A comparison of the effects of chlorothiazide and of metolazone in the treatment of hypertension

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Summary

1. A cross-over study was done in twenty patients with hypertension to compare the effects of chlorothiazide (0.5 g twice daily) and metolazone (5 mg daily) in combination with other anti-hypertensive agents.

2. Compared with absence of diuretic therapy, chlorothiazide and metolazone both produced significantly lower blood pressures.

3. Blood pressures on metolazone tended to be lower than on chlorothiazide but this difference was not statistically significant.

4. Both diuretics significantly lowered serum potassium concentrations and total body potassium to a similar degree, but the serum potassium did not fall below the normal range in any patient and no potassium supplements were needed. No electrocardiographic changes suggestive of hypokalaemia were noted.

5. Small but significant increases in serum bicarbonate, calcium, urea and uric acid were observed with both diuretics.

6. Patient acceptance was excellent and no adverse effects were encountered.

Key words: chlorothiazide, diuretics, hypertension, metolazone, potassium, whole-body counting.

Introduction

Chlorothiazide has been widely used for the treatment of hypertension and with a dose of 0.5 g twice daily we have rarely needed potassium supplements to maintain normal serum potassium. Dietary sodium is not restricted in our patients.

Metolazone (7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-o-tolyl-6-quinazolinesulphonamide) is a derivative of quinethazone. Studies by Belair, Kaiser, Van Denburg, Borrelli, Lawlor, Panasevich & Yelnosky (1969) indicated that metolazone may be relatively potassium sparing. Puschett & Rastegar (1974) in acute studies in man concluded that metolazone was only minimally kaliuretic at the highest rates of sodium excretion. On the other hand, hypokalaemia has been named as a principal side effect of metolazone in ascitic patients (Hillenbrand & Sherlock, 1971) and kaliuresis in the absence of natriuresis has been reported with the use of metolazone in special cases (Lowenthal & Shear, 1971).

This study was designed to compare the effects of chlorothiazide and metolazone on the blood pressure, potassium status and serum biochemistry.

Methods

Subjects

Twenty patients who had received chlorothiazide (0.5 g twice daily) in conjunction with other anti-hypertensive agents for at least 6 months were included. All had had stable blood pressures and had had no change of drug therapy for 3 months. Patients with liver disease, active gout, unstable cardiovascular disease, insulin-dependent diabetes mellitus, serum creatinine over 0.3 mmol/l, history of poor drug compliance and women of child-bearing age were excluded. Informed consent was obtained.

Trial design

History-taking, physical examination and retinal...
examination were carried out at the first visit. An electrocardiograph and measurement of total body potassium at the Australian Radiation Laboratory were performed before the trial and at the end of each 12 weeks period. Blood pressure was measured in the lying and standing position with a London School of Hygiene Sphygmomanometer by a single physician.

The systolic blood pressure and diastolic pressure, taken at the disappearance point (Korotkoff phase 5), were recorded. The patients were allocated by the random number method to chlorothiazide (0.5 g twice daily) or metolazone (5 mg daily) for the next 12 weeks. Other anti-hypertensive drugs were continued unchanged throughout the trial. Patients were seen every 4 weeks. Laboratory tests, namely urinalysis, full blood examination, serum sodium, potassium, bicarbonate, urea, creatinine, albumin, calcium, phosphate, uric acid, total protein, bilirubin and alkaline phosphatase, were carried out at each visit and patients were questioned about adverse reactions. At the end of 12 weeks, patients received the second diuretic for the next 12 weeks. Patients were then taken off their diuretic and were seen weekly for the next 4 weeks, at the end of which all observations and investigations including total body potassium were repeated.

Total body potassium was determined with a whole-body monitor (Duggleby, 1969). SEM of the method was 1.2%.

**Statistical analysis**

Mean values of blood pressure, body weight and biochemical results for three visits on each diuretic and values at the pre-trial visit and at 4 weeks after cessation of diuretic therapy were used for calculation. Student's paired t-test was used to test significance (two-tailed).

**Results**

Twenty patients (fourteen males and six females) aged 24–70 years (mean 46 years), with mean weight of 78 kg and mean height of 162 cm, were admitted to the trial. Apart from one case each of polycystic kidney, corrected renal artery stenosis, analgesic nephropathy and previous glomerulonephritis, all had essential hypertension. Seventeen patients completed the trial. Two defaulted and one patient was admitted to hospital for an unrelated condition.

The results (Table 1) show that compared with the values without diuretic therapy (mean blood pressures 149/94 mmHg supine and 140/94 mmHg

<table>
<thead>
<tr>
<th></th>
<th>No diuretic</th>
<th>Chlorothiazide vs no diuretic(1)</th>
<th>Metolazone vs no diuretic(1)</th>
<th>Metolazone vs chlorothiazide(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine Systolic</td>
<td>149</td>
<td>3.9</td>
<td>-11.5***</td>
<td>-14.6***</td>
</tr>
<tr>
<td>Diastolic</td>
<td>94</td>
<td>2.5</td>
<td>-8.4**</td>
<td>-8.6**</td>
</tr>
<tr>
<td>Erect Systolic</td>
<td>140</td>
<td>2.7</td>
<td>-11.6**</td>
<td>-14.6***</td>
</tr>
<tr>
<td>Diastolic</td>
<td>94</td>
<td>2.8</td>
<td>-8.6**</td>
<td>-10.3**</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78</td>
<td>2.5</td>
<td>-1.11**</td>
<td>-1.53**</td>
</tr>
<tr>
<td>Total body potassium (g)</td>
<td>125.9</td>
<td>7.3</td>
<td>-8.05**</td>
<td>-5.98*</td>
</tr>
<tr>
<td>Total body potassium (g/kg)</td>
<td>1.61</td>
<td>0.07</td>
<td>-0.09*</td>
<td>-0.06*</td>
</tr>
<tr>
<td>Blood concn. (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>143</td>
<td>0.4</td>
<td>-0.03</td>
<td>0.54</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.9</td>
<td>0.07</td>
<td>-0.73***</td>
<td>-0.92***</td>
</tr>
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<td>Bicarbonate</td>
<td>25.3</td>
<td>0.5</td>
<td>1.88**</td>
<td>3.88***</td>
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<td>Creatinine</td>
<td>0.11</td>
<td>0.01</td>
<td>-0.002</td>
<td>0</td>
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<tr>
<td>Urea</td>
<td>6.4</td>
<td>0.38</td>
<td>0.9*</td>
<td>1.4***</td>
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<td>2.28</td>
<td>0.03</td>
<td>1.02**</td>
<td>0.16***</td>
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<tr>
<td>Phosphate</td>
<td>1.06</td>
<td>0.04</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.37</td>
<td>0.02</td>
<td>0.06**</td>
<td>0.10***</td>
</tr>
</tbody>
</table>

(1) Mean of paired difference.
Both chlorothiazide and metolazone produced significantly lower blood pressure, although there was a tendency for blood pressures to be lower during the metolazone phase.

There was a decrease in body weight in the diuretic phase.

There were significantly lower total body potassium and serum potassium concentrations in both diuretic phases. No significant difference in total body potassium was found between the two diuretic phases. There was a significantly lower serum potassium with metolazone than with chlorothiazide. Despite these significant changes the mean serum potassium concentrations were 4.3 and 4.08 mmol/l for chlorothiazide and metolazone respectively, and in no case was the serum potassium below 3.5 mmol/l.

Significant increases were observed in serum bicarbonate, urea, calcium and uric acid in the diuretic phases.

No significant change in urinalysis, blood picture or electrocardiogram was found.

Discussion

Fofiu, Mroczek, Davidov & Finnerty (1974), using metolazone in a similar dose, found it to be as kaliuretic as chlorthalidone (100 mg/day), and to produce hypokalaemia in 33% of patients studied. In our series, despite a statistically significant reduction in serum potassium and total body potassium, hypokalaemia was not encountered. This suggests that metolazone in the dose used produces a kaliuresis comparable with that of chlorothiazide, which has been shown to be relatively less kaliuretic than other diuretics such as chlorthalidone (Louis, Doyle, Dawborn & Johnston, 1973).

We have found reductions in total body potassium with both chlorothiazide and metolazone treatments. Anderson, Godfrey, Hill, Munro-Faure & Sheldon (1971), in their study comparing the effects of hydrochlorothiazide and of frusemide, found no significant reduction in total body potassium despite a lowering in serum potassium. We found no evidence of the antikaliuretic effect which has been reported in acute studies in man (Puschett & Rastegar, 1974).

Like many other diuretics, both chlorothiazide and metolazone produced increased serum bicarbonate, uric acid, urea and calcium.

Patient acceptance was good. Metolazone appears to be as effective as chlorothiazide in the treatment of hypertension with the possible added advantage of being a smaller tablet which is taken once a day.

Acknowledgment

Metolazone was generously supplied by Pennwalt Corp., U.S.A.

References


