Efficacy of potassium and magnesium in essential hypertension: a double blind, placebo controlled, crossover study

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Abstract

***Objective*—To evaluate the antihypertensive activity of potassium given alone or in combination with magnesium in patients with mild hypertension.**

***Design*—A double blind, randomised, placebo controlled, crossover trial of 32 weeks' duration.**

***Settings*—Cardiology outpatient department, Sassoon General Hospitals, Pune, India.**

***Patients*—37 Adults with mild hypertension (diastolic blood pressure <110 mm Hg).**

***Intervention*—Patients received either placebo or potassium 60 mmol/day alone or in combination with magnesium 20 mmol/day in a crossover design. No other drug treatment was allowed.**

***Measurements*—Blood pressure and heart rate assessed at weekly intervals and biochemical parameters at monthly intervals.**

***Results*—Potassium alone or in combination with magnesium produced a significant reduction in systolic and diastolic blood pressures ($p<0.001$) and a significant reduction in serum cholesterol concentration ($p<0.05$); other biochemical variables did not change. Magnesium did not have an additional effect. Urinary potassium excretion increased significantly in the groups who received potassium alone or in combination with magnesium. The drug was well tolerated and compliance was satisfactory.**

***Conclusion*—Potassium 60 mmol/day lowers arterial blood pressure in patients with mild hypertension. Giving magnesium as well has no added advantage.**

Introduction

High arterial blood pressure reduces life expectancy, and its consequences constitute the phenomenon of essential hypertension. Epidemiological studies have shown that cardiovascular risks increase in proportion to blood pressure,[1,2] and treating mild hypertension has been shown to reduce cardiovascular mortality and morbidity.[3] Several studies suggest that the prevalence of hypertension varies inversely with the dietary intake of potassium[4-6] and magnesium.[7] In patients with hypertension and in their normotensive relatives a genetic defect in the handling of electrolytes has been observed by some investigators.[8,9] Dietary supplementation of potassium[10-14] and magnesium[15,16] has been shown to have a variable effect in hypertensive subjects, and potassium depletion has led to an increase in blood pressure in healthy normotensive men.[17] The present study was undertaken in patients with mild hypertension to investigate further the beneficial effect of potassium alone and in combination with magnesium.

Patients and methods

Adult hypertensive men and women attending the cardiology unit in the department of medicine, Sassoon General Hospitals, were included in this study. Patients were observed for one month without any treatment, and only those with a supine diastolic blood pressure between 90 and 110 mm Hg without any underlying cause were allowed to enter the trial. Previous antihypertensive drug treatment, if any, was discontinued for four weeks before they entered the trial.

Patients with renal failure, liver failure, ischaemic heart disease, stroke, or evidence of hyperkalaemia were excluded. Inclusion was based on detailed history, physical examination, and laboratory investigations. During the four week run in period patients were examined every fortnight for measurements of blood pressure, heart rate, and body weight. Blood samples were taken for measurement of urea, creatinine, sodium, potassium, magnesium, calcium, and cholesterol concentrations. All patients provided two separate 24 hour urine samples during the baseline period and at the end of each treatment period for determining 24 hour sodium and potassium excretion.

STUDY DESIGN

After giving informed consent the patients were entered into a double blind, controlled, randomised, crossover trial of eight weeks' treatment with coded liquid preparations named Kesol A, Kesol B, and Kesol C. A 15 ml measure was provided along with the drug bottle; the patients were advised to take one measureful, diluted with a glassful of water (200 ml) twice a day after meals. The total duration of the trial including the run in period was 32 weeks, and the patients were switched to taking another preparation after eight weeks plus a two week washout period. Hence at the end of the trial every patient had received all three preparations for eight weeks each. The investigators and the patients were not aware of the composition of the liquids, which were decoded only after the completion of the trial as Kesol A, matching placebo; Kesol B, potassium 30 mmol/15 ml; Kesol C potassium 30 mmol/15 ml plus magnesium 10 mmol/15 ml. The sources of potassium and magnesium were potassium chloride and magnesium chloride conforming to the standards of Indian Pharmacopoeia.[18] All the liquids were identical in appearance and taste. The patients did not alter their usual diet or restrict sodium intake during the study. Weekly measurements of blood pressure were taken at the same time of day by the same investigator in the same room.

Phase V diastolic blood pressure was measured with a mercury sphygmomanometer from the left arm, after a five minute rest in the supine position or two minutes in the standing position. Heart rate was recorded at the same time. At the end of the fourth and eighth week of each treatment period and at the end of the washout period blood was collected for measurement of biochemical variables. At every fortnightly visit any side effects reported by the patient were recorded, and compliance with drug treatment was assessed by asking the patient to return the drug bottle. The study protocol had been approved by the ethical committee of the hospital.

STATISTICAL ANALYSIS

Data were processed on a personal computer with Minitab software for statistical analysis (Minitab,

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University Park, Pennsylvania, United States). Differences between treatment groups were compared with the paired t test. Multiple regression analysis was used to examine the relation of change in blood pressure during treatment to different variables.

Results

Thirty seven patients completed this trial: eight men and 29 women with a mean age of 49·9 (SD 7·6) years. Table I gives their clinical features, demographic data, and biochemical variables. The mean supine systolic blood pressure was 155·1 (12·2) mm Hg and diastolic blood pressure was 100·4 (4·2) mm Hg.

Blood pressure—Systolic and diastolic blood pressures decreased with potassium alone or in combination with magnesium. After the second week of treatment supine and standing diastolic blood pressures were significantly lower than those before treatment and those after two weeks of placebo ($p<0·001$). Supine and standing systolic blood pressures were significantly reduced by the fourth and eighth week after both the drug treatments when compared with placebo ($p<0·001$, table II). There was no significant difference, however, in the results obtained with potassium alone or in combination with magnesium (reduction by 16 mm Hg potassium and 12 mm Hg respectively). The difference in blood pressures among the treatment groups was not affected by the order in which the drugs were given.

Biochemical analysis—The treatments did not produce any significant change in serum concentrations of sodium, potassium, calcium, magnesium, urea, or creatinine, but patients treated with potassium alone or with magnesium had lower serum cholesterol concentrations at the eighth week than did the placebo group. The mean 24 hour urinary potassium excretion increased significantly in the group that received potassium, but the 24 hour urinary sodium excretion did not change.

Three patients given placebo, four given potassium, and four given potassium plus magnesium complained of pain in the abdomen and nausea, but this passed off and did not require withdrawal of treatment. Patients' compliance was satisfactory with all three preparations. Of 37 patients, 31 preferred potassium and six potassium plus magnesium ($p<0·05$). In the multivariate analysis no significant correlations were found between change in blood pressure during treatment and several other variables—age, baseline urinary excretion of sodium and potassium, change in urinary electrolyte concentration, and change in body weight.

TABLE I—*Clinical and biochemical features of 37 patients with mild hypertension on entry to study. Values are means (SD)*

Sex ratio (M:F)	8:29
Age (years)	49·9 (7·6)
Duration of hypertension (years)	8·6 (1·4)
Systolic blood pressure (mm Hg):	
Supine	155·1 (12·2)
Standing	154·1 (11·6)
Diastolic blood pressure (mm Hg):	
Supine	100·4 (4·2)
Standing	99·7 (6·7)
Serum concentrations:	
Sodium (mmol/l)	130·5 (4·3)
Potassium (mmol/l)	3·6 (0·42)
Calcium (mmol/l)	2·56 (0·13)
Magnesium (mmol/l)	0·88 (0·14)
Cholesterol (mmol/l)	7·5 (1·2)
Creatinine (μmol/l)	76·02 (11·44)
Urea (mmol/l)	4·9 (1·3)
Urine content (mmol/24 h):	
Sodium	196 (17)
Potassium	62 (4)

Discussion

Several trials of potassium supplements have been conducted in patients with essential hypertension, but only a few of these have used the crossover design.[10-14] Most of these were short term trials, and none included a combination of potassium and magnesium for assessing the effect of magnesium in the treatment of hypertension.

This study showed the antihypertensive activity of potassium alone and with magnesium. The antihypertensive activity of potassium 60 mmol/day started in the second week and continued till the end of treatment with the drug. Magnesium did not have an additional antihypertensive effect even when given in the dose of 20 mmol/day along with 60 mmol/day of potassium. In our preliminary studies we failed to observe any antihypertensive activity of magnesium alone, which was in line with earlier reports[16 19]; hence it was used only in combination with potassium.

This study indicates that magnesium does not add to the antihypertensive activity of potassium. Potassium induced less of a fall in diastolic blood pressure when given along with magnesium, but this difference was not significant. This difference may be caused by an interference in utilisation and turnover of electrolytes. Epidemiological surveys suggest that the incidence of hypertension is inversely related to intake of potassium,[4-6] and the lower incidence of hypertension among vegetarians is claimed to be due to a diet rich in potassium.[20] Several investigators have reported antihypertensive activity with oral supplementation with potassium,[21-23] and our results substantiate these findings. Twenty six of our patients were taking thiazide diuretics before entry into the trial. Hypokalaemia is a recognised metabolic consequence of diuretic treatment in many non-oedematous hypertensive patients,[24] and this may explain the lower range of baseline serum potassium concentrations in our patients.

The exact mechanisms of the antihypertensive activity of potassium is not known, but its vasodilator activity,[25 26] the increased loss of water and sodium,[27] suppression of secretion of renin and angiotensin,[28] stimulation of the sodium-potassium pump, and reduction in adrenergic tone,[29] may contribute to the activity.

TABLE II—*Effect of drug treatment on blood pressure (mm Hg) in 37 patients with mild hypertension. Values are means (SD)*

	Blood pressure with placebo		Blood pressure with potassium		Blood pressure with potassium plus magnesium	
	Supine	Standing	Supine	Standing	Supine	Standing
Day 0:						
Systolic	154·0 (11·7)	158·0 (10·7)	158·0 (12·6)	156·2 (12·6)	158·0 (12·6)	150·0 (9·6)
Diastolic	100·4 (4·2)	100·2 (4·5)	100·9 (3·5)	100·9 (4·9)	100·2 (4·9)	98·8 (5·1)
Day 14:						
Systolic	156·4 (12·5)	155·8 (12·6)	151·6 (10·9)	151·7 (11·3)	151·8 (10·1)	152·7 (9·7)
Diastolic	99·2 (4·8)	99·0 (5·3)	92·4 (4·3)*	92·4 (4·6)*	94·9 (6·1)**	94·6 (6·5)**
Day 28:						
Systolic	156·1 (13·1)	155·7 (12·6)	146·4 (9·2)*	146·7 (9·4)*	148·1 (9·9)**	148·3 (10·1)**
Diastolic	98·9 (5·1)	99·0 (4·8)	86·5 (3·5)*	87·1 (3·2)*	89·7 (3·1)**	89·8 (4·2)**
Day 56:						
Systolic	155·7 (11·4)	156·4 (10·9)	143·6 (10·8)*	143·2 (10·8)*	146·8 (9·8)**	146·1 (10·3)**
Diastolic	97·6 (5·2)	98·1 (5·8)	84·5 (3·5)*	84·9 (4·1)*	88·0 (5·0)**	87·6 (3·9)**

*$p<0·001$, placebo v potassium. **$p<0·001$, placebo v potassium plus magnesium.

TABLE III—*Effect of drug treatment on biochemical parameters at day 56 in 37 patients with mild hypertension. Values are means (SD)*

	Placebo	Potassium	Potassium plus magnesium
Serum concentration:			
Sodium (mmol/l)	131·5 (4·9)	132·3 (4·5)	132·5 (5·4)
Potassium (mmol/l)	3·6 (8·4)	3·7 (8·5)	3·8 (8·6)
Calcium (mmol/l)	2·59 (8·13)	(2·58) (0·14)	2·52 (0·14)
Magnesium (mmol/l)	0·86 (0·14)	0·94 (0·14)	0·94 (0·13)
Cholesterol (mmol/l)	7·4 (0·4)	6·0 (0·32)*	6·1 (0·3)*
Creatinine (μmol/l)	75·14 (14·15)	73·38 (6·96)	70·72 (10·06)
Urea (mmol/l)	4·7 (1·1)	4·5 (1·1)	4·6 (1·1)
Urine content (mmol/24h):			
Sodium	198 (24)	184 (22)	196 (17)
Potassium	60 (4)	82 (6)*	80 (5)*

*$p<0·05$.

Our results also suggest that treatment with potassium lowers serum cholesterol concentrations, which will be an added advantage. Hence, moderate daily supplements of potassium could be a valuable alternative to pharmacological methods for controlling mild hypertension, especially in those who are not willing or able to restrict salt intake. Retrospective data suggest that a high intake of potassium may decrease mortality associated with stroke,[30] and a long term study to explore the added advantages, if any, of treating hypertension with potassium is worthwhile.

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Transmission of hepatitis B virus by blood transfusion in Yaounde, Cameroon

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Studies conducted in developing countries on the cost effectiveness of routine testing for hepatitis B surface antigen in blood transfusion units have yielded conflicting results.[1,2] To see whether a national screening programme for hepatitis B virus would be justified in Cameroon we conducted a case-control study to determine the prevalence of the virus in patients who had received transfusions.

Patients, methods, and results

We studied 76 children with sickle cell disease (age range 1-14 (mean 8·5) years) who had received at least three transfusions of blood that had not been screened for markers of hepatitis B virus; the last transfusion had been given at least four months before the study. Control patients (age range 1-16 (7·7) years) were recruited from consecutive children who presented at the hospital day clinic with minor ailments such as malaria and minor cuts; they did not have sickle cell disease and had not received transfusions. Consent from their parents or guardians was sought before blood samples were obtained. They were matched for age and social state with the children with sickle cell disease. The control group comprised 62 children as 14 children with sickle cell disease could not be matched.

Serum samples were tested for hepatitis B surface antigen and antibody to hepatitis B surface antigen (Hepanostica kit, Organon Teknika, Turnhout, Belgium). Alanine aminotransferase activity was measured by a colorimetric method (BioMérieux, Marcy-l'Etoile, France); normal values for Yaounde are 5-55 IU/l. Data were analysed with the χ^2 test or Fisher's exact test as necessary with a Statworks program.

The table gives the results obtained in the two groups of children. Heptitis B surface antigen was detected in nine (12%) of those with sickle cell disease and seven (11%) of the controls (p=0·8677) and antibody to hepatitis B surface antigen in 23 (30%) and 19 (31%) respectively (p=0·8907). Five of the patients were positive for both the antigen and the antibody compared with one of the controls. Thus at least 27 (36%) of the children with sickle cell disease had been in contact with hepatitis B virus (95% confidence interval 25 to 47%) compared with 25 (40%) of the controls (28 to 53%). Thus the overall rate of exposure to the virus was about 38% (52/138; 29 to 46%) and the

Prevalence of markers of hepatitis B virus and alanine aminotransferase activities among 76 patients with sickle cell disease and 62 controls. Values are numbers (percentages) of patients

Patients	Mean age (years)	Positive for hepatitis B surface antigen	Positive for antibody to hepatitis B surface antigen	Alanine aminotransferase activity (IU/l)		
				≤55	56-100	>100
Sickle cell disease	8·5	9 (12)	23 (30)	71 (93)	1 (1)	4 (5)
Controls	7·7	7 (11)	19 (31)	56 (90)	4 (6)	2 (3)
Total	8·1	16 (12)	42 (30)	127 (92)	5 (4)	6 (4)