Effect of Short-Term Supplementation of Potassium Chloride and Potassium Citrate on Blood Pressure in Hypertensives

Feng J. He, Nirmala D. Markandu, Rosemary Coltart, Jeffrey Barron, Graham A. MacGregor

Abstract—Randomized trials have shown that increasing potassium intake lowers blood pressure. However, most previous trials used potassium chloride, whereas potassium in fruits and vegetables is not a chloride salt. It is unclear whether a nonchloride salt of potassium has a greater or lesser effect on blood pressure compared with potassium chloride. We performed a randomized crossover trial comparing potassium chloride with potassium citrate (96 mmol/d, each for 1 week) in 14 hypertensive individuals. At baseline, blood pressure was 151±16/93±7 mm Hg with a 24-hour urinary potassium of 81±24 mmol. During the randomized crossover part of the study, blood pressure was 140±12/88±7 mm Hg with potassium chloride (24-hour urinary potassium: 164±36 mmol) and 138±12/88±6 mm Hg with potassium citrate (24-hour urinary potassium: 160±33 mmol). These blood pressures were significantly lower compared with that at baseline; however, there was no significant difference in blood pressure between potassium chloride and potassium citrate, mean difference (95% confidence interval): 1.6 (−2.3 to 5.6) mm Hg for systolic and 0.6 (−2.4 to 3.7) mm Hg for diastolic. Our results, in conjunction with the evidence from many previous trials that potassium chloride supplementation seems to indicate that potassium citrate has a similar effect on blood pressure as potassium chloride. These results support other evidence for an increase in potassium intake and indicate that potassium does not need to be given in the form of chloride to lower blood pressure. Increasing the consumption of foods high in potassium is likely to have the same effect on blood pressure as potassium chloride. (Hypertension. 2005;45:571-574.)

Key Words: blood pressure ■ potassium

Much evidence suggests that potassium intake plays an important role in regulating blood pressure. Clinical trials of potassium supplementation have shown a significant blood pressure-lowering effect, particularly in individuals with high blood pressure. However, most previous trials have used chloride salt of potassium (ie, potassium chloride), which is convenient for making the study double-blinded using Slow-K (slow-release potassium chloride) versus Slow-K placebo. Potassium in fruits and vegetables is not a chloride salt, but rather a mixture of potassium phosphate, sulfate, citrate, and many organic anions including proteins. It is unclear whether a nonchloride salt of potassium has a greater or lesser effect on blood pressure compared with potassium chloride.

A number of studies have shown that increasing the consumption of fruits and vegetables has a significant effect on blood pressure. A comparison of the DASH (Dietary Approaches to Stop Hypertension) study to clinical trials of potassium chloride supplementation seems to indicate that the decline in blood pressure with increasing fruits and vegetables is similar to that found when it is performed by supplementing potassium chloride in individuals with elevated blood pressure. To further study the effect of different potassium salts on blood pressure, we carried out a randomized crossover trial comparing potassium chloride with potassium citrate.

Methods

Fourteen individuals with essential hypertension (systolic ≥140 mm Hg and/or diastolic ≥90 mm Hg) referred by local general practitioners entered and completed the study. Patients had not received previous treatment or treatment had been stopped for at least 4 weeks or 8 weeks for patients using diuretics before the study. We excluded individuals with secondary cause of hypertension, malignant hypertension, renal failure, ischemic heart disease, cerebrovascular disease, pregnancy, diabetes mellitus, or those who were using oral contraceptives or any other drugs. The study was approved by the local hospital ethics committee. All subjects gave written informed consent. There were 11 men (9 white) and 3 women (2 white). Mean age was 51±9 years and average body mass index was 29.9±5.0 (kg/m²).

The study was designed as a randomized crossover study. After baseline assessments, which included blood pressure, body weight,
plasma and urinary electrolytes, individuals were randomized to receive either potassium chloride, 96 mmol/d (12 Slow-K tablets), or potassium citrate, 96 mmol/d (34 mL potassium citrate liquid). After 1 week on this treatment, individuals then crossed over to receive the other treatment for 1 additional week. There was a 1-week washout period between the 2 treatment periods. All subjects were advised to maintain their dietary habits and lifestyle, and to avoid intense physical exercise throughout the study. Blood pressure was measured in the same arm using an automatic digital blood pressure monitor (Omron HEM-705CP) after 5-minute rest in sitting position.8 Three readings of blood pressure were taken at 1- to 2-minute intervals and the mean of 3 readings was used in the data analysis. Two 24-hour urine collections were obtained at entry to the study, and on day 7 of potassium chloride, and on day 7 of potassium citrate. These blood pressures were significantly lower with potassium citrate compared with that at baseline (Table). The 24-hour urinary noradrenaline or adrenaline was not significantly different between potassium chloride and potassium citrate, whereas urinary noradrenaline/creatinine ratio was significantly lower with potassium citrate compared with that with potassium chloride. Both 24-hour urinary dopamine and dopamine/creatinine ratio were significantly lower with potassium citrate compared with that with potassium chloride. However, none of the urinary catecholamines was significantly different from those at baseline (Table).

Discussion

Many previous randomized trials have shown that potassium chloride supplementation lowers blood pressure,3,4 and it has been suggested that potassium chloride should be used for potassium replacement in clinical practice.9 Our study suggests that potassium citrate has a similar effect on blood pressure as potassium chloride, indicating that potassium ion may have an effect on blood pressure independent of its conjugate anions. These results suggest that potassium does not need to be given with chloride for a blood pressure-lowering effect and an increase in the consumption of foods high in potassium, although not in the form of potassium chloride, may have a similar effect on blood pressure as potassium chloride supplementation.

Unlike most of the previous potassium supplementation trials,3 which were performed in individuals with a low potassium intake, eg, 60 mmol/d on average, our study was in individuals with a relatively high potassium intake as indicated by a baseline 24-hour urinary potassium excretion of 81 mmol. The results suggest that increasing potassium intake has a significant effect on blood pressure in these individuals.

Our finding that potassium chloride and potassium citrate have a similar effect on blood pressure is supported by the DASH study.6 In the DASH study, an increase in the consumption of fruits and vegetables with an increase in 24-hour urinary potassium caused a decline in blood pressure of 7/3 mm Hg in individuals with mildly elevated blood pressure.6 This decrease in blood pressure is similar to that found in a carefully controlled double-blind study of potas-

Blood pressure and 24-hour urinary potassium excretion at baseline, on day 7 of potassium chloride, and on day 7 of potassium citrate in 14 patients with essential hypertension.

Results

At baseline, blood pressure was 151 ± 16/93 ± 7 mm Hg with a 24-hour urinary potassium excretion of 81 ± 24 mmol. During the randomized crossover part of the study, blood pressure was 140 ± 12/88 ± 7 mm Hg with a 24-hour urinary potassium of 164 ± 36 mmol on day 7 of potassium chloride, and blood pressure was 138 ± 12/88 ± 6 mm Hg with a 24-hour urinary potassium of 160 ± 33 mmol on day 7 of potassium citrate. These blood pressures were significantly lower compared with that at baseline; however, there was no significant difference in blood pressure between potassium chloride and potassium citrate (Figure; mean difference: 95% confidence interval, 1.6; range, −2.3 to 5.6 mm Hg; P = 0.385 for systolic; range, −2.4 to 3.7 mm Hg; P = 0.653 for diastolic blood pressure).

Plasma potassium was 4.2 ± 0.3 mmol/L at baseline. During the randomized crossover part of the study, plasma potassium was 4.6 ± 0.3 mmol/L with potassium chloride and 4.6 ± 0.3 mmol/L with potassium citrate. These values were significantly higher compared with that at baseline (increased by 0.4 mmol/L); however, there was no significant difference between potassium chloride and potassium citrate in plasma potassium (Table). Plasma bicarbonate was significantly higher with potassium citrate compared with that with potassium chloride. With potassium citrate, there was a significant reduction in 24-hour urinary calcium and calcium/creatinine ratio, and a significant increase in urine pH, compared with that with potassium chloride or at baseline. There was no significant difference between potassium chloride and potassium citrate in pulse rate, or body weight, or plasma sodium, chloride, calcium, phosphate, creatinine, or 24-hour urinary volume, sodium, or creatinine excretion. These values were not significantly different from those at baseline either (Table).

There was no significant difference between potassium chloride and potassium citrate in plasma renin activity or aldosterone; however, plasma aldosterone was significantly higher with both potassium chloride and potassium citrate compared with that at baseline (Table).
Pulse Rate, Body Weight, and Laboratory Data at Baseline, on Day 7 of Potassium Chloride, and on Day 7 of Potassium Citrate in 14 Hypertensive Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Potassium Chloride</th>
<th>Potassium Citrate</th>
<th>Potassium Chloride vs Potassium Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate, beat/min</td>
<td>70±14</td>
<td>66±10</td>
<td>67±8</td>
<td>-1.4 (-5.5 to 2.8) 0.490</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>92.7±18.6</td>
<td>92.4±18.2</td>
<td>92.6±18.4</td>
<td>-0.2 (-0.9 to 0.5) 0.523</td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>139±2.4</td>
<td>139±2.1</td>
<td>138±2.0</td>
<td>0.4 (-0.1 to 1.0) 0.111</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.2±0.3</td>
<td>4.6±0.3‡</td>
<td>4.6±0.3§</td>
<td>0.01 (-0.13 to 0.16) 0.838</td>
</tr>
<tr>
<td>Chloride, mmol/L</td>
<td>102±2.3</td>
<td>103±3.3</td>
<td>102±2.4</td>
<td>0.9 (-0.9 to 2.7) 0.282</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>27±2.3</td>
<td>27±2.9</td>
<td>29±2.2*</td>
<td>-2.0 (-4.0 to -0.03) 0.047</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.34±0.10</td>
<td>2.30±0.11</td>
<td>2.31±0.13</td>
<td>-0.01 (-0.07 to 0.05) 0.694</td>
</tr>
<tr>
<td>Phosphate, mmol/L</td>
<td>1.08±1.66</td>
<td>1.11±0.13</td>
<td>1.10±0.17</td>
<td>0.02 (-0.04 to 0.08) 0.526</td>
</tr>
<tr>
<td>Creatinine, umol/L</td>
<td>88±19</td>
<td>86±18</td>
<td>87±16</td>
<td>-1.1 (-4.1 to 1.9) 0.426</td>
</tr>
<tr>
<td>Renin activity, ng/mL per h</td>
<td>0.49±0.45</td>
<td>0.58±0.69</td>
<td>0.54±0.47</td>
<td>0.04 (-0.19 to 0.28) 0.706</td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td>351±144</td>
<td>442±165*</td>
<td>504±166†</td>
<td>-62 (-168 to 43) 0.223</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume, mL</td>
<td>1871±652</td>
<td>1886±809</td>
<td>2018±772</td>
<td>-132 (-384 to 120) 0.277</td>
</tr>
<tr>
<td>Sodium, mmol/24 h</td>
<td>161±69</td>
<td>139±52</td>
<td>145±65</td>
<td>-6 (-32 to 20) 0.627</td>
</tr>
<tr>
<td>Creatinine, mmol/24 h</td>
<td>16.1±4.4</td>
<td>15.4±5.2</td>
<td>16.0±5.3</td>
<td>-0.7 (-1.9 to 0.5) 0.246</td>
</tr>
<tr>
<td>Calcium, mmol/24 h</td>
<td>4.8±2.2</td>
<td>4.8±2.8</td>
<td>4.1±2.6*</td>
<td>0.7 (0.2 to 1.3) 0.008</td>
</tr>
<tr>
<td>Calcium/creatinine ratio</td>
<td>0.31±0.14</td>
<td>0.33±0.18</td>
<td>0.26±0.16*</td>
<td>0.06 (0.02 to 0.10) 0.003</td>
</tr>
<tr>
<td>pH</td>
<td>6.23±0.64</td>
<td>5.98±0.56</td>
<td>7.40±0.63‡</td>
<td>-1.4 (-1.89 to 0.95) &lt;0.001</td>
</tr>
<tr>
<td>Noradrenaline, nmol/24 h</td>
<td>228±75</td>
<td>266±89</td>
<td>232±81</td>
<td>34 (-14 to 81) 0.150</td>
</tr>
<tr>
<td>Noradrenaline/creatinine ratio, nmol/µmol</td>
<td>14.96±6.00</td>
<td>17.86±4.95</td>
<td>15.23±5.63</td>
<td>2.63 (0.03 to 5.23) 0.048</td>
</tr>
<tr>
<td>Adrenaline, nmol/24 h</td>
<td>27.4±10.2</td>
<td>25.6±9.7</td>
<td>26.4±11.4</td>
<td>-0.9 (-7.9 to 6.1) 0.795</td>
</tr>
<tr>
<td>Adrenaline/creatinine ratio, nmol/µmol</td>
<td>1.82±0.82</td>
<td>1.74±0.56</td>
<td>1.75±0.90</td>
<td>-0.01 (-0.57 to 0.54) 0.959</td>
</tr>
<tr>
<td>Dopamine (µmol/24h)</td>
<td>1847±584</td>
<td>1995±713</td>
<td>1710±565</td>
<td>284 (84 to 484) 0.009</td>
</tr>
<tr>
<td>Dopamine/creatinine ratio, nmol/µmol</td>
<td>117±33</td>
<td>132±38</td>
<td>109±24</td>
<td>23 (7 to 39) 0.007</td>
</tr>
</tbody>
</table>

*P<0.05; †P<0.01; ‡P<0.001 compared with baseline.

Our results are also supported by the study by Morris et al, who compared potassium bicarbonate with potassium chloride, and showed that these 2 potassium salts were equally effective in lowering blood pressure in individuals with high blood pressure. However, our finding is in contrast with the study by Overlack et al, who studied the effect of potassium chloride 120 mmol/d for 8 weeks and potassium citrate 120 mmol/d for 8 weeks in 25 patients with essential hypertension. They found a significant decline in blood pressure with potassium citrate, but no significant change in blood pressure with potassium chloride. The latter observation contrasted with most of the potassium chloride supplementation trials in hypertensive individuals. Another study by Mullen and O’Connor compared potassium chloride with potassium citrate in 24 normotensive individuals and showed that neither potassium salt had any significant effect on blood pressure. It is likely that this study is underpowered to detect a small change in blood pressure with potassium supplementation in normotensive individuals.

Our study also showed that potassium citrate had a significant effect on reducing urinary calcium and calcium/creatinine ratio. This is consistent with other studies that showed that a higher potassium intake was associated with a lower urinary calcium excretion and a higher bone mass. Because acid–base homeostasis also influences urinary calcium excretion and different potassium salts have different effects on acid–base balance, it is difficult to know whether the change in urinary calcium observed in the studies of potassium supplementation is caused by the change in potassium or acid–base balance. A number of studies by Lemann et al suggest that the effect of potassium on urinary calcium excretion may be independent of its effect on acid–base balance, but by giving a potassium salt as a citrate or bicarbonate, there is a greater effect in reducing urinary calcium and calcium/creatinine ratio compared with potassium chloride. From our study, it is unclear whether potassium ion has an independent effect on urinary calcium excretion and different potassium salts have different effects on acid–base balance, but by giving a potassium salt as a citrate or bicarbonate, there is a greater effect in reducing urinary calcium and calcium/creatinine ratio compared with potassium chloride.
potassium chloride. This is in agreement with the findings by Ball et al.\(^{20}\) who showed a decrease in urinary dopamine after oral sodium bicarbonate and an increase in urine dopamine with oral sodium, potassium, or ammonium chloride. A common mechanism is the alkalosis induced by potassium citrate or sodium bicarbonate and the alkalosis may reduce renal dopamine production. However, it is unclear how far the change in urinary dopamine would influence the effect of potassium on blood pressure.

The potential limitations of our study include: (1) the study was not double-blinded; however, the use of automatic digital blood pressure monitor could have eliminated the observer bias in the blood pressure measurement; (2) there was no placebo-controlled period; therefore, the placebo effect cannot be ruled out. (Interpretation of changes from baseline should be performed cautiously because of the potential for regression to the mean, especially for blood pressure because the trial enrolled persons with elevated blood pressure,); and (3) The number of individuals studied is small. With the sample size of 14, the study has a power of 90% to detect a difference of 5.9 mm Hg or more in systolic blood pressure between potassium chloride and potassium citrate, and a power of 80% to detect a difference of 5.1 mm Hg or more in systolic blood pressure, given a standard deviation of the difference of 6.8. A difference of 5 to 6 mm Hg in systolic blood pressure would be considered clinically significant. However, our study would be underpowered to detect a difference in systolic blood pressure of <5.1 mm Hg, which would be considered important from a population viewpoint. In view of these potential limitations, a larger double-blind placebo-controlled trial with a longer duration is underway to further study the effect of different potassium salts on blood pressure and also to study whether increasing potassium intake has other beneficial effects on human health,\(^2\) as suggested by epidemiological studies in humans and experimental studies in animals.

In conclusion, our study suggests that in patients with essential hypertension, potassium chloride and potassium citrate have a similar effect on blood pressure. These results support other evidence for an increase in potassium intake and indicate that potassium does not need to be given in the form of potassium chloride to lower blood pressure. Increasing the consumption of foods high in potassium is likely to have the same effect on blood pressure as potassium chloride.

### Perspectives

Many randomized trials have shown that potassium chloride supplementation lowers blood pressure. However, potassium in fruits and vegetables is not a chloride salt, but a mixture of potassium phosphate, sulfate, citrate, and many organic anions including proteins. Our study suggests that a nonchloride salt of potassium (potassium citrate) has a similar effect on blood pressure as potassium chloride. These results support other evidence for an increase in potassium intake and this would best be performed by an increase in fruit and vegetable consumption, which in themselves may have other beneficial effects on health independent of potassium intake.

### Acknowledgments

We thank Lawrence Ruddock for double-checking the data of this study. We also thank other staff of the Blood Pressure Unit, including clinicians, scientists, and technicians, for help with the study. We are grateful to Alliance Pharmaceuticals Ltd for providing Slow-K.

### References

Effect of Short-Term Supplementation of Potassium Chloride and Potassium Citrate on Blood Pressure in Hypertensives

Feng J. He, Nirmala D. Markandu, Rosemary Coltart, Jeffrey Barron and Graham A. MacGregor

Hypertension. 2005;45:571-574; originally published online February 21, 2005;
doi: 10.1161/01.HYP.0000158264.36590.19

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 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/45/4/571

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/