies.

The supine diastolic blood pressure after 4 weeks on placebo alone was 91 - 100 mmHg in 17 patients, 101 - 110 mmHg in 4 and 111 - 120 mmHg in 5. The hypertension was classified as mild, moderate or severe according to an index29 derived from the blood pressure, the optic fundi, an ECG, a chest radiograph, urinalysis, the serum urea level and the cerebrovascular history. No patient in this study was classed as having severe hypertension using these criteria; all were in World Health Organization stages I or II.30 The age range was 32 - 60 years with a mean of 48.9 years for the enalapril group and 48.6 years for the propranolol group. The average weights were 78.2 kg and 76.4 kg respectively. There were 16 males and 10 females in the study.

Patients were randomly assigned to receive treatment with either enalapril (13 patients) or propranolol (13 patients) at the end of week 4 of the baseline period. Patients in the enalapril group received one 5 mg tablet in the morning and evening and patients in the propranolol group received one 40 mg tablet morning and evening.

The trial was divided into three parts, the first of which consisted of 12 weeks (weeks 0 - 12) on either enalapril or propranolol, titrated every 4 weeks to maximum doses of 20 mg enalapril twice daily or 120 mg propranolol twice daily to achieve a target blood pressure below 90 mmHg. The second part of the trial, which extended from weeks 14 to 26, consisted of either continuation of the current therapy (enalapril or propranolol) or the addition of 25 mg or (after 4 weeks) 50 mg hydrochlorothiazide to achieve a supine diastolic pressure of less than 90 mmHg. During the third part of the trial, which extended from weeks 28 to 48, no further increases in the dosage of hydrochlorothiazide or addition of other antihypertensive drugs were allowed, i.e. the patients were maintained on the therapy assigned during part 2.

Blood pressure and pulse rate were recorded at 2-weekly intervals during parts 1 and 2 of the trial and at 4-weekly intervals during part 3. Patients were seen at the same time of day by the same investigator. The arterial blood pressure (systolic and diastolic phase V) and pulse rate were measured with the patient recumbent after being supine for at least 10 minutes, and in a standing position 2 minutes after rising. Blood pressures were measured three times with an automated blood pressure recorder (Kontron-Searle Physiometrics) to minimize observer bias and digit preference. Body weight was recorded at each visit.

A careful clinical history was taken, physical examination, chest radiography and ECG were performed and complete laboratory investigations were carried out at the initial visit, at the end of the placebo period and at the end of each part of the trial, i.e. at weeks 12, 26 and 48. The complete laboratory investigation consisted of testing of the urine for protein, glucose, pH and specific gravity, microscopy and culture of the urine, measurement of the haemoglobin value, haematocrit, white cell count and differential count, and determination of the urea, creatinine, glucose, sodium, potassium, chloride, bicarbonate, SGOT, SGPT, alkaline phosphatase, bilirubin and uric acid levels, the total serum protein and serum albumin, cholesterol, calcium and phosphorus levels, and the antinuclear antibody titre.

Throughout the study, criteria for withdrawal from the trial were a pulse rate of less than 48/min, signs of heart failure, a plasma potassium level above 5.7 mmol/l or below 3.0 mmol/l, development of signs of renal failure, evidence of agranulocytosis or neutropenia, or any serious adverse experience.

Blood pressures and heart rates at the end of the 4th pretreatment placebo-controlled week were taken as reference values and compared with blood pressures and heart rates in subsequent weeks by a sequential paired-comparisons t-testing. All values were calculated as means and standard errors of means.

Results

Of the 26 patients who entered the trial, 7 were lost to follow-up during part 1.

Blood pressure

The results are summarized in Figs 1-3. The mean blood pressure at the end of the 4th pretreatment placebo-controlled week (week 0) was 156/96 ± 4/4 mmHg supine and 148/95 ± 4/3 mmHg standing for the enalapril group and 156/99 ± 3/2 mmHg supine and 143/96 ± 4/4 mmHg standing for the propranolol group. Basal supine and standing pressures for the two groups did not differ statistically.

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Fig. 1. Supine and standing systolic and diastolic blood pressures (mean ± SE) for the enalapril and propranolol groups during part 1 of the trial (weeks 0 - 12). Levels of statistical significance on all figures refer to a comparison of mean values v. those at week 0 by paired t-testing.

Fig. 2. Supine and standing systolic and diastolic blood pressures (mean ± SE) for the enalapril and propranolol groups during part 2 of the study (weeks 14-26 compared with placebo (week 0). The number of patients taking hydrochlorothiazide in addition to either enalapril or propranolol is also shown.
During part 1 of the trial (Fig. 1) the reduction in supine and standing systolic and diastolic pressures produced by enalapril was only significant at week 8, but the blood pressures achieved after 12 weeks were not significantly different from pretreatment values. The only significant decrease in the propranolol group was in supine diastolic pressure at week 10, but once again the final values achieved after 12 weeks were not significantly different from pretreatment values. In patients on enalapril and in those on propranolol the supine systolic blood pressure at the end of week 12 increased by 3 mmHg and decreased by 1 mmHg respectively, the standing systolic blood pressure increased by 6 mmHg and 7 mmHg respectively, the supine diastolic blood pressure increased by 3 mmHg and decreased by 4 mmHg respectively, and the standing diastolic blood pressure increased by 1 mmHg and decreased by 2 mmHg respectively. None of the corresponding measurements at the 12th week for the enalapril and propranolol groups differed significantly from each other at the 5% level (t-test between independent groups).

During part 2 of the trial (Fig. 2) there were significant reductions in the standing systolic blood pressure at weeks 20 and 26, in the supine systolic blood pressure at weeks 22 and 26, and in the standing diastolic blood pressure at weeks 22 and 26 in the enalapril-treated group. In the propranolol-treated group there were significant reductions in the supine systolic blood pressure at weeks 22 and 26 and in the supine and standing diastolic blood pressure at weeks 22, 24 and 26. The enalapril-treated group included 6 patients on treatment with hydrochlorothiazide by week 26, while 5 patients in the propranolol-treated group required hydrochlorothiazide by the 26th week. In the enalapril- and propranolol-treated groups values at the end of week 26 differed from baseline values as follows: the supine systolic blood pressure decreased by 18 mmHg and 13 mmHg respectively; the standing systolic blood pressure decreased by 15 mmHg and 12 mmHg respectively; the supine diastolic blood pressure decreased by 10 mmHg and 8 mmHg respectively; the supine diastolic blood pressure decreased by 10 mmHg in both groups; and the standing diastolic blood pressure decreased by 11 mmHg and 9 mmHg respectively. Once again corresponding measurements at the end of the trial period for the enalapril and propranolol groups did not differ significantly from each other.

Heart rate

There were no significant changes in heart rate in the enalapril-treated group throughout the study. In the propranolol-treated group, however, both the supine and standing heart rate decreased significantly from means of 72/min supine and 76/min standing to means of 62/min and 64/min respectively at the ends of weeks 12 and 26 and to 63/min and 66/min at the end of week 48.

Laboratory data

No significant changes in mean values for any laboratory data and no therapy-related abnormalities in any of the tests measured in any patient in either of the two treatment groups were noted. No electrocardiographic or radiological changes were noted in any of the patients.

Side-effects

No subject in the enalapril-treated group had any therapy-related complaints. Two patients on propranolol were withdrawn from the trial as a result of adverse reactions. One patient developed bronchospasm after 14 weeks on therapy and the other went into acute renal failure after 32 weeks on therapy. In spite of extensive investigation (unfortunately not including renal biopsy) the cause of the renal disease in the latter patient was never established, but it is unlikely that propranolol was responsible.

Discussion

During the first part of the study, in which the effects of enalapril and propranolol were compared in patients with mild-to-moderate essential hypertension, no significant change in blood pressure was observed with either drug. During the second and third parts of the study, in which hydrochlorothiazide was added to enalapril or propranolol if required, the blood pressure response was better. There were no significant differences between the blood pressure responses to enalapril and propranolol (either with or without hydrochlorothiazide). The mean supine diastolic blood pressure was significantly reduced in the patients receiving enalapril and hydrochlorothiazide at 4 out of 6 visits during the third part of the study, and at 3 out
of 6 visits in those receiving propranolol and hydrochlorothiazide.  

The present findings are in contrast with those of Bollaz et al., 16 Brunner et al., 17 de Leeuw et al. 20 and Nelson et al., 21 who found significant reductions in blood pressure in patients treated with enalapril, either alone 20 or in combination with hydrochlorothiazide. 21,22 Furthermore, enalapril has been found to be more effective than \( \beta \)-blockers in controlling mild-to-moderate hypertension. 22  

Our results may largely be due to the fact that the population group we studied (black South Africans) has been described as not responding to \( \beta \)-blocker therapy as well as South African Indian or white patients. 22,23 In a study on black South African patients, Seecd 24 found that blood pressure reduction was not significantly different with atenolol compared with placebo. In other studies conducted out on black Kenyan patients, 21 black Zimbabweans, 25 black Americans 26 and Jamaicans 27 there was no significant reduction in blood pressure with \( \beta \)-blockers compared with placebo. In a study on black patients in Texas 28 and in the Bahamas 26 diuretics were found to produce significantly greater reductions in blood pressure than \( \beta \)-blockers.  

The reason for the inadequate antihypertensive effect of \( \beta \)-blockers in black patients is uncertain, but it may be related to the mechanism of action of these drugs. It has been postulated that \( \beta \)-blockers decrease blood pressure by inhibiting renal renin release, 29 although this is not well established. \( \beta \)-blockers are generally more effective in 'high-renin' groups, 29 and high-renin hypertensives commonly have 'low-renin' hypertension. 26 In studies on Xhosa people in South Africa 30 as well as on a black West Indian community in the UK, 27 Sever et al. 31 found that black patients tended to have lower plasma renin activities than whites. These observations are in agreement with the work of other authors. 32,33 Explanations offered for the high incidence of 'low-renin' hypertension in the black population include a high salt intake, 43 an attenuated response of renin release to various stimuli, 34,35 a higher incidence of plasma volume expansion 26 and a true ethnic difference, i.e. a genetically determined low plasma renin activity. 26  

The lower plasma renin activity in black patients than in whites may account for the poor blood pressure response in the former group to drugs that interfere with the renin-angiotensin system. These drugs include \( \beta \)-blockers, as already discussed, as well as ACE inhibitors. Patients with low-renin hypertension would not be expected to respond to ACE inhibition. 42 Moser and Lunn 43 reported a study on responses to captopril and hydrochlorothiazide in 38 black hypertensives in the Bahamas and also reviewed other similar multicentre studies. They concluded that blood pressure in white patients responded significantly better to captopril than to placebo, and that captopril and hydrochlorothiazide produced approximately equal reductions in blood pressure. In black patients, however, only hydrochlorothiazide significantly reduced blood pressure, while the mean blood pressure response to captopril was only slightly better than that to placebo. In a study on the antihypertensive effect of enalapril, Chrysant et al. 25 concluded that white patients responded better to enalapril than did blacks.  

Our study therefore establishes that neither enalapril nor propranolol given alone is a consistently effective antihypertensive agent in black South Africans. The addition of a thiazide diuretic improves blood pressure control; however, we have no data — and the study was not designed — to establish whether these blood pressure responses are better than those which would have been obtained on a diuretic alone. Thiazide diuretics stimulate renin release, and it is therefore likely that thiazides and drugs which inhibit the renin-angiotensin system have an additive effect on blood pressure, and are therefore a rational combination.
Isoxicam and indomethacin in acute osteo-arthritis
A GP multicentre double-blind comparison

Summary
A study was conducted in general practice to assess the efficacy and safety of isoxicam 200 mg once daily compared with indomethacin 25 mg 3 times a day in the treatment of acute exacerbations of osteo-arthritis. The trial was conducted as a multicentre, double-blind, randomized parallel-group study with ‘dummy loading’ of the medications. Thirty-one general practitioners entered 309 patients in the study. Of these, 139 patients on isoxicam and 137 on indomethacin completed the treatment. The most common sites of osteo-arthritis were the knee (100 patients) and the hip (79 patients). On examination at 7 days and 14 days there was a significant improvement in both treatment groups. After 7 days the number of patients (18 on isoxicam and 20 on indomethacin) and the hip (79 patients). On examination at 7 days and 14 days there was a significant improvement in both treatment groups. After 7 days the number of patients (18 on isoxicam and 20 on indomethacin) and the hip (79 patients) experienced definite drug-related adverse reactions as against 19 in the indomethacin group. A total of 38 patients (16 on isoxicam and 20 on indomethacin) suffered probably drug-related effects. Isoxicam therefore appeared to be better tolerated than indomethacin.

Osteo-arthritis is a common condition in general practice. ‘Chronic rheumatism’ is said to be the commonest chronic illness in general practice in Great Britain.1 In a practice of 2,500 patients, approximately 100 per year will consult the doctor about this condition.1 Of these only 10 will have rheumatoid arthritis,2 illustrating the disparity of experience between specialized hospital clinics and general practice. This figure may be even higher since osteo-arthritis may be undiagnosed in conditions labelled as ‘sprains and strains’ (75 patients consulting per year) and ‘acute back’ (50 patients).2 It has been further estimated that some form of arthritis or rheumatism accounts for 20% of a family doctor’s time in the UK.2 Thus there is an ever-present need for medications to treat arthritis and musculoskeletal conditions in primary care.

The South African Academy of Family Practice/Primary Care Research Committee has as its policy that medications to be used in primary care should be researched in that situation (in particular controlled studies should be carried out before registration).14

Isoxicam is a new non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic activity. It is a benzo-thiazine derivative of the oxicam class of drugs which are enolic acids, as opposed to most NSAIDs which are carboxylic acids.

Pharmacokinetic studies have shown the drug to have a half-life of 30 hours, which permits a once-a-day dosage. It is slowly but completely metabolized and accumulation occurs until a steady-state plasma concentration is reached at 5-12 days.3 In studies in rheumatoid arthritis, osteo-arthritis, acute musculoskeletal disease, ankylosing spondylitis and gout, isoxicam has been shown to be effective and safe.4

Patients and methods
Thirty-one general practitioners (centres) in the Western Cape and central Natal regions participated in the study. All patients presenting to these practices with acute episodes of osteo-arthritis were eligible for the study subject to the principles of the Declaration of Helsinki and certain exclusions. Specific exclusion criteria included: (i) pregnancy; (ii) any other form of joint disease; (iii) active peptic ulcer; (iv) cardiorespiratory disease severe enough to interfere with everyday activities; (v) severe renal or hepatic dysfunction (blood urea level more than 70 mmol/l or serum glutamic oxalo-acetic transaminase level more than 70 U/l); (vi) use of oral anticoagulants; and (vii) a history of allergic reactions to aspirin or other NSAIDs.