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Comparative effects of potassium chloride and bicarbonate on thiazide-induced reduction in urinary calcium excretion

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Comparative effects of potassium chloride and bicarbonate on thiazide-induced reduction in urinary calcium excretion.

Background. The chronic low-grade metabolic acidosis that occurs in various renal disorders and in normal people, and that is related both to dietary net acid load and age-related renal functional decline, may contribute to osteoporosis by increasing urine calcium excretion. Administration of potassium (K) alkali salts neutralizes acid and lowers urine calcium excretion. Urine calcium excretion also can be reduced by the administration of thiazide diuretics, which are often given with supplemental K to avoid hypokalemia. We determined whether the K alkali salt potassium bicarbonate ($KHCO_3$) and the thiazide diuretic hydrochlorothiazide (HCTZ) combined is more effective in reducing urinary calcium than $KHCO_3$ alone or HCTZ combined with the conventionally coadministered nonalkalinizing K salt potassium chloride (KCl).

Methods. Thirty-one healthy men and women aged 50 or greater were recruited for a four-week, double-blind, randomized study. After a baseline period of 10 days with three 24-hour urine and arterialized blood collections, subjects were randomized to receive either HCTZ (50 mg) plus potassium (60 mmol daily) as either the chloride or bicarbonate salt. Another 19 women received potassium bicarbonate (60 mmol) alone. After two weeks, triplicate collections of 24-hour urines and arterialized bloods were repeated.

Results. Urinary calcium excretion decreased significantly in all groups. $KHCO_3$ alone and HCTZ + KCl induced similar decreases (-0.70 ± 0.60 vs. -0.80 ± 1.0 mmol/day, respectively). Compared with those treatments, the combination of HCTZ + $KHCO_3$ induced more than a twofold greater decrease in urinary calcium excretion (-1.8 ± 1.2 mmol/day, $P < 0.05$). Both HCTZ + $KHCO_3$ and $KHCO_3$ alone reduced net acid excretion significantly ($P < 0.05$) to values of less than zero.

Conclusions. $KHCO_3$ was superior to KCl as an adjunct to HCTZ, inducing a twofold greater reduction in urine calcium excretion, and completely neutralizing endogenous acid production so as to correct the pre-existing mild metabolic acidosis that an acid-producing diet usually induces in older people. Accordingly, for reducing urine calcium excretion in stone disease and osteoporosis, the combination of HCTZ + $KHCO_3$ may be preferable to that of HCTZ + KCl.

Key words: acid-base balance, metabolic acidosis, osteoporosis, hydrochlorothiazide, renal stones.

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Metabolic acidosis has been shown in in vitro and in vivo studies both to dissolve bone directly and to increase osteoclast activity, which increases bone resorption, releasing skeletal calcium for renal excretion [1]. Metabolic acidosis also promotes bone resorption and renal calcium excretion by directly inhibiting renal tubular calcium reabsorption [2]. States of chronic metabolic acidosis, such as those accompanying renal tubular acidosis and uremia, are associated with low bone mineral density. However, otherwise healthy people can also have a chronic low-grade metabolic acidosis, expressed as a rise in steady-state blood hydrogen ion levels and a fall in steady-state plasma bicarbonate levels, which results from eating the typically high net acid-producing American diets and from the decline in renal function that accompanies increasing age [3, 4]. Neutralizing acidosis with potassium bicarbonate reduces bone resorption, presumably in part by direct effects on bone and in part by promoting renal retention of calcium [5].

Urinary calcium excretion ($U_{Ca}V$) in humans can also be reduced by the administration of thiazide diuretics, which have been found to improve bone mass [6–8] and to reduce fracture risk in older subjects [9–12]. Combined treatment with an alkalinizing salt of potassium and thiazide might then be particularly useful in preserving bone because of their additive effects in reducing urine calcium excretion and by the additional direct beneficial effect on bone of alkali administration. Coadministration of potassium with thiazides is appropriate, since thiazides usually increase renal potassium excretion, although potassium depletion is usually prevented or corrected by administration of the nonalkalinizing salt potassium chloride.

To our knowledge, the effect of coadministration of an alkalinizing salt of potassium on the magnitude of thiazide-induced reduction of $U_{Ca}V$ has been studied only in patients with hypercalciuric calcium nephrolithia-

sis. In such patients, no difference in urine calcium excretion was found comparing thiazide alone with thiazide plus potassium citrate [13, 14]. In rats treated with thiazide, the addition of potassium bicarbonate did not reduce urine calcium excretion further and appeared to block the hypocalciuric response to thiazide [15].

Patients with hypercalciuria and calcium nephrolithiasis may not be the ideal population to test whether thiazides can augment the hypocalciuric effect of alkalinizing potassium salts, since they have a pre-existing disorder of calcium metabolism and potential damage to the kidney that might alter their renal responses to hypocalciuric agents. Accordingly, in the present study, we examined the effect of combined thiazide and potassium bicarbonate on urine calcium excretion in otherwise healthy older subjects. We chose older men and women eating typical acid-producing diets, since such subjects are at higher risk for osteoporosis and have low-grade metabolic acidosis. In addition, we investigated whether the effect of combined thiazide and potassium bicarbonate is more effective in reducing urinary calcium than potassium bicarbonate alone or thiazide combined with the conventionally coadministered nonalkalinizing K salt potassium chloride.

METHODS

We compared the effect on renal calcium excretion of the combination of hydrochlorothiazide (HCTZ) and an alkalinizing salt of potassium, potassium bicarbonate, with that of the combination of hydrochlorothiazide and the nonalkalinizing salt potassium chloride. The study was a double-blind, randomized study in free-living subjects, comparing the effect of oral administration of 60 mEq (given as 20 mEq TID with meals) of either potassium chloride (KCl) or potassium bicarbonate ($KHCO_3$) in combination with 50 mg/day (given as 25 mg BID) of HCTZ. The HCTZ + KCl group comprised 13 subjects and the HCTZ + $KHCO_3$ group comprised 18 subjects. A third group of patients treated with 60 mmol/day $KHCO_3$ alone were studied for comparative purposes ($KHCO_3$ group, $N = 19$ subjects). The subjects remained on their self-selected diets throughout the study and were instructed not to change their customary dietary habits during the study. Baseline periods were 7 to 14 days, and the treatment periods were 14 days. In the two groups receiving HCTZ, subjects returned to clinic for blood collections and to submit 24-hour collections on three days during each of the two periods, with treatment period collections performed between days 7 and 14 of treatment. The $KHCO_3$ only group returned for collections only twice during baseline and treatment periods.

Although administration of $KHCO_3$ alone is known to reduce urine calcium excretion, for comparative purposes, we needed to know the magnitude of its effect under the same experimental conditions in which the combination of potassium bicarbonate and thiazide was tested, including subject characteristics, dose of potassium bicarbonate, and study design. This permitted us to determine whether the combined effect of thiazide and potassium bicarbonate was substantially different from that of potassium bicarbonate alone. Since potassium chloride is without effect on calcium excretion [16, 17], this design also permitted us to determine in humans whether the urine calcium-lowering effects of thiazide and potassium bicarbonate are additive. The latter question is important inasmuch as Goulding and McIntosh reported that in rats, potassium bicarbonate blocks the hypocalciuric effect of HCTZ [15].

Healthy men and women over the age of 50 years were recruited. The women were at least five-years postmenopausal and not on estrogen replacement. Exclusion criteria included the use of steroid hormones in the past two years, the use of bisphosphonates in the past five years, and any medical condition that increased bone turnover (immobilization, renal disease, metabolic disease, etc.).

Arterialized venous blood specimens were obtained without stasis, fist clenching, or exposure to air. Spontaneously voided urine specimens were maintained under mineral oil and were preserved with thymol. Urine calcium was determined by atomic absorption spectrophotometry. Plasma and urine total carbon dioxide content was determined by either manometry (using the Natelson microgasometer) or thermal conductivity (Corning CO_2 analyzer); the two methods have similar precision (Natelson, CV = 1.2%; Ericson, CV = 0.7%) and, within an examined range of values of total carbon dioxide content from 22 to 33 mmol/L, yield nearly identical values [$\Delta x = 0.1 \pm 0.5$ (SD) mmol/L; $N = 27$]. Plasma bicarbonate concentration and carbon dioxide tension were calculated from the measured values of blood pH and plasma carbon dioxide content utilizing the Henderson-Hasselbalch equation, where pK′ (6.1, 37°C) was corrected for pH and body temperature [18], and the solubility coefficient of carbon dioxide in plasma (0.0301, 37°C) was corrected for body temperature [18]. Blood pH values were also corrected for body temperature [18]. Urine bicarbonate concentration was calculated from the measured values of urine pH and carbon dioxide content using the Henderson-Hasselbalch equation, where the solubility coefficient of CO_2 is taken as 0.0309 and pK′ is corrected for ionic strength

$$pK' = 6.33 - 0.5([Na^+] + [K^+])^{1/2}$$

where Na^+ and K^+ concentrations are expressed in Eq/L. Net acid excretion (NAE) was calculated as the sum of the excretion rates of titratable acid and ammonium minus that of bicarbonate. Titratable acid concentration was determined by titration, and urine ammonium concentration

Table 1. Baseline values

Item	HCTZ + KCl	HCTZ + $KHCO_3$	$KHCO_3$
Age *years*	63 ± 6	61 ± 15	62 ± 7
Sex *M:F*	5:8	5:13	0:19
Weight *kg*	68 ± 16	72 ± 17	65 ± 8
Height *cm*	167 ± 12	169 ± 11	161 ± 7
Body mass index kg/m^2	24.2 ± 2.9	25.1 ± 3.7	25.2 ± 3.2
Blood pH	7.40 ± 0.01	7.41 ± 0.02	—
Blood PCO_2 *mm Hg*	40 ± 2	40 ± 3	—
Plasma HCO_3 *mEq/L*	24 ± 1	25 ± 2	—
Serum K *mmol/L*	4.3 ± 0.2	4.3 ± 0.3	4.3 ± 0.2
UNaV *mEq/d*	121 ± 52	127 ± 46	110 ± 30
UClV *mEq/d*	118 ± 40	119 ± 45	107 ± 28
UKV *mEq/d*	75 ± 19	63 ± 24	70 ± 32
UNAEV *mEq/d*	42 ± 20	43 ± 18	28 ± 14
UCaV *mmol/d*	4.0 ± 2.2	3.6 ± 2.5	3.6 ± 1.4
UPO4V *mmol/d*	9.1 ± 3.0	8.5 ± 3.0	8.6 ± 2.3
Cl_{Cr} *mL/min/1.73* m^2	86 ± 21	83 ± 13	76 ± 15

Table 2. Change from baseline

	ΔHCTZ + KCl (N = 13)	ΔHCTZ+ $KHCO_3$ (N = 18)	Δ$KHCO_3$ (N = 19)
Blood			
pH	0.03 ± 0.02[a]	0.04 ± 0.02[a]	nd
HCO_3 *mEq/L*	1.2 ± 1.4[a]	3.2 ± 1.2[a,b]	nd
K *mEq/L*	−0.1 ± 0.4[c,d]	−0.4 ± 0.2[a,b,d]	0.1 ± 0.3[b,c]
Urine			
K *mEq/d*	58 ± 21	46 ± 17	48 ± 23
Na *mEq/d*	13 ± 31	21 ± 36	−10 ± 41
Ca *mmol/d*	−0.80 ± 1.00[a]	−1.82 ± 1.15[a,b,d]	−0.70 ± 0.60[a]
NAE *mEq/d*	5 ± 19[c,d]	−52 ± 12[b,d]	−38 ± 19[b,c]

HCTZ, thiazide; KHCO3, potassium bicarbonate; KCl, potassium chloride; nd, not done

[a] $P < 0.05$ compared with baseline

[b] Different from HCTZ + KCl, $P < 0.05$

[c] Different from HCTZ + KHCO3, $P < 0.05$

[d] Different from KHCO3, $P < 0.05$.

was determined as previously described [5]. Net endogenous acid production was estimated from NAE.

Data points for each subject were the average of those obtained from the three initial and the two or three final blood and urine samples. For each variable for each subject, we computed the magnitude of change from baseline (that is, delta values) and then performed one-way analysis of variance (ANOVA) on those delta values to determine whether the mean delta values among the three treatment groups differed significantly. When the three treatment means were found to differ, we performed, post hoc, the Student–Newman–Keuls test for paired comparisons between groups to determine which means were significantly different from each other. The paired *t*-test was used to assess significant changes produced within groups. Data are reported as mean ± SD. All statistical analyses were done using Sigmastat (Jandel Inc., San Rafael, CA, USA).

All studies were approved by the University of California San Francisco Institutional Review Board.

RESULTS

At baseline, there was no significant difference in the 24-hour urinary excretion rates of sodium, potassium, or calcium among groups (Table 1). $U_{Ca}V$ was normal in all groups (average 3.7 ± 2.0 mmol/day). Subject compliance was measured by weekly pill counts and urinary potassium excretion. The increase in potassium excretion was consistent with the taking of 60 mEq of potassium per day, indicating that the subjects were highly compliant with the regimen (Table 2); there was no significant difference among groups.

Renal function, as measured by repeated 24-hour urine creatinine clearances (mL/min/1.73 m^2), was not significantly different among groups before treatment (Table 1) or within groups in response to treatment.

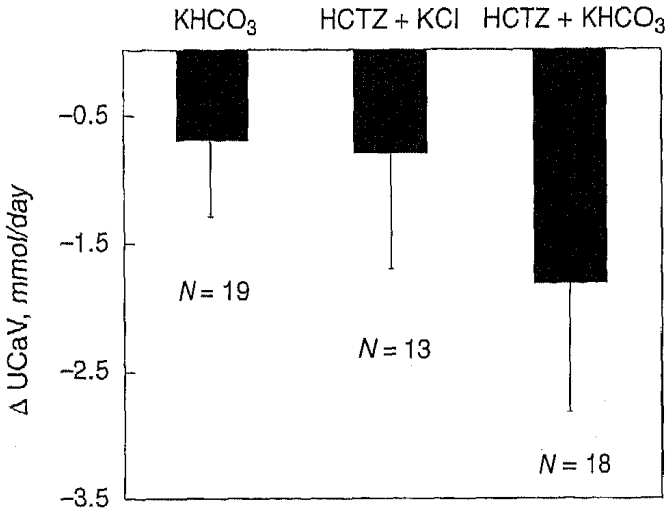

Fig. 1. Change in urine calcium excretion ($\Delta U_{Ca}V$) in the three treatment groups.

Urinary calcium excretion decreased significantly in all groups (Table 2 and Fig. 1). With $KHCO_3$ alone and HCTZ + KCl, $U_{Ca}V$ decreased to approximately the same extent (−0.70 ± 0.60 vs. −0.80 ± 1.00 mmol/day, $P < 0.001$ and $P < 0.002$, respectively). The combination of HCTZ + $KHCO_3$ was superior to either group in reducing $U_{Ca}V$ (−1.82 ± 1.24 mmol/day), inducing more than a twofold greater reduction in urine calcium excretion than did either HCTZ + KCl or $KHCO_3$ alone ($P < 0.05$).

There was a clear direct relationship between the decline in urine calcium excretion and the absolute value of the baseline urine calcium excretion ($P < 0.01$) in both groups treated with HCTZ, but not in the group treated with $KHCO_3$ alone. For the HCTZ + $KHCO_3$ group, the regression analysis was $\Delta U_{Ca}V = -20.6 - 0.325 \cdot U_{Ca}V$; for the HCTZ + KCl group, the regression analysis was $\Delta U_{Ca}V = +13.7 - 0.322 \cdot U_{Ca}V$. For each treatment group and for all three treatments groups combined, the magnitude of the change in urine Ca did not

correlate with the dose of potassium administered per kg body weight or per gram of creatinine excreted. Finally, for each HCTZ treatment group, the magnitude of the change in urine Ca did not correlate with the dose of HCTZ administered (per gram of creatinine excreted).

Data were also analyzed to determine whether the combination of HCTZ + $KHCO_3$ or $KHCO_3$ alone was superior to that of HCTZ + KCl in neutralizing the net acid load of the diet (Table 2). HCTZ + KCl had essentially no effect on NAE. Both HCTZ + $KHCO_3$ and $KHCO_3$ reduced NAE significantly and to slightly negative values: for HCTZ + $KHCO_3$, −10 mEq/day (baseline, 42 mEq/day; change with treatment, −52 mEq/day); for $KHCO_3$, −10 mEq/day (baseline, 28 mEq/day; change with treatment, −38 mEq/day).

Blood pH rose from baseline in both thiazide groups ($P < 0.001$), as did the plasma bicarbonate concentration (HCTZ + KCl, $P < 0.01$; HCTZ + $KHCO_3$, $P < 0.001$; Table 2). Serum potassium concentration decreased in the thiazide groups, although all serum potassium levels remained within the limits of normal (3.5 to 4.5 mEq/L).

There were no significant changes in body weights with any treatment.

DISCUSSION

Urinary calcium excretion decreased significantly in response to the administration of HCTZ in combination with either $KHCO_3$ or KCl and in response to the administration of $KHCO_3$ alone. Previous studies have shown that in normal, healthy people, thiazides decrease urine calcium excretion [19] and that potassium alkali salts also decrease urine calcium excretion [5, 20]. Urine calcium excretion therefore decreased as expected in the $KHCO_3$ group and in both HCTZ groups. With respect to reducing urine calcium, HCTZ + $KHCO_3$ should have been at least as effective as $KHCO_3$ treatment alone. In fact, the effects of the two treatments were additive so that treatment with HCTZ and $KHCO_3$ combined doubled the decrement in urinary calcium observed with either $KHCO_3$ treatment alone or that observed during combined treatment with HCTZ and KCl.

In this study, neither HCTZ nor KCl alone was tested. It might be argued that the chloride component of KCl, by promoting urine calcium excretion, mitigated the hypocalciuric effect of HCTZ and thereby accounted for some of the differential effect of HCTZ + $KHCO_3$ versus HCTZ + KCl on urine calcium excretion. However, chloride is not calciuric when administered as potassium chloride [16, 17]. The contrasting effect of various potassium salts on $U_{Ca}V$ was specifically studied by Sakhaee et al [16] and Lemann [17], both of whom found that compared with control, potassium chloride had no effect on $U_{Ca}V$, whereas potassium bicarbonate (or citrate) significantly reduced it. Therefore, it seems unlikely that potassium chloride would have mitigated the hypocalciuric effect of HCTZ. HCTZ alone can decrease urine calcium excretion, but often causes hypokalemia, particularly in the doses used in the present study. Potassium deficiency has been shown to promote urinary calcium loss, which is reversed by potassium supplementation [abstract; Lemann et al, *J Bone Miner Res* 5(Suppl 2):S203, 1990] [17]. Testing HCTZ alone therefore was not considered to be a necessary arm of our study.

Might the combination of HCTZ plus $KHCO_3$ work even better in subjects with hypercalciuria than in normal subjects? In subjects with hypercalciuria and renal stones, HCTZ or potassium citrate are commonly used treatments but are given for different reasons: HCTZ to facilitate renal reclamation of calcium and potassium citrate as an alkalinizing agent to correct hypocitraturia, which is an independent risk factor for stone formation. Thus, subjects who are both hypercalciuric and hypocitraturic are placed on both medications. Our data suggest that it may be reasonable to place subjects who are hypercalciuric on both HCTZ and an alkalinizing salt of potassium whether or not they have hypocitraturia.

Although sodium chloride intake was not controlled in our subjects and increased sodium chloride intake is known to increase the rate of calcium excretion in the urine, in our subjects, mean sodium and chloride excretion, and therefore presumably also consumption, did not differ significantly among groups, and hence cannot account for the observed differences in $U_{Ca}V$. Creatinine clearance also did not differ among groups. Subjects were excluded from the study if they were taking any medication or had any medical conditions that affected bone or calcium metabolism.

Blood pH and plasma bicarbonate concentration increased slightly but significantly in the HCTZ + $KHCO_3$ group, but not in the HCTZ + KCl group (Table 2). However, the values remained within the range considered to be normal. By reducing NAE to near zero values, the effect of HCTZ + $KHCO_3$ may be viewed as resetting blood pH and plasma bicarbonate to a nonacidotic level rather than to an alkalotic level.

It may be asked of what physiologic significance is a decrease in urine calcium excretion of the magnitude observed with HCTZ + $KHCO_3$, namely 1.8 mmol/day (73 mg/day). Perimenopausal women on an average calcium diet of 16.5 mmol/day (661 mg/day) have an average negative calcium balance of between 0.60 and 0.78 mmol/day (24 to 31 mg/day) [21]. Men and women with untreated osteoporosis on a 30 mmol/day (1200 mg/day) calcium diet have been shown to have an average negative calcium balance of 0.25 mmol/day (10 mg/day) [22]. A decrease in the amount of urinary calcium loss of 1.8 mmol/day (73 mg/day) in the HCTZ + $KHCO_3$ group might then induce a positive calcium balance in patients with osteoporosis. In a preliminary report of patients with

large negative calcium balances [mean, 2.4 mmol/day (96 mg/day) associated with idiopathic hypercalciuria], the combination of thiazide with an alkalinizing salt of potassium induced substantial positive calcium balances [mean, 3.1 mmol/day (124 mg/day)] and reduced urinary excretion of the bone resorption marker, hydroxyproline (abstract; Lemann et al, *Clin Res* 39:469A, 1991).

With increasing age, bone mineral density progressively declines, leading to osteoporosis and increased risk of fracture. Several studies have suggested that thiazide therapy alone may slow decline or increase bone mineral density [6–8] and decrease the risk for fractures [9, 10, 12]. Ray et al, in a nested case-control study of medical records in Canadian residents (905 hip fractures and 5137 matched controls), demonstrated a decreasing risk of hip fracture with increasing duration of thiazide use [10]. LaCroix et al prospectively studied 9518 men and women 65 years and older and demonstrated a reduction of approximately one third in the relative risk of hip fracture in those subjects taking thiazide diuretics [9]. In a large population study of 83,728 women, Feskanich et al reported that thiazide users had a 31% lower risk of hip fracture [12]. If the reduction in urine calcium excretion induced by thiazide therapy alone plays an important role in its apparent osteoprotective effect, combining thiazide therapy with an alkalinizing salt of potassium alkali might substantially augment that effect.

In summary, in the present study, $KHCO_3$ was superior to KCl as an adjunct to HCTZ, not only inducing a twofold greater reduction in urine calcium excretion, but also completely neutralizing endogenous acid production and therefore correcting the pre-existing mild metabolic acidosis that normally accompanies ingestion of an acid-producing diet in older people. Accordingly, for stone disease and osteoporosis treatment and prevention, the combination of HCTZ + $KHCO_3$ may be preferable to that of HCTZ + KCl.

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