Potassium Chloride Lowers Blood Pressure and Causes Natriuresis in Older Patients with Hypertension

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ABSTRACT

Epidemiologic surveys, experimental studies in animals, and clinical trials in young and middle-aged patients with hypertension indicate that dietary potassium lowers blood pressure. The mechanism of the antihypertensive effect is not well defined. Variations in serum potassium within the physiologic range may directly affect vascular smooth muscle tone. Potassium may also influence the regulation of blood pressure through effects on sodium handling, aldosterone secretion, the renin/angiotensin system, renal kallikrein, eicosanoids, and atrial natriuretic peptide. This study was undertaken to confirm the blood pressure-lowering effect of potassium in older patients and to determine the mechanism of the antihypertensive effect. Twenty-two patients ≥60 yr of age were admitted to a Clinical Research Unit for 8 days after a 2-wk period free of antihypertensive medication. Patients were placed on an isocaloric diet containing 200 mmol/day of Na+, 70 mmol/day of K+, and 500 mg/day of Ca++. and were treated in a randomized, double-blinded manner with either potassium chloride (120 mmol/day) or placebo. After 4 days, patients were crossed over to the alternate treatment. Systolic blood pressure decreased 8.6 mm Hg (95% confidence interval −14.6, −2.6), and diastolic blood pressure decreased 4.0 mm Hg (−6.9, −1.0) during potassium chloride supplementation. There was no significant change in blood pressure during treatment with placebo. Serum K+ was 3.9 ± 0.1 mmol/L after 3 days of placebo and 4.3 ± 0.1 after 4 days of potassium chloride (P < 0.002). Urinary sodium excretion averaged 192 ± 11 mmol/day after placebo and 221 ± 8 after potassium treatment (P < 0.02). Potassium treatment was not associated with changes in supine or captopril-stimulated PRA, GFR, atrial natriuretic peptide level, or urinary excretion of thromboxane B2 or 6-keto-prostaglandin F1α. It was concluded that potassium chloride lowers blood pressure and increased sodium excretion in older patients with mild hypertension. The blood pressure effect may be due in part to potassium-induced natriuresis.

Key Words: Sodium, renin, atrial natriuretic peptide, eicosanoid, geriatric

Dietary potassium appears to be an important modulator of systemic blood pressure (1–3). Large population surveys indicate an inverse relationship between blood pressure and potassium intake within populations, with both lower mean blood pressure and a lower prevalence of hypertension among individuals with higher dietary potassium intake (4–8). In the United States, blacks tend to have higher blood pressure and lower potassium intake than whites (9,10). Furthermore, migration from an area of high potassium intake to an area of low potassium intake has been associated with an increase in blood pressure (11,12). These types of data suggest an association between low potassium intake and the risk of hypertension, but they cannot establish a therapeutic role for potassium in hypertension.

Experimental and clinical studies do suggest such a role. In several rat models of hypertension including the spontaneously hypertensive rat (13–16), the Dahl salt-sensitive rat (17), and the DOCA salt-loaded rat (18), high-potassium diets decrease blood pressure. In humans, we and others have documented a modest blood pressure-lowering effect of oral potassium in young and middle-aged patients with untreated hypertension (19–26). Additionally, potassium supplementation lowers blood pressure in hypertensive patients with diuretic-induced hypokalemia (27) and mineralocorticoid-induced hypertension (28). On the other hand, dietary potassium restriction increases blood pressure (29–31).

The mechanism of the blood pressure-lowering effect of potassium is unclear (1–3). Many studies have demonstrated short-term changes in sodium excretion after changes in dietary potassium (19,20, 22,29–32). Other possible antihypertensive mechanisms include direct vasodilatation (33), as well as
effects mediated by renin [34,35], kallikrein [36], atrial natriuretic peptide (ANP) [37], eicosanoids [37], divalent cation metabolism [2], and sympathetic nervous system activity [1,2].

We undertook the study presented here to determine if oral potassium supplements decrease blood pressure in older patients with hypertension and, if so, to determine the mechanism by which potassium supplementation lowers blood pressure. A racially mixed, older study population was chosen for several reasons. Previous work indicated a greater effect for black patients than white patients and for systolic pressure than diastolic pressure [24]. Because systolic blood pressure (SBP) tends to rise with age, we hypothesized that older patients would have a more significant blood pressure response. Furthermore, higher potassium intake has been associated with a lower risk of stroke [38], which is of particular relevance to this age group.

The results of this randomized, double-blind crossover study indicate that potassium chloride supplementation does lower blood pressure and cause increased sodium excretion in these patients; the decrease in blood pressure with potassium treatment is not associated with detectable changes in PRA, ANP level, eicosanoid excretion, or renal function.

METHODS

Study Population

We studied 22 patients of ≥60 yr of age with mild to moderate essential hypertension. Patients were recruited from the Piedmont Health Survey of the Elderly [39] and from those responding to newspaper advertisements. Hypertension was defined as SBP greater than 150 mm Hg, diastolic blood pressure (DBP) greater than 90 mm Hg, or any lower blood pressure if the patient were taking prescribed antihypertensive medication. Patients were excluded from participation for any of the following reasons: (1) severe hypertension (SBP greater than 200 mm Hg, DBP greater than 114 mm Hg, or history of malignant hypertension); (2) stroke, transient ischemic attack, or myocardial infarction within the previous 6 months; (3) active angina or congestive heart failure; (4) serum creatinine ≥1.8 mg/dL; or (5) contraindication to high potassium intake (active peptic ulcer, digoxin therapy, hyperkalemia, significant dysrhythmia). The protocol was approved by the Institutional Review Board, and written informed consent was obtained. After a 2-wk period free of all antihypertensive medications, patients were admitted to the clinical research unit (CRU) for 8 days.

Maneuver

Patients were treated with either microencapsulated potassium chloride (Micro-K Extencaps; A.H. Robins Company, Richmond, VA) (40 mmol orally three times daily) or with placebo capsules identical in appearance, according to a double-blinded randomization scheme. After 4 days, patients were crossed over to the alternate treatment. Patients were fed a 200-mmol sodium, 70-mmol potassium, 500-mg calcium diet with caloric value matched to their preadmission diet on the basis of diet history, height, weight, and activity level. The sequence and content of meals in the first period were repeated during Period 2. Patients were encouraged to continue to be active (not at bed rest) during their CRU stay.

Outcome Measures

The CRU nurse measured blood pressure at 10 a.m. and 5 p.m. each day. Blood pressure was measured with a mercury sphygmomanometer supine three times and again three times after the patient was standing for 5 min. Urine was collected during the final 24 h of each treatment period to quantify sodium and potassium excretion. The last six patients to complete the protocol also had urine collected on Days 2 and 3 of each period.

On the morning of the fourth day of each period, a spot urine specimen was collected for determination of thromboxane B2 (TXB2) and 6-keto-prostaglandin F1α (6-keto-PGF1α). Patients were then given a protein-free breakfast, and an i.v. catheter was placed for blood sampling. After the patient had been supine for 30 min, blood was drawn for determinations of serum chemistries, PRA, and ANP. Subsequently, the patient was given a 25-mg oral dose of captopril. One hour later, blood was again sampled for measurement of PRA.

The urinary clearance of [125I]iothalamate was then measured [40] as an index of GFR. Patients were given 15 mL/kg of water to drink over 60 min. Urine was collected by spontaneous voiding, and additional water was given to maintain urine flow >3 mL/min. After this urine flow rate was established, 0.2 μCi/kg of [125I]iothalamate was injected s.c. After an equilibration period of at least 60 min, the first clearance period was begun. Each study consisted of two consecutive clearance periods of 30 to 60 min. Plasma [125I]iothalamate concentration was determined by a gamma counter. Plasma values for each period were calculated as the log mean of the bracketing values at the beginning and end of each period. Clearances were calculated by using the standard formula UV/P, with each measurement representing the mean of two periods. The data were normalized for body surface area and were expressed as milliliters per minute per 1.73 square meter.

Laboratory Analysis

Serum and urine sodium, potassium, and creatinine, as well as serum glucose and lipids, were deter-
mined in a commercial reference laboratory by standard methods. PRA, ANP, and urine eicosanoids were determined by RIA. The PRA assay for angiotensin I and the RIA for ANP were performed by using commercial kits (PRA assay, Dupont, NEN Research Products, Boston, MA; ANP assay, Peninsula Laboratories, Belmont, CA). For the ANP assay, a known amount of radiolabeled standard was added to each sample and ANP was extracted from plasma with 90% ethanol/6% water/4% acetic acid on Sep-Pak C18 cartridges (Waters Associates, Inc., Milford, MA) conditioned with 4% acetic acid. Results are corrected for recovery and are expressed in picograms per milliliter.

Eicosanoids were extracted from urine with C18 cartridges as previously described (41) and were then separated by HPLC by using a Waters Model 840 system and a Pecosphere HS3-C18 column (Perkin Elmer, Norwalk, CT). Eicosanoids were eluted with a linear gradient from 100% 0.017 M orthophosphoric acid to 100% acetonitrile over 10 min at 3 mL/min. Appropriate fractions were collected on the basis of retention times of known standards. The eluate was dried under nitrogen and resuspended in RIA buffer. RIA for 6-keto-PGF₁, and TXB₂ were performed as previously described (42). Results are corrected for recovery and are expressed in picograms per milligram of creatinine.

Statistical Analysis

Data are expressed as the mean ± SE except where noted. On each day, the mean of all blood pressure

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics⁷</th>
<th></th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>66.5 ± 5.8</td>
</tr>
<tr>
<td>Sex</td>
<td>12 Male/9 Female</td>
</tr>
<tr>
<td>Race</td>
<td>15 White/6 Black</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>111 ± 9</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>4.1 ± 0.4</td>
</tr>
</tbody>
</table>

* Values are means ± SD.

TABLE 2. Blood pressures during treatment with placebo or potassium chloride (KCl)⁷

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 4</th>
<th>Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>149.8 ± 3.4</td>
<td>150.5 ± 4.8</td>
<td>0.7 (−6.9, 8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>DBP</td>
<td>86.1 ± 2.1</td>
<td>85.9 ± 2.6</td>
<td>−0.1 (−3.3, 3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>MAP</td>
<td>107.3 ± 2.3</td>
<td>107.4 ± 3.0</td>
<td>0.1 (−4.3, 4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>KCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>154.8 ± 2.9</td>
<td>146.2 ± 4.0</td>
<td>−8.6 (−14.6, −2.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>DBP</td>
<td>88.2 ± 2.0</td>
<td>84.2 ± 2.3</td>
<td>−4.0 (−6.9, −1.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>MAP</td>
<td>110.4 ± 2.0</td>
<td>104.9 ± 2.5</td>
<td>−5.5 (−9.3, −1.7)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

* Blood pressures (mm Hg) are means ± SE. Changes in blood pressure are means with 95% confidence interval. N = 21. NS, not significant.
shown in Figure 1. Although there was no change over time during placebo treatment, the mean MAP showed a downward trend from Day 1 during potassium supplementation. Blood pressure decreased by at least 5 mm Hg in 4 of 21 patients during placebo treatment and in 10 of 21 patients during potassium treatment. In the subgroup of six black patients, SBP decreased $4.2 \pm 9.1$ mm Hg, whereas DBP fell by $3.3 \pm 4.6$ mm Hg and MAP fell by $3.6 \pm 6.0$ mm Hg.

In a crossover study such as this, the outcome variable can potentially be influenced by time (period effect) and by the sequence of the treatments (43,45). Figure 2 shows the change in MAP from Day 1 to Day 4 of each period for those patients who received placebo first ($N = 10$) and those who received potassium chloride first ($N = 11$). These two groups were indistinguishable on the basis of their baseline characteristics, indicating successful randomization. Greater decreases in blood pressure tended to occur during the first rather than the second period ($P = 0.06$), regardless of treatment received. There was no effect of the sequence of treatment on the change in MAP ($P = 0.35$), which is determined by comparing the mean response (over both periods) of patients who received placebo first with that of the patients who received potassium first. The effect of potassium chloride versus placebo treatment can be appreciated by noting that during both periods, greater decreases in MAP occurred in patients treated with potassium. The effect of treatment alone (independent of time or sequence of treatment) was significant at the $P = 0.02$ level.

As shown in Table 3, serum potassium and urinary potassium excretion were significantly increased on the fourth day of potassium treatment, although no patient became hyperkalemic. Urinary sodium excretion was also significantly higher on the fourth day of potassium treatment. The time course of the natriuretic response is shown in Figure 3 for a subgroup of six patients. Four of these six patients received potassium treatment before placebo, which may account for the still elevated sodium excretion on Day 2 for the placebo group. For this small subgroup, sodium excretion was significantly higher ($P = 0.02$) on Day 3 of potassium treatment versus placebo. Body weight fell during both treatments ($P = 0.01$ for both treatments). There was, however, no significant difference in weight change between treatments (Table 3). There were no significant effects of potassium treatment on blood glucose, total cholesterol, high-density lipoprotein cholesterol, or triglycerides.
TABLE 3. Serum concentration and urinary excretion of potassium and sodium and weight change after 4 days of treatment with placebo or potassium chloride

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>KCl</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K⁺ (mmol/L)</td>
<td>3.9 ± 0.1</td>
<td>4.3 ± 0.1</td>
<td>0.002</td>
</tr>
<tr>
<td>UNaV (mmol/day)</td>
<td>70 ± 4</td>
<td>179 ± 4</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum Na⁺ (mmol/L)</td>
<td>138 ± 1</td>
<td>138 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>UNaO (mmol/day)</td>
<td>192 ± 11</td>
<td>221 ± 8</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight Change (kg)</td>
<td>−0.8 ± 0.3</td>
<td>−0.6 ± 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values are means ± SE. N = 21. NS, not significant. UNaV, urinary excretion of potassium; UNaO, urinary excretion of sodium.

Figure 3. Daily sodium excretion (UNaV) in a subgroup of six patients during treatment with placebo (open symbols) and potassium chloride (closed symbols). Mean ± SE.

Potassium chloride treatment was not associated with changes in any of the other outcome variables measured after 4 days of treatment (Table 4). ANP levels were numerically lower during potassium treatment, but the difference was not statistically significant. We detected no significant differences in PRA at baseline or after stimulation with captopril. There was also no differences in urinary TXB₂, urinary 6-keto-PGF₁α, or GFR.

DISCUSSION

In the study presented here, we report a blood pressure-lowering effect of potassium chloride in an older, racially mixed population with mild hypertension. The effect of potassium on blood pressure is evident after only 4 days of treatment. We also observed a trend for the effect of time on blood pressure; blood pressure tended to decrease more in the first treatment period than in the second. This is attributable to the tendency for blood pressure to fall upon hospitalization, independent of specific treatment (46). Despite the time effect, the magnitude of the treatment effect in our study (8.6 mm Hg mean decrease in SBP, 4.0 mm Hg mean decrease in DBP) is almost identical to that found in a recent meta-analysis of published trials of potassium in generally younger patients with hypertension (26).

In contrast, Grimm et al. (47) found no effect of dietary potassium chloride in sparing the need for standard drug therapy. Differences in patient population and sodium intake may explain the disparity. Almost all of the patients in the study of Grimm et al. were white males. Although the study presented here did not include enough black patients to allow racial comparisons, blacks (or perhaps any patients with salt-sensitive hypertension) may be more responsive to potassium. Patients in the study of Grimm et al. were on a relatively low sodium diet (100 mmol/day). When sodium intake is not restricted, studies in both rats (16) and humans (19,23,24) indicate a greater blood-pressure lowering effect of potassium.

In the study presented here, the blood pressure response was accompanied by a significant natri-
uresis, consistent with previous reports in humans (19,20,22,30). Although cumulative balance studies were not done, urinary sodium excretion exceeded sodium intake on the fourth day of potassium treatment, indicating that sodium balance was probably not achieved. Clearly, continued negative sodium balance cannot, and does not, continue indefinitely (48), but a previous randomized trial (24) with the same potassium dose showed that the blood pressure effect does persist at 8 wk.

It remains unclear whether the blood pressure effect is due totally to decreased intravascular volume resulting from the initial transient increase in sodium excretion. We probably underestimated the prestudy caloric intake of our patients, which resulted in a significant fall in weight during both treatment periods. The fact that weight did not fall to a greater extent after potassium treatment argues against relative volume depletion as the sole mechanism of the blood pressure effect. It is possible that net potassium retention and the resulting increase in serum potassium contributed to the blood pressure effect by direct vascular smooth muscle relaxation (33).

Potassium can potentially affect many other factors that are important in the regulation of blood pressure. These include modification of aldosterone secretion (49), renin release (34,35), renal eicosanoid (37,50) and renal kallikrein (36) production, divalent cation metabolism (2,51), and sympathetic nervous system activity (1,2). The effects of potassium on aldosterone secretion have been well documented. Increased plasma potassium concentration is a potent stimulus for aldosterone secretion (49,52), which mitigates the natriuretic effect of potassium.

Previous studies have shown no consistent effect of potassium on PRA (34,35). In the study presented here, there was no difference in PRA between placebo and potassium periods. We attempted to bring out a possible effect of potassium by stimulation of renin release by using converting enzyme inhibition, but again, no effect of potassium supplementation was evident. Although we cannot rule out a contribution by local vascular renin/angiotensin, it seems unlikely that the blood pressure response is directly mediated by renin.

We also observed no effect of potassium on renal TXB₂ and 6-keto-PGF₁α excretion. The relative production of eicosanoid vasoconstrictors to vasodilators may influence SBP in pregnancy-induced hypertension (53,54) and in the treatment of essential hypertension (55). Potassium depletion has been shown to increase renal TXA₂ production in rats (50). We hypothesized that potassium supplementation might suppress urinary thromboxane production, leading to a relative excess of the vasodilator eicosanoid prostacyclin. We found no such effect in our patients. The metabolites we measured are thought to reflect primarily renal sources (56). Our study does not rule out the possibility that platelet and endothelial eicosanoid production might be modified by potassium supplementation.

We speculated that the release of ANP might be increased by potassium supplementation, leading to both natriuresis and vasodilatation. In fact, ANP levels tended to be lower after potassium treatment, perhaps reflecting a decrease in atrial distention after potassium-induced natriuresis. Barden et al. (37) found a statistically significant decrease in ANP levels in normotensive females treated with potassium.

The dose-response relationship for the blood pressure-lowering effect of potassium is not yet known (1). Siani et al. (23) noted a significant reduction in blood pressure during treatment with 48 mmol/day of potassium chloride in pharmacologic form, but not with 24 mmol/day. Although increased potassium content of the diet without using pharmacologic supplements also lowers blood pressure (19,21), the optimal amount of potassium in relation to sodium is unclear.

The anion accompanying potassium has been chloride in almost all of the clinical trials of pharmacologic potassium. In 1928, Addison (57) reported an uncontrolled case series in which blood pressure decreased during treatment with the bromide and chloride salts of potassium as well. There is no evidence that chloride itself lowers blood pressure. Indeed, recent data suggest that chloride may contribute to salt (NaCl) sensitivity (58).

Increasing dietary potassium may decrease the risk of cardiovascular morbidity on a population basis, even though not all hypertensive patients respond with a decrease in blood pressure. In the rat (59) and in humans (38), there is an inverse association between dietary potassium and stroke risk, apparently independent of the effects of potassium intake on blood pressure. The mechanism of such a protective effect of potassium on the vasculature is unknown. We observed no changes in serum lipids during potassium treatment in this study, suggesting that if potassium does protect small arteries from damage, the beneficial effect may not be on the basis of changes in serum lipids.

In summary, we demonstrated a blood pressure-lowering effect of potassium chloride supplementation in an older population with mild hypertension, associated with increased sodium excretion. Although the mechanism of the effect is not entirely clear, altered sodium handling appears to be implicated. Determination of the potential utility of potassium supplementation as a therapeutic adjunct in older patients with essential hypertension awaits a long-term clinical trial.
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