Changes in urinary parameters after oral of potassium-sodium citrate and magnesium oxide to prevent urolithiasis

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ADULT UROLOGY

Title: CHANGES IN URINARY PARAMETERS AFTER ORAL ADMINISTRATION OF POTASSIUM - SODIUM CITRATE AND MAGNESIUM OXIDE TO PREVENT UROLITHIASIS.

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Running Head: Change in urinary parameters to prevent stones

ABSTRACT

Objectives. Urinary citrate and magnesium have been known as the inhibitors of calcium oxalate (CaOx) stone. Supplementation with potassium-magnesium citrate prevents the recurrence of CaOx stones. The present study examines urinary parameters among normal individuals and patients with CaOx stones after the oral administration of potassium-sodium citrate (KNa-Cit) and magnesium oxide (MgO).

Methods. Twenty-five male volunteers aged 21 to 42 years without a history of urinary stones were administered with either KNa-Cit or MgO or with both. Fourteen patients with recurrent CaOx stones were also administered with both supplements, and 24-hour urine samples were collected thereafter to determine urinary parameters.

Results. The administration of both KNa-Cit and MgO to normal individuals increased the excretion of citrate, magnesium and potassium, by 70.0%, 44.2% and 50.0%, respectively. These parameters increased less when KNa-Cit or MgO were administered individually. After administration with both supplements to stone patients, citrate, magnesium and potassium levels increased, by 62.1%, 63.3% and 25.3%, respectively, and oxalate also decreased by 66.5%. The ion-activity product index of CaOx was significantly more decreased by the combination than by either compound alone or before administration to normal individuals and to patients.

Conclusions. The combination of KNa-Cit and MgO is more effective than either supplement alone in inhibiting the crystallization of CaOx stones. The combination may improve the urinary parameters of patients with stones accompanied by hypocitraturia and / or hypomagnesiuria.

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INTRODUCTION

The advent of minimally invasive surgical options such as extracorporeal shockwave lithotripsy and laser lithotripsy has significantly changed treatment strategies for urolithiasis. Consequently, many urologists might not consider preventing recurrent urolithiasis due to the complexity of metabolic evaluation. The recurrence rate of idiopathic calcium oxalate (CaOx) stones is high, so a preventive program is important to reduce the considerable costs of surgical approaches to urolithiasis [1]. The formation of CaOx is probably a multifactorial process involving a disturbance in the balance between supersaturating and inhibitory factors. Citrate inhibits the development of CaOx stones by forming soluble complexes with urinary calcium and thereby decreasing urinary CaOx saturation. Citrate also inhibits the nucleation, growth [2] and agglomeration [3] of CaOx crystals. Magnesium reduces urinary CaOx saturation by forming magnesium oxalate, which is more soluble than CaOx in the urinary tract [4,5]. Magnesium may also form complexes with oxalate in the gastrointestinal tract, thus reducing the absorption of oxalate from the intestine [6,7]. Additionally, the administration of magnesium salts elevates urinary pH and increases the excretion of citrate. Magnesium also inhibits the nucleation and growth of CaOx crystals in vitro [8, 9]. Alkaline citrate such as potassium citrate has reduced the clinical recurrence rate of CaOx stones in randomized studies [10]. On the other hand, magnesium salts cannot prevent recurrent CaOx stones [11]. Thus, magnesium salts alone are not presently recommended as a prophylactic [12]. Another study has recently revealed that supplementation with potassium-magnesium citrate (KMg-Cit) reduces the recurrent rate [13]. However, KMg-Cit and potassium citrate are not commercially available in Japan. The present study examines whether a combination of available citrate and magnesium supplements can reproduce the effect of KMg-Cit on urinary parameters and discusses a potential alternative strategy to prevent recurrent urolithiasis.

MATERIAL AND METHODS

SUBJECT

Twenty-five male volunteers aged 21 to 42 years (mean age, 31 years) without a history of urolithiasis participated in the volunteer study. Their physical findings and routine laboratory tests were all within the normal range. None used regular dietary supplements or had a history of peptic ulcer, chronic diarrhea, cardiac disease, or renal dysfunction. Fourteen patients (4 females and 10 males; mean age, 52.9 years) who had 2 or more CaOx stone episodes and at least 1 calculus within the previous 2 years participated in the patient study. None of the patients had specific clinical disorders, such as distal renal tubular acidosis, primary hyperparathyroidism, or active urinary tract infection, or were prescribed with medication other than test supplements during the study. All patients and healthy volunteers gave written informed consent to participate in the study.

SUPPLEMENTS

The supplements included potassium-sodium citrate (KNa-Cit) (Uralyt®, Torii Pharma. Co., Japan), and magnesium oxide (MgO) (Maglax®, Yoshida Pharma. Co., Japan). One tablet of KNa-Cit contained 231.5 mg of potassium-citrate and 195.0 mg of sodium-citrate, and one tablet of MgO contained 250 mg of magnesium oxide.

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VOLUNTEER STUDY

Twenty-five volunteers participated in the experiment that consisted of 2 control and 3 challenge phases as follows: 1) control phase 1 (before challenge), no supplements; 2) citrate phase, 2 KNa-Cit tablets taken 3 times daily each after meal for 7 days; 3) magnesium phase, 1 MgO tablet taken twice each day after meals for 7 days; 4) combination phase, KNa-Cit and MgO tablets taken concurrently as described above for the citrate and magnesium phase; 5) control phase 2 (after challenge), no supplements. During the combination phase, participants consumed about 13.7, 13.7, 24.8 and 34.0 mEq of daily potassium, sodium, magnesium and citrate, respectively, through the administration of KNa-Cit and MgO. The intervals between each phase were 7 to 10 days to avoid effects from the other challenge phases. Three 24-hour urine samples were collected during control phases 1 and 2. During the challenge phases, 24-hour urine samples were collected at 3 and 7 days after supplement administration. Blood samples were obtained on the last day of each phase. All participants were instructed to maintain their usual dietary habits throughout the study period. Water intake was at least 1,500 ml per day. Alcohol and hard exercise were prohibited when the 24-hour urine samples were collected.

PATIENT STUDY

We examined the control and combination phases in patients with recurrent CaOx stones. Samples of 24-hour urine were collected once during the control phase and once 7 days after administering the same daily dose of KNa-Cit and MgO as in the volunteer study. The patients were also instructed to maintain their normal dietary habits like the volunteers.

COLLECTION OF 24-HOUR URINE SAMPLES

Participants collected the entire void volume at each urination. Almost half of the urine was mixed with 10 ml of 6N hydrochloric acid to determine oxalate, and the other half was mixed with 10 ml of sodium azide to measure urinary pH and to determine factors other than oxalate. The samples were stored at 4°C during the experimental period, and total urine volume were determined. The samples were clarified by centrifugation for 10 minutes at 750 x g before subsequent analysis.

SAMPLE   ANALYSIS

Urinary citrate and oxalate values were determined using a commercial kit (R-Biopharm GmbH, Inc., Germany) based on an enzymatic method and by capillary electrophoresis, respectively. Urinary pH was measured using a pH Meter 34 (Beckman Coulter, Inc., USA). Urinary creatinine, calcium, uric acid, phosphorus and magnesium were determined by the alkaline picrate, o-cresolphthalein comlexone, uricase, molybdate blue and xylidyl blue methods, respectively. Sodium, potassium and chloride were determined using ion-selective electrodes. Based on 24-hour urinary excretion, we defined hyperoxaluria as 45 mg or more excreted, hypercalciuria as 400 mg or more, hyperuricosuria as 750 mg or more, hypocitraturia as 320 mg or less, hypomagnesiuria as 75 mg or less according to the Japanese criteria. The ion-activity product indices of CaOx (AP (CaOx) index) and CaP (AP (CaP) index) in urine were calculated according to the formula of Tiselius[14]. Serum creatinine, magnesium, calcium, uric acid and phosphorus were also determined.

STATISTICAL ANALYSIS

Data were analyzed using Stat View 5.0 for Windows, (SAS Institute Inc, Cary NC). Values are presented as means plus or minus the standard error. Repeated measured analysis of variance models (ANOVA) compared each phase in the volunteer study, and multiple comparisons were performed by Dunnet's test. The Wilcoxon t-test compared the control and the combination phases in the patient study. A p value of < 0.05 was considered significant.

RESULTS

VOLUNTEER STUDY

Urinary parameters of each phase at day 7 of the volunteer study are summarized in TABLE I. The parameters of each phase similarly changed at days 3 and 7. All volunteers participated in all phases. Of the 25 volunteers, 2 had hypocitraturia, 3 had hypomagnesiuria and 3 had hyperuricosuria. None were hyperoxaluric or hypercalciuric. During the combination phase urinary pH, citrate and potassium remarkably increased compared with the other phases, and urinary magnesium increased as it did during the magnesium phase. Although citrate excretion was enhanced during all challenge phases, most citrate was excreted during the combination phase. Compared with control phase 1, citrate, magnesium and potassium excretion increased during the combination phase by 70.0%, 44.2% and 50.0%, respectively. Magnesium excretion was not enhanced during the citrate phase. Urinary

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calcium became elevated during the magnesium phase ($p < 0.05$), but not during the citrate or combination phases. Sodium excretion was enhanced during the citrate and combination phases but not significantly. The magnesium to calcium ratio significantly increased during both the magnesium and combination phases, but more so during the latter phase. For standardization, the 24-hour volume was established at 1.5 liters to calculate the ion-activity product index so that urine volume differed during each phase. The AP (CaOx) index and AP (CaP) index decreased during the challenge phases, especially during the combination phase. Urinary uric acid, phosphorus, chloride, oxalate and creatinine did not significantly change at each challenge phase. During control phase 2, the urinary parameters returned to the levels of control phase 1. No serum parameter significantly changed during any phase (data not shown). One adverse effect of MgO was loose stools in three volunteers during two of the challenge phases, but this was not sufficiently severe for them to withdraw from the study. No adverse reactions such as gastrointestinal discomfort developed during the citrate and combination phases.

PATIENT STUDY

Urinary parameters during the control and combination phases with KNa-Cit and MgO are listed in TABLE II. Of 14 patients, 11 had hypocitraturia. Of these, 1 was hyperoxaluric, 4 were hypomagnesiuric and 1 was hypercalciuric. One each was hypomagnesiuric or hyperoxaluric with normal citrate excretion. Like the volunteer study, urinary pH, potassium, magnesium and citrate were increased during the combination phase by 0.45 units, 25.3%, 63.3% and 62.1%, respectively. Moreover, urinary oxalate was reduced by 66.5% compared with the control phase. Of the 11 patients with hypocitraturia, citrate excretion improved in 9 to within normal limits. Oxalate excretion decreased in all patients, the level fell below 40 mg.

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Of 5 patients with hypomagnesiuria urinary magnesium increased in 4 to over 80 mg. Calcium excretion increased to over 400 mg in one patient with normal calcium excretion, but decreased to the normal range in a hypercalciuric patient after therapy. Excretion of potassium and of sodium did not change in 6 and 7 patients, respectively. The AP (CaOx) index decreased during the combination phase similarly to that in the volunteer study, but the AP (CaP) index did not change. None of the patients developed adverse reactions during the combination phase.

COMMENT

A long term study of KMg-Cit [13] has shown that 88.1% of the patients with calcium stones taking KMg-Cit were free of stones compared with 36.4% of those given a placebo. Because this response is not affected by the values of urinary biochemistry before administration, this strategy can non-selectively prevent CaOx stones. Based on their results, we examined the effects of KNa-Cit and MgO supplements. The combination administered to volunteers elevated urinary pH and increased the excretion of urinary citrate and magnesium more than either supplement alone. In the patient study, the changes in urinary pH, citrate, and magnesium were similar to those of the volunteers except for oxalate excretion, which decreased. Pak et al. showed in a short term study that KMg-Cit elevates urinary pH, citrate, magnesium and potassium by 0.62 units, 389 mg, 44 mg and 51 mEq, respectively [15]. Compared with our combination therapy, more citrate and potassium was excreted in their study. The reason is that the daily amounts of citrate and potassium reported in Pak's study were higher than in ours (citrate 73.5 vs. 34.0 mEq; potassium 49 vs. 13.6 mEq). However, urinary citrate increased in 9 of 11 patients with hypocitraturia to within the normal range in

our series. Therefore, we considered that the oral citrate load in our study was sufficient for the improvement of citrate excretion. Although KMg-Cit did not change oxalate excretion [15], our combination therapy decreased urinary oxalate in all patients. This might be because the study of Pak et al. included 5 volunteers in addition to 5 patients. Moreover, the ion-activity product index of CaOx prominently decreased during the combination phase in both the volunteers and patients. We therefore considered that the combination of KNa-Cit and MgO inhibits the crystallization of CaOx stones as effectively as KMg-Cit and more effectively than either administered alone.

Hypocitraturia is considered a correctable cause of calcium urolithiasis, and occurs in 19% to 63% of patients with urolithiasis [16]. Hypomagnesiuria does not usually present alone, and most patients with hypomagnesiuria also have hypocitraturia. The causes of hypomagnesiuria are inflammatory bowel disease associated with malabsorption, and thiazide drugs. Wuermser et al.[17] reported that thiazide-induced hypokalemia, hypocitraturia and hypomagnesiuria are improved by KMg-Cit. The present study found that the combination of KNa-Cit and MgO should improve urinary parameters among hypocitraturic patients, especially, those who also have hypomagnesiuria.

Excessive salt intake might be a risk for the development of calculus, since renal tubular reabsorption is inhibited by expansion of the extracellular fluid volume induced by sodium, and calcium excretion is consequently increased [18,19]. Thus, Pak et al. proposed that sodium citrate should not be used to prevent CaOx stones [20]. One KNa-Cit tablet in the present study contained about 52 mg of sodium. Sodium excretion was definitely increased during the citrate and combination phases and in the patient study, but calcium excretion did not change

during these two phases and slightly increased in the patients. Hofbauer et al. reported that the administration of KNa-Cit did not alter calcium excretion in patients with idiopathic calcium stones [21]. Although caution should be applied when administering KNa-Cit for patients who consume an excess of salt or for those with hypercalciuria, that KNa-Cit increases the risk of calcium stone formation remains inconclusive. We found that calcium excretion increased during the magnesium phase in agreement with previous findings [22]. Moreover, we found that calcium excretion was diminished by the combination phase compared with MgO alone, probably due to the formation of soluble complex with urinary citrate and calcium. This result suggests that combination therapy provides more protection than MgO alone against calcium stone formation.

The study limitations are that it was a short-term investigation of a small population. Moreover, age was not matched between volunteers and patients, and diets were not standardized. Although no adverse effects appeared to be associated with KNa-Cit together with MgO, whether long term use is tolerable remains unknown. Future controlled studies should follow up patients for longer periods.

CONCLUSIONS

A combination of KNa-Cit and MgO enhanced the excretion of citrate and magnesium compared with either alone, in both normal volunteers and patients with recurrent CaOx stones. Moreover, the combination prominently inhibited the crystallization of CaOx stones. Therefore, the combination may particularly be advantageous for stone patients with

hypocitraturic and / or hypomagnesiuric.

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TABLE I. *Urinary parameters of 25 volunteers during 2 control and 3 challenge phases*

Phase	Control 1	Citrate	Magnesium	Combination	Control 2
Total volume (l/day)	1.09 ± 0.06	1.20 ± 0.08	1.19 ± 0.13	1.26 ± 0.08	1.16 ± 0.05
pH	6.19 ± 0.08	6.51 ± 0.07	6.25 ± 0.07	6.77 ± 0.09	6.18 ± 0.05
Sodium (mEq/day)	172.1 ± 0.90	203.0 ± 15.0	188.3 ± 13.3	202.3 ± 12.5	174.0 ± 8.7
Potassium (mEq/day)	42.8 ± 2.2	58.0 ± 3.8*	46.2 ± 2.7	64.6 ± 3.5*	43.2 ± 2.3
Chloride (mEq/day)	182.3 ± 8.8	197.0 ± 15.1	196.0 ± 11.8	193.4 ± 10.9	173.5 ± 8.7
Calcium (mg/day)	163.8 ± 12.3	161.8 ± 13.3	202.3 ± 15.8*	160.0 ± 13.9	160.8 ± 10.7
Phosphorus (mg/day)	807.4 ± 34.3	847.7 ± 45.6	767.0 ± 46.6	782.3 ± 50.0	824.7 ± 34.3
Uric acid (mg/day)	612.6 ± 30.3	664.2 ± 38.9	627.2 ± 32.4	699.4 ± 43.5	631.3 ± 26.2
Magnesium (mg/day)	82.7 ± 4.9	91.9 ± 7.7*	131.6 ± 9.1*	119.3 ± 7.8*	83.6 ± 4.9
Citrate (mg/day)	343.7 ± 36.4	494.9 ± 49.3*	436.4 ± 42.5†	584.5 ± 74.9*	348.0 ± 31.8
Oxalate (mg/day)	23.1 ± 1.3	22.0 ± 1.3	20.9 ± 1.5	21.6 ± 1.4	20.2 ± 1.1
Creatinine / body weight (mg/kg/day)	23.7 ± 0.70	23.9 ± 0.82	23.0 ± 0.86	23.0 ± 0.74	23.1 ± 0.52
Magnesium / calcium ratio	0.54 ± 0.03	0.63 ± 0.05	0.70 ± 0.05*	0.85 ± 0.07*	0.56 ± 0.04
AP (CaOx) index	0.93 ± 0.07	0.69 ± 0.04*	0.84 ± 0.07	0.60 ± 0.05*	0.91 ± 0.08
AP (CaP) index	24.4 ± 2.1	19.3 ± 1.5†	23.9 ± 2.0	16.8 ± 1.7*	22.2 ± 1.7

Significance of differences was determined by repeated analysis of variance.

: $P < 0.01$ compared to control 1 values.

† *: $P < 0.05$ compared to control 1 values.*

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TABLE II. *Urinary parameters of 14 patients with calcium oxalate stone during control or combination therapy*			
	Control	**Combination**	*P* value*
Total volume (l/day)	1.6 ± 0.41	1.6 ± 0.27	NS
pH	6.35 ± 0.15	6.80 ± 0.10	< 0.05
Sodium (mEq/day)	182.5 ± 16.8	208.7 ± 19.3	NS
Potassium (mEq/day)	40.6 ± 5.4	50.9 ± 3.5	< 0.05
Chrolide (mEq/day)	190.2 ± 16.3	205.5 ± 18.3	NS
Calcium (mg/day)	221.5 ± 32.0	250.4 ± 28.2	NS
Phosphorus (mg/day)	699.4 ± 65.5	657.5 ± 64.1	NS
Uric acid (mg/day)	562.6 ± 59.3	577.1 ± 56.9	NS
Magnesium (mg/day)	87.7 ± 8.1	143.2 ± 15.7	< 0.01
Citrate (mg/day)	241.5 ± 57.0	391.5 ± 54.1	< 0.01
Oxalate (mg/day)	29.0 ± 3.3	19.3 ± 2.3	< 0.01
Creatinine / body weight (mg/kg/day)	19.0 ± 1.7	20.1 ± 1.7	NS
Magnesium / calcium ratio	0.40 ± 0.04	0.58 ± 0.08	< 0.05
AP (CaOx) index	0.99 ± 0.12	0.60 ± 0.07	< 0.01
AP (CaP) index	20.0 ± 3.4	21.5 ± 3.0	NS

Wilcoxon t-test