Effects of hydrochlorothiazide plus sotalol on acute urinary electrolyte excretion in normal subjects

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Summary

Twenty-four-hour urinary outputs, total volume and urinary chloride (Cl), sodium (Na), potassium (K), calcium, magnesium (Mg), total inorganic phosphate and creatinine levels were measured in 12 biologically equivalent healthy volunteers given single oral doses of placebo, hydrochlorothiazide (HCTZ) 50 mg and a combination of HCTZ and sotalol (STL) 320 mg in a double-blind, random study.

HCTZ and HCTZ + STL increased urinary volume and Na, K, Cl, phosphate and Mg levels significantly and to a similar extent. Since HCTZ causes hyperkaliuresis and hypermagnesiuresis with or without simultaneous administration of STL, the latter does not change the acute effects of HCTZ in healthy subjects.

Diuretics are considered drugs of first choice in the treatment of arterial hypertension; however, these drugs have recognized deleterious effects, including somatic depletion of potassium (K)\(^{2,3}\) and magnesium (Mg)\(^{4,5}\) and derangements in carbohydrate, purine and lipid metabolism.\(^{6,7,10}\) Depletion of K is regarded as particularly important because, although it seldom develops during chronic diuretic treatment unless other causes of K deficiency are also present, serious cardiac arrhythmias may supervene. In addition, it has been suggested that K deficit contributes to the evolution and maintenance of elevated blood pressure,\(^{11}\) thus hampering the antihypertensive effect of diuretics. Several measures have been proposed to counteract the hyperkaliuretic effects of diuretics, including limitation of dietary sodium (Na) intake and the co-administration of K supplements or K-retaining diuretics such as amiloride, triamterene or spironolactone.\(^{5,4}\)

The idea that cardiac arrhythmias complicating prolonged diuretic therapy are usually due to K depletion has recently been challenged in support of the view that urinary Mg loss is the principal causative factor.\(^{2,4}\) Ionic K is actively pumped into myocardial cells irrespective of the serum K level, provided that normal activity of Na-K-ATPase is maintained.\(^{6}\) This active process depends upon an adequate intracellular concentration of Mg (acting as a co-factor to the enzyme) and is inhibited when Mg depletion occurs.\(^{5,12}\) Moreover, the myocardial concentration of free cytosolic Ca is increased by Mg depletion, further destabilizing the myocardial electrochemical balance.\(^{6,5}\)

The objective of this study was to determine whether the well-established hyperkaliuretic and hypermagnesiuretic effects of hydrochlorothiazide (HCTZ) 50 mg are modified by the co-administration of the β-adrenergic blocking agent sotalol (STL) 320 mg to healthy young volunteers.

Subjects and methods

Twelve healthy adult male students volunteered to participate in the study after a full explanation of its implications. All were Whites aged 18 - 22 years and none had taken any prescribed medication during the previous 2 months. None was obese or had any history of renal, cardiovascular or metabolic disorder. Smokers were not included in the study.

A standardized diet containing 130 - 160 mmol Na and 3,5-4 litres water (including 2,5 litres tap-water) was given on test days and during the preceding 24-hour control period. Subjects received placebo, HCTZ 50 mg and a combination of HCTZ 50 mg and STL 320 mg (presented in identical form) separately and in random order on 3 different treatment days at least 7 days apart. Medications were given at 08h00 with 100 ml tap-water. Volunteers were confined to a metabolic ward for the first 10 hours after administration of medication. Thereafter they were allowed to return home until 07h00 the following day. During the urine-collection period all exercise and ingestion of alcohol or caffeine and any medicine other than the trial material were forbidden.

On treatment days venous blood was drawn just before medication and 6 ± 1 h and 24 ± 1 h later for measurement of plasma concentrations of chloride (Cl), Na, K, total calcium (Ca), Mg, carbon dioxide (CO\(_2\)), total inorganic phosphate, creatinine and urate.

All laboratory analyses were carried out by technologists unaware of the protocol. All urine passed on control and treatment days was collected at 3, 6, 12 and 24 hours after dosing and analysed accordingly on treatment days. Urinary volume and contents of Cl, Na, K, Ca, Mg, total inorganic phosphate and creatinine were measured.

Solute concentrations in both urine and serum specimens were analysed as follows: the Na, K, Cl and total bicarbonate contents were measured by the ion-selective technique using a Nova 4 analyser. Total inorganic phosphate was measured colorimetrically with a Clinical Sciences kit. Ca and Mg concentrations were measured by atomic absorption using a Varian 275 instrument. Creatinine and urate were measured colorimetrically using Boehringer Mannheim kits. Colorimetric determinations were carried out on a Beckman 3 spectrophotometer.

Mathematical methods

The mean experimental values for urinary volume and solutes accumulated by the end of each period after administration were
fitted as functions of time by a mathematical model which has been described previously.10 Urinary flow was calculated and the time to maximal flow after administration evaluated via an iterative computer design.11

Standard statistical parametrical techniques, paired t test and linear correlation and regression were used. Normality of frequency distributions and homoscedasticity of sample variances were evaluated via the chi-square test and the F ratio respectively. All statistical tests were two-tailed and a P value of 0.05 was considered the limit of significance.

Results

No significant differences were detected in the 24-hour accumulated mean urinary output as regards volume and electrolytes after placebo and on control days.

Accumulated 24-hour excretions are shown in Table I.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>HCTZ</th>
<th>HCTZ + STL</th>
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<tbody>
<tr>
<td>Volume (l)</td>
<td>2.69 ± 0.12</td>
<td>3.34 ± 0.12**</td>
<td>3.13 ± 0.14*</td>
</tr>
<tr>
<td>Na (mmol)</td>
<td>146.4 ± 9.7</td>
<td>306.5 ± 12.8***</td>
<td>242.2 ± 16.7***</td>
</tr>
<tr>
<td>K (mmol)</td>
<td>55.8 ± 4.2</td>
<td>70.2 ± 3.4**</td>
<td>82.5 ± 4.9***</td>
</tr>
<tr>
<td>Cl (mmol)</td>
<td>184.2 ± 10.1</td>
<td>359.5 ± 13.4***</td>
<td>305.2 ± 15.0***</td>
</tr>
<tr>
<td>Mg (mmol)</td>
<td>5.15 ± 0.47</td>
<td>6.38 ± 0.41*</td>
<td>6.16 ± 0.44*</td>
</tr>
<tr>
<td>Ca (mmol)</td>
<td>4.46 ± 0.41</td>
<td>4.27 ± 0.34</td>
<td>3.89 ± 0.47</td>
</tr>
<tr>
<td>Phosphate</td>
<td>28.2 ± 1.0</td>
<td>33.1 ± 2.4*</td>
<td>33.0 ± 2.3*</td>
</tr>
<tr>
<td>Creatinine</td>
<td>19.1 ± 0.8</td>
<td>19.4 ± 1.0</td>
<td>19.2 ± 1.3</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SEM.

Significances of the differences with respect to the corresponding mean values on placebo:

*P<0.05;
**P<0.005;
***P<0.001.

Both active treatments caused significant increases in 24-hour urinary outputs in terms of volume and Cl, Na, K, phosphate and Mg content. Ca and creatinine excretions were unchanged.

The time courses for volume, Cl, Na and K practically coincided after HCTZ or HCTZ + STL, as revealed by the times to peak excretions after dosage which were calculated as 2.68, 1.95, 1.96 and 2.66 hours respectively after HCTZ and 3.17, 2.44, 2.45 and 2.90 hours respectively after HCTZ + STL. Peak excretions of Mg, phosphate and creatinine were delayed in relation to those of volume and the other electrolytes, occurring 4.11, 6.30 and 4.39 hours respectively after HCTZ and 4.83, 6.55 and 4.88 hours respectively after HCTZ + STL. These delays were less apparent (although still present) after placebo.

Serum values of the variables measured did not change in a clinically significant manner.

Discussion

The mathematical methods used for describing urinary flows have been discussed elsewhere.10,11,12 The fact that HCTZ + STL significantly increased urinary output in terms of volume and Cl, Na, K, Mg and phosphate levels confirms that the co-administration of STL 320 mg does not change the acute renal actions of HCTZ 50 mg, despite the fact that non-selective β-blocking agents usually reduce renal blood flow. This was possibly reflected by the finding that the time to peak excretion of all solutes was slightly longer after HCTZ + STL than after HCTZ alone.

Most antihypertensive diuretics tested under similar conditions so far (chlorthalidone,13 clorexolone14 and HCTZ11), cause significant urinary Mg and K losses. The present results from a small sample of healthy, biologically equivalent subjects indicate that the effect of a single dose of HCTZ + STL is indistinguishable from that of HCTZ in this regard.

If the preliminary findings reported in the present study are confirmed, prolonged daily treatment with HCTZ or HCTZ + STL could lead to clinically significant depletion of somatic Mg and K. Serum K and Mg levels should therefore be monitored and the institution of adequate prophylactic measures should be considered.15

Urinary volume and Cl, Na and K levels approximately coincided after both active preparations, but urinary Mg was delayed with respect to other urinary electrolytes, confirming studies indicating that excretion of this cation is not Cl- or Na-dependent but involves intervention by hormones other than aldosterone.5

Diuretics cause a rise in tissue catecholamine levels and Mg depletion which, in turn, further augment each other.8,12 Myocardial electrolytic imbalance due to a rise in catecholamine levels and Mg depletion is a likely determinant of cardiac arrhythmias.5-7 Whereas β-adrenergic blockade does not influence diuretic-induced Mg losses, some benefits may be obtained from the co-administration of these agents since β-blockers should moderate the catecholamine-mediated effects of diuretics.

The changes found in serum variables could be expected on the basis of established knowledge of the acute systemic effects of distal tubular diuretics.

REFERENCES