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SHORT COMMUNICATION

Acute Effect of Hydrochlorothiazide on Renal Calcium and Magnesium Handling in Postmenopausal Women

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Summary

A single 50 mg dose of hydrochlorothiazide (HCTZ) decreases the urinary excretion of calcium ($U_{Ca}V$), clearance (C_{Ca}) and fractional excretion (FE_{Ca}) of calcium. This is accompanied by an increase of total calcium and ionized calcium (Ca^{2+}) concentrations in the serum. On the other hand, HCTZ increases fractional excretion of magnesium (FE_{Mg}) and decreases serum Mg^{2+} concentrations. Moreover, HCTZ decreases markedly clearance of phosphate (C_{Pi}) and fractional excretion of phosphate (FE_{Pi}) and increases serum phosphate (P_i) concentrations in healthy postmenopausal women. It is concluded that intrinsic renal cellular control promptly uncouples calcium and magnesium tubular reabsorption even without K^+ depletion.

Key words

Calcium excretion • Magnesium excretion • Phosphate excretion • Hydrochlorothiazide • Intrinsic cellular control

Introduction

Thiazides inhibit kidney excretion of calcium by inhibiting Na^+, Cl^--cotransporter and secondary decrease of transmembrane potential, opening of voltage-operating Ca^{2+} channel which appears to be a limiting step of calcium resorption in the distal tubule (Bleich and Greger 1997). This inhibition is used for the prevention of renal recurrent calcium urolithiasis in patients with hypercalciuria (Lamberg and Kuhlback 1957, Yendt and Cohanim 1978) and notably in postmenopausal women to improve their calcium balance (Broulík and Pacovský 1991, Cauley *et al.* 1993). The popularity of this treatment increased after the discovery of osteoclast inhibition (Hall and Schaublein 1994, Bouthiauy *et al.* 1994) and osteoblast stimulation (Lau *et al.* 1996) by thiazides. In contrast to calcium retention, magnesium excretion is variable during acute thiazide administration (Ai-Ghamdi *et al.* 1994), while it is increased during long-term thiazide treatment (Ryan *et al.* 1984, Dai *et al.* 1997a). Kidney K^+ depletion has been suggested to cause hypermagnesiuria (Bleich and Greger 1997) and the combination of thiazides with K^+ sparing diuretics was recommended (Dai *et al.* 1997a). However, additional mechanisms participate in increased magnesiuria. Most of them have been studied in isolated tubules or immortalized kidney cells (Quamme 1997). However, the treatment of osteoporosis by HCTZ requires a better

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understanding of HCTZ action on mineral excretion by the kidney.

To evaluate the mechanisms of magnesium excretion without K^+ depletion, the effect of 50 mg of hydrochlorothiazide (HCTZ, Léčiva, Prague, Czech Republic) on mineral excretion was examined in 30 postmenopausal women with normal systemic blood pressure, kidney function and electrolyte balance (Table 1). Postmenopausal women were investigated because this is a group of patients with the highest risk of calcium and magnesium depletion and HCTZ is the only drug used to inhibit calcium urinary excretion. Moreover, postmenopausal women could be treated with HCTZ, which would enable to extend this acute study into the chronic stage in the future.

The mineral balance was examined for 24 h before and after HCTZ administration. Analyses were performed on Kodak Ektachem analyzer 700 (Eastman Kodak Co., Rochester, NY, USA) and the concentrations of Ca^{2+} and Mg^{2+} were assessed on an Electrolyte Analyzer NOVA 8 (Nova Biomedical, Waltham, MA, USA). The statistical analysis was performed by both the paired t-test and paired Wilcoxon tests.

Table 1. Pertinent data of postmenopausal women

Variable		Before	After	P
Systolic BP	(mm Hg)	137.8±3.3	127.8±4.1	<0.001
Diastolic BP	(mm Hg)	83.3±1.8	79.8±1.9	<0.01
Serum Na^+ concentration	(mmol/l)	145.3±0.6	144.8±0.5	
Urinary Na^+ concentration	(mmol/day)	190.6±10.8	229.2±13.0	<0.01
Serum K^+ concentration	(mmol/l)	4.3±0.1	4.7±0.2	<0.05
Urinary K^+ concentration	(mmol/day)	58.1±3.8	59.7±3.6	
Serum creatinine	(μmol/l)	76.1±2.3	79.9±2.6	<0.01
Creatinine clearance	(ml/s)	1.53±0.06	1.35±0.07	<0.01

Values are expressed as mean ± S.E.M.

A single dose of 50 mg HCTZ decreased the systemic blood pressure and increased Na^+ urinary excretion with no change in K^+ excretion. Serum Na^+ concentration did not change and K^+ concentration even increased. The clearance of endogenous creatinine decreased slightly with an increase of serum creatinine concentration (Table 1).

HCTZ markedly reduced $U_{Ca}V$, C_{Ca} and FE_{Ca} with a small increase of both total and ionized calcium concentrations (Table 2). C_{Mg} and FE_{Mg} increased by more than 50 % with an insignificant increase of urinary magnesium excretion and an insignificant change of total, but reduced serum Mg^{2+} concentration. Thus, the calcium and magnesium excretion uncoupling was evident though no K^+ depletion was present. FE_{Pi} decreased markedly with increased urinary phosphate excretion and enhanced serum P_i concentration. Thus, even the interaction of phosphate depletion with increased magnesium excretion could be excluded.

Various hormones, e.g. PTH, calcitonin, vasopressin and glucagon modulate the calcium and magnesium excretion. However, their effects act in the same direction (Quamme 1997), which was not the case in our study. The same is true for the membrane Ca^{2+}/Mg^{2+}-sensing receptor in the basolateral membrane of the thick ascending limb of Henle's loop and the distal convoluted tubule.

The changes of renal magnesium excretion are not simply due to changes in plasma or filtered magnesium and they develop in the course of several hours (Shafik and Quamme 1989, Quamme 1997). The tubular adaptation occurs within the thick ascending limb of Henle's loop and the distal tubule (Shafik and Quamme 1989, Quamme and Dai 1990, Dai *et al.* 1997b) and because of the lack of data on the mechanism of adaptation it was called just "intrinsic (kidney) cellular control" of magnesium resorption. It is the only known mechanism uncoupling calcium and magnesium excretion (Quamme 1997) and the presented human study is the first to confirm previous experimental studies.

Table 2. Mineral balance in postmenopausal women

Variable		Before	After	P
Serum Ca^{2+} concentration	(mmol/l)	1.16±0.03	1.26±0.02	<0.001
Serum calcium	(mmol/l)	2.30±0.02	2.37±0.02	<0.01
Urinary calcium	(mmol/day)	5.83±0.34	5.15±0.37	<0.02
Clearance of calcium	(ml/s)	0.029±0.002	0.025±0.002	<0.02
FE_{Ca}		0.021±0.002	0.019±0.001	<0.01
Serum Mg^{2+} concentration	(mmol/l)	0.49±0.03	0.48±0.01	<0.001
Serum Mg concentration	(mmol/l)	0.788±0.012	0.803±0.011	
Urinary Mg excretion	(mmol/day)	4.09±0.33	4.26±0.33	
Clearance of magnesium	(ml/s)	0.060±0.005	0.061±0.005	
FE_{Mg}		0.041±0.003	0.061±0.014	<0.001
Serum P_i	(mmol/l)	1.11±0.03	1.33±0.04	<0.001
Urinary P_i	(mmol/day)	20.25±1.62	20.52±1.62	<0.01
Clearance P_i	(ml/s)	0.28±0.02	0.19±0.02	<0.001
FE_{Pi}		0.179±0.013	0.135±0.010	<0.001

Values are expressed as mean ± S.E.M.

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