DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF POTASSIUM CHLORIDE IN THE TREATMENT OF MILD HYPERTENSION

Laura P. Svetkey, William E. Yarger, John R. Feussner, Elizabeth DeLong, and Paul E. Klotman

SUMMARY Epidemiological and experimental data suggest blood pressure-lowering effects of dietary potassium. A randomized, double-blind clinical trial was used to assess blood pressure response to orally administered potassium, 120 mEq/day, and to placebo in 101 adults with mild hypertension. Blood pressure was measured with a random-zero sphygmomanometer every 2 weeks of this 8-week trial. Systolic blood pressure in the potassium-treated group decreased by 6.4 ± 13.7 (SD) mm Hg (p < 0.025) compared with 0.11 ± 13.0 mm Hg in the placebo-treated group (p = 0.96). Diastolic blood pressure in the potassium-treated group decreased by 4.1 ± 8.3 mm Hg (p < 0.05) compared with a 1.6 ± 6.5 mm Hg decrease in placebo-treated subjects (p = 0.09). Baseline blood pressure of potassium-treated subjects was unexpectedly higher than that of controls. After correcting for baseline variation, blood pressure still decreased 3.4/1.8 mm Hg more in potassium recipients than in placebo recipients (p = 0.14 and 0.24, respectively). Blood pressure decreased by 19/13 mm Hg in five blacks taking potassium versus a 1/0 mm Hg increase in seven blacks taking placebo. Compliance with the potassium regimen was 91.5% by pill count; only one subject discontinued treatment because of side effects. In conclusion, 120 mEq/day of microencapsulated potassium chloride was well tolerated in adults with mild hypertension. An antihypertensive effect of potassium cannot be ruled out despite the fact that there was no statistically significant difference between potassium-treated and placebo-treated subjects after adjustment for differences in baseline blood pressure. Systolic blood pressure was affected more than diastolic blood pressure. Blacks may be particularly sensitive to blood pressure-lowering effects of potassium chloride. A larger clinical trial stratified by baseline blood pressure and race is required. (Hypertension 9: 444-450, 1987)

Key Words • hypertension • potassium • therapy

Addison² stated in 1928 that "a potash (potassium) poor diet" causes hypertension and that "the giving of potassium chloride...is associated with a drop in blood pressure." Subsequent experimental, epidemiological, and clinical data support this claim.³-¹⁴

In experimental models of renovascular, genetic, and salt-sensitive hypertension, high potassium intake has been shown to attenuate the development of hypertension.²-⁶ Epidemiological surveys similarly imply potassium deficiency and suggest a protective effect of high potassium intake. An inverse relationship exists between blood pressure and dietary potassium when comparing both large populations⁷-⁹ and individuals within a population.⁸, ¹⁰-¹² Furthermore, movement from an area of low potassium intake to an area of high potassium intake is associated with a decrease in blood pressure.¹³-¹⁶

Evidence for a therapeutic effect of potassium in established hypertension has also been accumulating. Dietary and parenterally administered potassium lowers blood pressure in various animal models of hypertension.², ³, ¹⁷-²¹ Clinical trials suggest that oral potassium has a blood pressure-lowering effect in normal humans with or without a family history of hypertension.
POTASSIUM IN THE TREATMENT OF HYPERTENSION/Svetkey, et al. 445

and in patients with essential hypertension. Unfortunately, these studies are inconclusive. Small numbers of subjects, 1, 22, 23, 25-31, 32, 33, 34 small doses of potassium, 22-31 and unblinded 22-28, 31, 32 or uncontrolled 26, 27, 31-33 study design limit the usefulness of published human trials.

If confirmed, these findings could have an enormous impact on the prevention and treatment of hypertension. On the one hand, if increased potassium intake prevents hypertension, changes in dietary habits and food preservation could reduce the risk of hypertension and its consequent morbidity and mortality. Rose 35 has calculated that a 3 mm Hg decrease in the mean blood pressure of a population would substantially reduce the incidence of hypertension-related cardiovascular events in that population. In addition, if an antihypertensive effect of potassium in established hypertension is confirmed, dietary and pharmacological supplementation with potassium would enhance our ability to treat hypertension with low risk and at low expense. In addition, controversial pharmacotherapy for mild hypertension 36 could be replaced with dietary interventions.

We hypothesized that supplemental potassium chloride would significantly lower the blood pressure of ambulatory adults with mild hypertension. A double-blind, placebo-controlled randomized trial, using a large dose of oral potassium chloride (120 mEq/day) and a sample size of 100, was chosen to address this important issue.

Patients and Methods

Patient Selection

Ambulatory hypertensive adults were recruited from the Duke Hypertension Center and the Durham Veterans Administration Medical Center Hypertension Clinic. Subjects were excluded from entry if history or physical examination revealed any of the following: a single diastolic blood pressure exceeding 114 mm Hg, prior episode of malignant hypertension or hypertensive encephalopathy, angina, myocardial infarction within the previous 6 months, congestive heart failure, arrhythmia, cerebrovascular accident, transient ischemic attacks, or the presence of a terminal illness. Secondary hypertension was excluded by history, physical examination, serum electrolyte levels, and measurements of renal function (plasma creatinine concentration, creatinine clearance, and complete urinalysis). Subjects who might be at risk from high potassium intake were also excluded: those with renal insufficiency or baseline serum potassium values greater than 5.0 mEq/L, those taking digitalis preparations, and those with chronic diarrhea or history of ulcer disease. Pregnant and nursing women were excluded.

Termination Criteria

Criteria for removal from the study were average diastolic blood pressure on any clinic visit greater than 105 mm Hg, intolerable side effects, development of new target-organ damage, serum potassium greater than 5.5 mEq/L, serum creatinine greater than 1.5 mg/dl or doubled from baseline value, hemoglobin decreased by 2 g/dl, or evidence of gastrointestinal bleeding.
Statistical Analysis

The sample size (n = 100) was calculated to have an 80% power to detect a change in blood pressure of 5 mm Hg with significance at the 5% level (two-tailed). These calculations were based on an estimated standard deviation of multiple blood pressure readings in an individual of 10 mm Hg. A target sample size of 120 (60 in each treatment group) allowed for a 20% dropout rate. The actual dropout rate was 12.9%. Each blood pressure measurement consists of the average of three readings. Mean arterial pressure was calculated as \( (2 \times \text{diastolic blood pressure}) + \text{systolic blood pressure})/3 \). Changes in blood pressure within each treatment group were analyzed using the paired t test. Comparisons between the two treatment groups were made with a linear regression model that adjusted for differences in baseline blood pressure. Additional hypothesis tests investigated the interaction between treatment-group assignment. Because of this effect and the unexpected difference in initial systolic blood pressure; that is, the higher the blood pressure before a subject received the study drug, the greater the decrease in blood pressure in that subject, regardless of treatment-group assignment. Because of this effect and the unexpected difference in initial systolic blood pressure between the two groups (147.5 ± 13.1 mm Hg in the potassium-treated group vs 142.1 ± 14.3 mm Hg in the placebo-treated group), comparisons between treatment groups are reported both as mean changes in blood pressure in each treatment group and as residual changes after including the effect of baseline blood pressure in a linear regression model. Blood pressures at baseline and after 8 weeks of treatment are presented in Table 3. Only subjects completing the full 8-week protocol are included (n = 101), although three subjects receiving placebo were removed from the trial as a result of an increase in blood pressure above the protocol limit of 105 mm Hg, one subject experienced unexplained polycythemia, and one subject was advised by their personal physician to stop taking the study drug despite an average diastolic blood pressure of 92 mm Hg.

Side effects were generally mild (Table 2). Abdominal pain and "gas" were more common in the potassium-treated group (18 vs 9%, \( p = 0.18 \), and 20 vs 10%, \( p = 0.22 \), respectively), but, as noted, only one subject stopped taking potassium because of gastrointestinal symptoms.

No subject was removed from the study because of altered renal function (creatinine > 1.5 mg/dl), evidence of gastrointestinal bleeding (guaiac positive stool or decreased hemoglobin), or hyperkalemia (serum potassium > 5.6 mEq/L), although mean serum potassium increased slightly in the potassium-treated group (from 4.4 ± 0.4 to 4.7 ± 0.4 mEq/L; \( p = 0.0004 \) by paired t test). No significant changes in other laboratory parameters were observed during the 8-week study.

In both groups, change in blood pressure over the 8 weeks of observation was correlated with baseline blood pressure; that is, the higher the blood pressure before a subject received the study drug, the greater the decrease in blood pressure in that subject, regardless of treatment-group assignment. Because of this effect and the unexpected difference in initial systolic blood pressure between the two groups (147.5 ± 13.1 mm Hg in the potassium-treated group vs 142.1 ± 14.3 mm Hg in the placebo-treated group), comparisons between treatment groups are reported both as mean changes in blood pressure in each treatment group and as residual changes after including the effect of baseline blood pressure in a linear regression model. Blood pressures at baseline and after 8 weeks of treatment are presented in Table 3. Only subjects completing the full 8-week protocol are included (n = 101), although three subjects receiving placebo were removed from the trial as a result of an increase in blood pressure above the protocol limit of 105 mm Hg, one subject experienced unexplained polycythemia, and one subject was advised by their personal physician to stop taking the study drug despite an average diastolic blood pressure of 92 mm Hg.

### Table 1. Effects of 8 Weeks of Treatment with Potassium Supplementation or Placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Potassium (n = 59)</th>
<th>Placebo (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.8 ± 14.4</td>
<td>84.6 ± 16.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76.9 ± 14.1</td>
<td>74.8 ± 12.9</td>
</tr>
<tr>
<td>Compliance (%)</td>
<td>91.5 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>No. of dropouts</td>
<td>5(8)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. Percentage of dropouts is shown in parentheses.
Potassium was more or less effective in any group defined by age, sex, weight, severity of hypertension, or degree of compliance. However, Table 4 demonstrates that in the five blacks receiving potassium blood pressure decreased by 19 ± 24/13 ± 10 mm Hg compared with a 1 ± 7/0 ± 6 mm Hg increase in blood pressure in seven blacks taking placebo. Table 4 also shows that potassium-treated and placebo-treated blacks were similar in age and baseline plasma potassium levels. Body weight was initially higher in the potassium-treated blacks (p = 0.10), but it did not change in either group after 8 weeks of treatment.

Discussion

Several nutritional factors, such as sodium, calcium, magnesium, and fat, as well as potassium, have been linked to the pathogenesis and treatment of high blood pressure. Previous reports suggest that potassium balance may be related to blood pressure in two different ways. Potassium deficiency may be etiologically linked to the development of high blood pressure, and potassium supplementation may lower blood pressure in persons with established hypertension. The former effect of potassium, if confirmed, would encourage widespread nutritional interventions aimed at preventing hypertension. The latter effect suggests a possible role for dietary or pharmacological potassium in the treatment of hypertension.

Dietary potassium intake is linked to hypertension by population surveys in which the incidence of hypertension and its cardiovascular consequences are inversely related to the amount of dietary potassium consumed. Furthermore, movement from an area of high potassium intake to an area of low potassium intake is associated with increases in blood pressure. These associations generally are attributed to differences in sodium intake. However, in rural Japan, where sodium consumption is uniformly high, hypertension is less common in a village of apple farmers, where potassium intake is also high, than in a village with similar sodium but lower potassium intake. In general, persons who consume large quantities of potassium have lower blood pressure than persons with similar sodium intake but lower potassium consumption.

Table 3: Systolic, Diastolic, and Mean Arterial Pressure Response to 8 Weeks of Treatment with Potassium or Placebo

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>Adjusted difference</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potassium (n = 54)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Decrease</td>
<td>147.5 ± 13.1</td>
<td>141.1 ± 13.0</td>
<td>6.4 ± 13.7 (p = 0.025)</td>
<td>142.1 ± 14.3</td>
</tr>
<tr>
<td>Diastolic Decrease</td>
<td>95.2 ± 3.2</td>
<td>91.1 ± 8.3</td>
<td>4.1 ± 8.3 (p = 0.05)</td>
<td>94.1 ± 3.0</td>
</tr>
<tr>
<td>Mean arterial Decrease</td>
<td>112.6 ± 5.5</td>
<td>107.8 ± 8.5</td>
<td>4.8 ± 9.1 (p = 0.0005)</td>
<td>110.1 ± 5.3</td>
</tr>
</tbody>
</table>

**Placebo (n = 47)**

Values are means ± SD. The p values in parentheses represent paired t test comparisons within each treatment group. Adjusted differences are residual differences between the two treatment groups after adjusting for the effect of baseline blood pressure on change in blood pressure. Adjusted p values represent comparisons between the two treatment groups after adjusting for the effect of baseline blood pressure.
tension in blacks is more common and is associated with more severe target-organ damage than in whites, at least one large population survey shows that blacks ingest both less sodium and less potassium than whites.9

Animal models of hypertension also provide support for a role of potassium in the pathogenesis of hypertension.2,4 For instance, salt-sensitive rats on a high potassium, high sodium diet do not manifest the same degree of hypertension as similar rats on a low potassium, high sodium diet.2, 4 Similarly, in the two-kidney, one clip model of renovascular hypertension, potassium attenuates the degree of blood pressure elevation that develops after renal artery clipping.1 In humans as well, potassium may decrease the hypertensive response to increased sodium intake.3, 6

These experimental and epidemiological data suggest that potassium deficiency is etiological in hypertension and, conversely, that increased potassium intake protects against the development of hypertension. If these findings are confirmed, steps could be taken to increase the potassium intake of the population as a whole.

A related issue is the potential therapeutic role of potassium in persons with established hypertension. Potassium supplementation was associated with a small but statistically significant decrease in blood pressure in two double-blind, placebo-controlled crossover trials.25, 29 A blood pressure-lowering effect of potassium was found in these studies despite the small numbers of subjects studied (20 and 23, respectively), small doses of supplemental potassium (64 mEq/day in both studies), and the statistical hazards of crossover study design. In addition, Kaplan et al.30 reported improved blood pressure control in 16 hypertensive subjects with diuretic-induced hypokalemia when potassium was replete. However, the general applicability of the latter finding is unclear because of the small number of highly selected subjects studied. Potassium may have other effects on cardiovascular risk, independent of effects on blood pressure. Tobian et al.47 recently reported that stroke-prone spontaneously hypertensive rats fed a high potassium diet have a markedly decreased incidence of cerebrovascular events that occurs without any demonstrable effect on blood pressure.

Our study was designed to determine whether oral potassium supplementation is an efficacious and feasible therapeutic modality in an unselected group of adults with essential hypertension. After 8 weeks of 120 mEq per day of supplemental potassium or placebo, blood pressure decreased by an average of 6.4 ± 13.7/4.1 ± 8.3 mm Hg in the potassium-treated group, as contrasted with a negligible decrease in blood pressure in the placebo-treated group. An antihypertensive effect of potassium cannot be ruled out despite the fact that there were no statistically significant differences between treatment groups after adjusting for differences in baseline blood pressure. While small, the effect on mean blood pressure (a decrease of 4.8 ± 9.1 mm Hg compared with a decrease of 1.1 ± 7.7 mm Hg in the control group) may be clinically important. Rose35 has suggested that the prevalence and incidence of hypertension in a population are directly related to the mean blood pressure in that population. Furthermore, the small excess cardiovascular risk in the very large subset of the population with mild hypertension is translated into a large number of hypertension-related morbid events because that subset is so large. Therefore, Rose5 postulates that decreasing the mean blood pressure in a large population by as little as 3 mm Hg will reduce the number of persons with mild hypertension and therefore substantially reduce the number of people at excess risk of cardiovascular morbidity and mortality. Widespread increase in potassium consumption in this country might lead to a reduction in mean blood pressure of at least 3 mm Hg.

This study identifies subgroups in which further investigation of the effects of potassium on blood pressure is warranted. The effects of potassium on systolic blood pressure in the entire group and on systolic and diastolic blood pressure in blacks are particularly intriguing. Thirty-four percent of subjects had a 10 mm Hg or greater decrease in systolic blood pressure while taking supplemental potassium, as contrasted with 16% of subjects taking placebo. Because of the high prevalence of isolated systolic hypertension in the elderly, this subgroup might be particularly susceptible to an effect of potassium on systolic blood pressure. In addition, the dramatic decrease (19 ± 24/13 ± 10 mm Hg) in blood pressure in the small number of blacks taking potassium suggests that this subgroup may be particularly sensitive to the blood pressure-lowering effects of potassium. Although these subgroups were

### Table 4. Effects of 8 Weeks of Potassium or Placebo Therapy in Black Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>Change</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>156 ± 28</td>
<td>137 ± 14</td>
<td>−19 ± 24</td>
<td>136 ± 8</td>
<td>136 ± 10</td>
<td>1.0 ± 7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>98 ± 3</td>
<td>85 ± 12</td>
<td>−13 ± 10</td>
<td>96 ± 6</td>
<td>96 ± 7</td>
<td>0 ± 6</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48 ± 14</td>
<td>—</td>
<td>—</td>
<td>46 ± 13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Plasma K⁺ (mEq/L)</td>
<td>4.3 ± 0.2</td>
<td>—</td>
<td>—</td>
<td>4.5 ± 0.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88 ± 15</td>
<td>87 ± 16</td>
<td>—</td>
<td>80 ± 8</td>
<td>81 ± 8</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are means ± SD.
not specifically addressed by this study, our data suggest that future research should investigate the effect of supplemental potassium on hypertension in these two hypertensive groups.

Three placebo recipients were prematurely removed from the study protocol because of progression of hypertension to diastolic blood pressures in excess of 105 mm Hg. No potassium-treated subject exhibited this degree of hypertension during the study. High potassium intake has been reported to protect humans from the progression of hypertension.31-34 In the present study, however, the sample size was too small and the observation period too short to draw any conclusions about this issue.

The present study demonstrated that short-term ingestion of 120 mEq of potassium per day in the form of microencapsulated potassium chloride is feasible. Over 90% of potassium doses were taken, despite suggestions in the medical literature that this type of intervention is not acceptable to patients.48 In addition, potassium intake of 170 to 270 mEq daily (50–150 mEq in the average American diet49-50 plus 120 mEq in supplemental potassium) was well tolerated. Clinically evident irritation of gastric mucosa did not occur, nor was occult gastrointestinal bleeding detected. The incidence of gastrointestinal side effects and dropout rates were comparable in the two treatment groups. Serum potassium levels increased by an average of 0.23 ± 0.46 mEq/L in subjects taking potassium but remained within the normal range. No other laboratory abnormalities could be attributed to potassium ingestion.

In summary, previous uncontrolled clinical trials and small crossover studies have suggested that potassium chloride lowers blood pressure.1-22-24 The current study, performed in a randomized, double-blind fashion in a large group with well-documented mild essential hypertension, does not conclusively establish potassium as an antihypertensive agent. However, despite the lack of a statistically significant difference in blood pressure between treatment groups after adjusting for baseline pressures, a blood pressure–lowering effect of potassium cannot be ruled out. Systolic blood pressure may be particularly sensitive to blood pressure–lowering effects of potassium and should be investigated further. This study also suggests that the effect of potassium on blood pressure of blacks with essential hypertension needs further investigation. The effect of potassium on blood pressure in essential hypertension and the role of potassium in the pathogenesis of hypertension have broad implications for our understanding and management of high blood pressure. At this time it would be premature to make recommendations concerning the treatment or prevention of high blood pressure with dietary or pharmacological potassium. A larger clinical trial stratified a priori by baseline blood pressure and race, or limited to a particular subgroup such as systolic hypertension in the elderly, is required to resolve the question of therapeutic utility. Epidemiological surveys as well as prospective studies will determine whether public health efforts to increase dietary potassium intake might prevent the development of hypertension.

Acknowledgments
The authors thank Linda Scherich and Carol Aronson for assistance with preparation of the manuscript; James Fitzwilliam and William Stead, M.D., for assistance with data management; Lee Daly, P.A.-C., for assistance with patient care; and the A. H. Robins Pharmaceutical Company for its contribution to the support of this project.

References
1. Addison W. The uses of sodium chloride, potassium chloride, sodium bromide and potassium bromide in cases of arterial hypertension which are amenable to potassium chloride. Can Med Assoc J 1928;18:281-285
20. Aoki K, Yamori Y, Ooshima A, Okamoto K. Effects of high or
low sodium intake in spontaneously hypertensive rats. Jpn Circ J 1972;36:539–545


41. MacGregor GA. Sodium and potassium intake and blood pressure. Hypertension 1983;5(suppl III):III-79–III-84


Double-blind, placebo-controlled trial of potassium chloride in the treatment of mild hypertension.
L P Svetkey, W E Yarger, J R Feussner, E DeLong and P E Klotman

Hypertension. 1987;9:444-450
doi: 10.1161/01.HYP.9.5.444

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/9/5/444

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/