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Acute Oral Alkali Citrate Load in Healthy Humans – Response of Blood and Urinary Citrate, Mineral Metabolism, and Factors Related to Stone Formation*

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Summary. In ten healthy volunteers (♂/♀ = 5/5) the effects of two doses (2.5 and 5.0 g) of orally ingested alkali citrate (AC) on serum citrate, variables of mineral metabolism in serum, the urinary excretion of citrate, sodium and minerals were studied and compared with the effects of an oral vehicle load. Also, phosphate crystalluria and the supersaturation of several stone forming phases in urine were evaluated under all loads. The data allow to conclude that 1) the rise in serum citrate may result from citrate absorbed intestinally under AC; 2) systemic metabolic alkalosis is not detectable with the chosen AC doses but may be reflected by the more alkaline urinary pH and a higher citrate excretion; 3) mineral metabolism, serum ionized calcium, parathormone, calcitonin and urinary cyclic AMP included, are more or less stable under acute loads of AC; 4) postprandial phosphate crystalluria is more pronounced with increasing AC, but despite this the direct correlation with the supersaturation of hydroxyapatite is progressively weakened with both doses AC suggesting that the inhibitory effects of this drug may dominate over its effects upon initiation of precipitation.

Key words: Alkali citrate, Phosphate crystalluria, Supersaturation, Systemic metabolic alkalosis.

Introduction

At present, an effective and reliable prophylaxis of idiopathic recurrent calcium urolithiasis (RCU) is regarded as a prerequisite for the long-term control of this disorder. For some years, considerable success has been achieved with the use of drugs, for example thiazides, allopurinol and phosphates. Three main factors are involved: 1) improved insight into pathophysiology, 2) the meticulous elucidation of those effects of drugs which justify their use to counter partial disturbances in stone disease, 3) the reliable documentation of the specific success rates and the side effects in long-term studies.

The aim of any anti-stone drug treatment is, in the absence of undesired effects, to achieve a reduction in the supersaturation of urine with stone-forming salts, or an augmentation of the potential of urinary inhibitors of precipitation, crystal growth and stone formation. Citrate, a complexor of calcium ions [30] and a documented in vitro inhibitor of crystal-forming processes [4, 5, 15] can theoretically be regarded as a candidate for such a role. Moreover, urinary citrate is reduced in calcium urolithiasis [22, 25]. The etiology of this defect is as yet unknown, but an intracellular metabolic acidosis and potassium deficiency of the renal tubular cells are accompanied by low urinary citrate [29]. Exogenous administration of citrate, in combination with alkali for the correction of the acidosis would, therefore, have a rational basis as a possible treatment of renal stone disease. Before citrate can be recommended in the prophylaxis of calcium stone disease a number of aspects of the acute effects of oral alkali citrate (AC) must be investigated since they may influence its long-term effects. Thus, a number of questions are still unresolved regarding a) the serum levels of citrate and the concomitant concentrations of ionized calcium, parathormone (PTH) and calcitonin (CT) after oral AC, b) the development of sufficient hypercitraturia in the physico-chemical sense, i.e. reduction of the supersaturation of urine with respect to stone-forming phases under a given dose of oral AC, and c) the degree of phosphate-crystalluria which is regularly associated with AC. A knowledge of these effects of AC would permit a more sensible assessment of its role in the treatment of stone disease. In the present study, therefore, we report our observations in healthy subjects during an acute short-term oral load with two different doses of AC.

* Parts of this work were presented at the European Urolithiasis Symposium, held in Vienna, from March 21 to 23, 1985

Participants and Methods

Ten healthy subjects (♂/♀ = 5/5) age 21–40 years (mean age: ♂ 27.0 ± SD 2.6 ♀ 27.6 ± SD 7.4), weighing 51–88 kg (mean: ♂ 81 ± 3, ♀ 56 ± 3) participated in the present study. All had given their informed consent.

At the time of the study renal function was normal (serum creatinine 0.7–1.3 mg · dl^{-1}; mean values: ♂ 1.11 ± SD 0.13, ♀ 0.85 ± 0.07), there were no signs of urinary tract infection (as evaluated by the Uricult test, Boehringer, Mannheim; FRG), and no metabolic disturbances, including urolithiasis. They were allowed to eat normally until the evening preceding the study. Following a 12–14 h overnight fast, they presented at our clinical laboratory at 8 a.m. The investigations outlined below were conducted with concomitant measurement of the endogenous creatinine clearance and careful observation by experienced personnel. After an adaptation period of approx. 30 min 300 ml of camomile tea made with deionized water was given to stimulate diuresis. Shortly afterwards the bladder was voided. Fourty-five min later (time −45min), fasting blood was taken via an indwelling catheter from an antecubital vein without using a tourniquet (sample B), and after an additional 45 min (time 0 min) the bladder was voided (period B). Thereafter a load test was performed.

The effect of oral AC[1] was studied in analogy to the intake of drugs under home conditions in the following manner:

1) dose 1; 2.5 g of orange-coloured (see vehicle) granulate, dissolved in 25 ml of distilled water per 10 kg body weight; this dose supplies 11 mM potassium, 11 mM sodium and 8.8 mM citrate, and represents a dose successful in the alkalization of the urine for the prevention of idiopathic uric acid lithiasis.

2) dose 2; 5 g, prepared as described under 1). The doubling of dose 1 was chosen, since it was well tolerated in pilot studies of selected participants, and because, as yet, little is known about the degree and the duration of AC-mediated changes of variables in blood and urine (see section Analyses).

3) vehicle; distilled water as under 1), coloured to match the substance under study, i.e. containing 12 mg orange-yellow.

The chosen preparation was taken within 10 min of a breakfast consisting of 1 roll, 1 boiled egg, 20 g of butter, 1 portion of jam and 1–2 cups of camomile tea. The postprandial observation period was 270 min, subdivided into three further periods of 90 min each (periods I, II, III) during mild diuresis. Blood samples were taken at 45, 135, 225 min (samples I, II, III). The order of the intake of the loads 1)–3) was determined by drawing lots before the start of the study. The interval between two loads was at least one week.

Analyses

Routine methods or established techniques were used to determine blood and urine estimations of: creatinine, potassium, sodium, magnesium, chloride, phosphate, uric acid, total CO_2, pH, bicarbonate, citrate [16], sulfate [33], ammonium [7], pyrophosphate [8], oxalate [13], cAMP (kit, Amersham-Buchler, Braunschweig; FRG); complexometry was used for the determination of total serum calcium, spectrophotometry for ionized calcium in serum ultrafiltrate [12], radioimmunoassay for PTH [24] and CT [9]. Crystalluria was evaluated by polarization microscopy, but in contrast to the original description [35], on Millipore filter (type GSWP, 0.22 μM, Millipore, Molsheim; France). Only spheroid phosphate crystals, presumably hydroxyapatite (HAP), were observed. The relative instability and absence of CaOx crystals above pH 6 [2] and pH 6.5 respectively [34], and the risk of increased formation of calcium phosphate crystals in this pH range [17, 34] made this technique suitable for the present study. Evaluation of the inhibitory activity on the calcium phosphate system was not done because of the known difficulties of equilibrating hydroxyapatite with urines already supersaturated with respect to this phase [18], as was the case in the present study (see Table 3).

Calculations, Presentation of Data, Statistics

In order to eliminate errors due to incomplete voiding of the bladder, the excretion of substances was matched to creatinine level in the same samples. For the evaluation of crystalluria a score was used: 1 spheroid (S) per filter = 0.2 S = 0.25, 2–10 S = 0.5, 10–30 S = 1, 30–50 S = 2, > 50 S = 3. Ionic strength, the percentage of activity of free ions (calcium, magnesium, oxalate), the relative supersaturation of the urine with respect to crystal- and stone-forming phases, were calculated by means of the "EQUIL" program [10] in the modification of Werness et al. [36] (software kindly donated by Drs. W. G. Robertson, B. Finlayson, L. H. Smith). Results are presented either as mean ± 1 SEM (blood) or as median and range of the individual values (urine). Since a Gaussian distribution was not always present, the significance of the differences was examined using the U test.

Results

Both doses of AC were tolerated by all participants, with no side effects.

1. Data from Blood

a) Absolute Values. For some of the measured variables, sex differences were detectable under basal conditions (sample B). Creatinine, uric acid, serum total calcium and magnesium, potassium, and CT are significantly lower in the female than in the male, whereas citrate was significantly higher in the former (data not presented). While this sex difference for CT has only recently become known [11], it has been documented previously for the other variables. In all of these either no change was detectable with a load of vehicle or AC, and the relative changes from the baseline values were roughly identical in male and female. Capillary pH varied between 7.37 and 7.41, and neither with the vehicle nor with AC (both doses) were any significant differences detectable at the different times for both sexes. Therefore, Table 1 contains only the pooled results from male and female participants for those variables which appear important for the interprepation of the effects of AC under controlled trial conditions.

The basal values of ionized calcium differed significantly. Therefore, the relative changes from the baseline values are additionally presented for ionized calcium and a number of other variables (see section b). The absolute values revealed certain tendencies (Table 1): with vehicle, citrate increased only briefly, but for longer with the double dose of AC; CT stays stable; PTH, serum total calcium and phosphate tended

1 Oxalyt-C; Dr. Madaus & Co, Cologne; FRG

Table 1. Influence of either a normal (Dose 1), or a twofold (Dose 2), oral dose of alkali citrate, as compared with a conventional breakfast (Vehicle), on serum citrate, potassium, and a number of associated variables of mineral metabolism. Depicted are the pooled data from healthy male and female subjects (n = 10). For all details of the study see Methods. PTH: parathyroid hormone. B, I, II, III represent blood samples taken before (−45 min), and 45, 135, and 225 min, respectively, after the load. Means ± SEM (below)

	Vehicle				Dose 1				Dose 2			
	B	I	II	III	B	I	II	III	B	I	II	III
Citrate;	2.36	2.51	2.42	2.24	2.19	2.89[b]	2.39	2.30	2.06	3.43[b]	2.59	2.42
mg/dl	0.16	0.15	0.16	0.13	0.14	0.22	0.23	0.16	0.11	0.30	0.24	0.18
Potassium;	4.90	4.23	4.25	4.26	4.67	4.37	4.23	4.23	4.78	4.79[a]	4.47	4.15
mM/l	0.21	0.19	0.17	0.19	0.18	0.20	0.24	0.23	0.14	0.28	0.28	0.28
Ionised Calcium;	4.20	4.42	4.65	4.74	4.55[a]	4.35	4.53	4.70	4.66[b]	4.32	4.60	4.48
mg/dl	0.15	0.13	0.10	0.12	0.10	0.18	0.19	0.11	0.11	0.17	0.08	0.08
Total Calcium;	9.45	9.44	9.47	9.56	9.56	9.48	9.28	9.35	9.42	9.30	9.29	9.42
mg/dl	0.20	0.21	0.20	0.18	0.18	0.17	0.15	01.3	0.09	0.10	0.12	0.13
Phosphate;	3.56	3.17	3.44	3.68	3.64	2.93	3.21	3.41	3.53	3.0	3.3	3.34[a]
mg/dl	0.14	0.10	0.17	0.14	0.13	0.19	0.18	0.20	0.21	0.15	0.14	0.12
Calcitonin;	74	71	74	86	75	73	78	82	77	74	76	84
pg/ml	9	9	8	11	10	11	8	10	9	12	11	9
Parathyroid Hormone;	268	259	310	279	315	278	252[a]	344	280	230	291	258
pg-equiv/ml	36	23	26	27	47	25	15	42	28	20	19	27

[a] $p < 0.05$

[b] $p < 0.01$ versus values in the respective blood sample under Vehicle

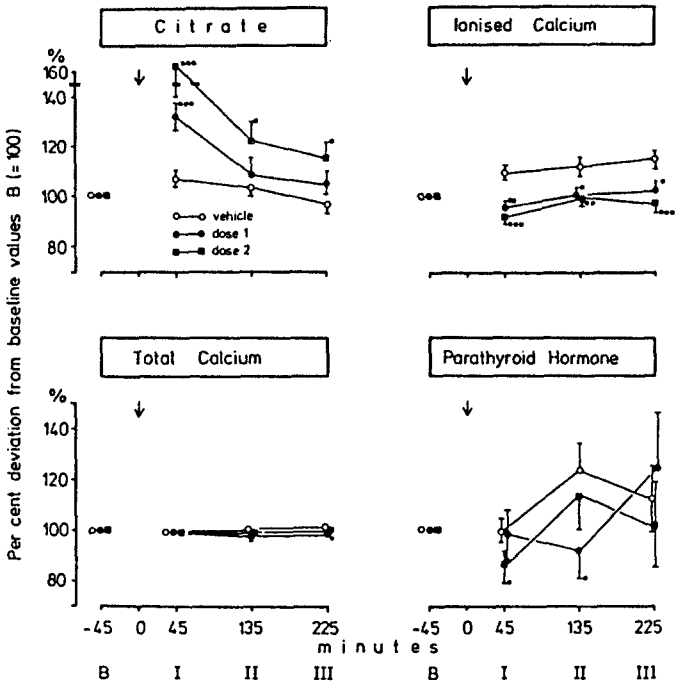

Fig. 1. Relative changes from baseline values (sample B) of serum citrate, ionized and total calcium, parathyroid hormone, as influenced by either the two doses of oral alkali citrate or the vehicle. The *arrow* indicates the start of loading at 0 min. For other details see legend to Table 1 and Methods. Means ± SEM. ^{0}: $p < 0.05$, ^{00}: $p < 0.01$, ^{000}: $p < 0.001$, versus the values in the respective blood samples under Vehicle

to decrease, while the movements of ionized calcium with AC remain unclear, owing to the low basal values before the vehicle load. If this value were only fortuitiously lower than the basal values before the AC load (both doses), ionized calcium with AC (samples I, II, III) would be only slightly lower or unchanged (see section b). The tendency towards low postprandial potassium levels (vehicle) was not influenced by dose 1, but considerably diminished by AC dose 2.

b) Relative Values. Citrate increases in a significant, dose dependent fashion and within 45 min with both AC loads (dose 1 approx. 32, dose 2 approx. 65%). The pre-load basal levels were not regained by 225 min (sample III).

Ionized calcium increased with vehicle due to the above mentioned low basal values. Therefore, when related to these values, those with AC (both doses) were significantly lowered. Conversely, if these critical postprandial values under vehicle were related to a basal value of 4.60 mg · dl^{-1} (= mean value of both preexperimental values before the AC loads), the significance of the differences between vehicle and AC loads would disappear. The PTH values scatter with increasing duration of observation (at 135 and 225 min); nevertheless, the mean values after ingestion of AC dose 1 (45 min) or AC dose 2 (135 min) are significantly lower than with vehicle. At the same points total serum Ca levels are statistically unchanged, although slightly decreased at 225 min (AC dose 1).

Table 2. Influence of oral alkali citrate on urinary pH, citrate, potassium, and sodium, the last three expressed in mM substance per mM associated urinary creatinine. B, I, II, III represent urine periods collected before (−90 − 0 min), and 0–90, 90–180, and 180–270 min, respectively, after the load. For further explanations see legend to Table 1 and Methods. Medians and range (below)

	Vehicle				Dose 1				Dose 2			
	B	I	II	III	B	I	II	III	B	I	II	III
pH;	6.22	6.38	6.22	5.99	6.28	6.49	6.70	6.37	6.54	7.27[a]	7.21[c]	6.72[a]
	5.50–7.84	5.30–7.34	5.40–7.06	5.40–6.88	5.18–7.04	5.50–7.70	5.45–7.32	5.50–7.22	5.30–7.48	6.42–7.92	6.68–7.44	5.50–7.08
Citrate;	0.16	0.20	0.25	0.19	0.14	0.31[a]	0.33	0.25	0.17	0.37[b]	0.35	0.24
mM/mM	0.08–0.62	0.90–0.52	0.09–0.52	0.06–0.69	0.07–0.47	0.20–054	0.16–0.61	0.10–0.43	0.05–0.53	0.20–1.09	0.16–1.27	0.06–0.91
Potassium;	5.73	5.63	6.62	7.67	6.73	9.54[a]	8.34	9.24	4.71	10.4[b]	9.13[a]	7.63
mM/mM	2.27–11.80	2.26–8.70	3.87–12.2	1.28–21.5	2.35–19.1	3.11–12.0	3.73–14.10	4.83–15.0	0.29–9.78	0.87–20.90	5.44–18.24	4.94–19.30
Sodium	5.96	6.19	8.84	7.15	8.59	6.74	9.54	7.27	10.10	12.20[a]	13.40	9.46
mM/mM	0.43–19.40	0.47–21.70	0.30–21.80	0.13–27.60	3.17–22.20	3.31–23.60	3.37–22.60	2.99–24.90	0.06–18.40	0.12–27.20	1.87–24.20	1.64–40.70

a $p < 0.05$
b $p < 0.01$
c $p < 0.005$ versus the respective urine period under Vehicle

2. Data from Urine

a) Various Substances, pH. As expected, creatinine and creatinine clearance were lower in the female than in the male during the basal control period B; a postprandial rise in clearance by 6–11% (not significant) was observed in both sexes, independent of AC (data not shown). Citrate in the females of the present study (all less than 40 years old) was always 1.5–2.5 times higher than in the males, a fact already reported [25]. A postprandial rise, independent of sex and AC, was seen for uric acid, pyrophosphate, phosphate and cAMP (data not shown). The following text refers to pooled data (♂ + ♀).

Table 2 contains those data for which a change under oral AC could be expected on the basis of its components; such changes have been reported elsewhere [6, 23]. An AC-mediated significant rise in pH over 180 min (periods I, II) after the administration of dose 2 was noticed, but not after dose 1, while the rise in pH mediated by the test meal is negligibly low. Similarly, potassium increased markedly under AC dose 2 (periods I, II) and only briefly (period I) under dose 1. The median basal values (B) of sodium and all individual postprandial sodium values varied considerably, making the estimation of the influence of administered sodium difficult. Urinary sodium was elevated only once (dose 2; period I). A significant increase in citrate is observed after both AC doses within 90 min (period I), and a non-significant increase within 180 min (period II). The mean postprandial rise in urinary citrate after oral AC was approximately identical (135 and 118% for dose 1 and 2, respectively).

b) Relative Values (Fig. 2). This figure is designed to elucidate the renal response to any of the three loads by excluding the disparate basal values (period B; see section a). Therefore, the medians of the per cent changes (period B, −90 − 0 min = 100) in the excretion of a number of variables not contained in Table 2 (except for sodium) are presented[2]. On this basis, the significantly enhanced natriuresis under AC dose 2 was not accompanied by enhanced calciuria, magnesiuria or phosphaturia, and cAMP is increased only during the first 90 min (period I; dose 2). Postprandial median oxalate with AC was always higher than under vehicle, but only with the AC dose 2 (period I) was oxalate significantly elevated.

c) Activity of Free Ions (Fig. 3). The percentage of free ions of calcium, magnesium, oxalate (molar concentrations of total Ca, Mg, oxalate in the same sample = 100) increased slightly postprandially. With both doses of AC free Ca^{++} and Mg^{++} ions decreased significantly, whereas those of oxalate remained statistically unchanged.

2 all individual relative and absolute values can be requested from the author (POS)

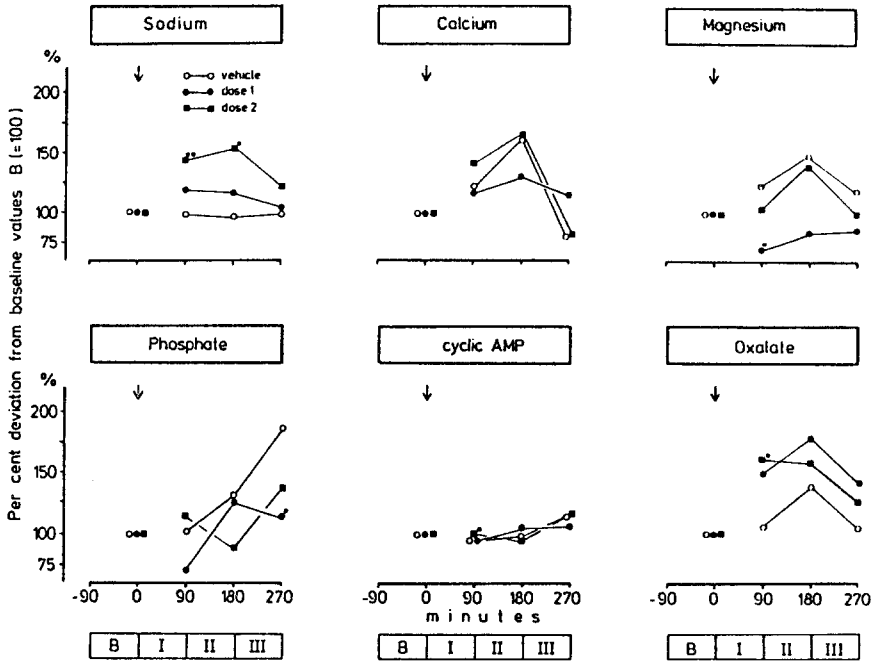

Fig. 2. Median relative changes from baseline values (period B) of urinary sodium, calcium, magnesium, phosphate, cAMP, oxalate, as influenced either by the two doses oral alkali citrate or by the vehicle. *Arrows* indicate start of load at 0 min. For other details see Results and Methods, and the legend to Table 2. ^{0}: $p < 0.05$, ^{00}: $p < 0.01$, versus the values in the respective urine period under Vehicle

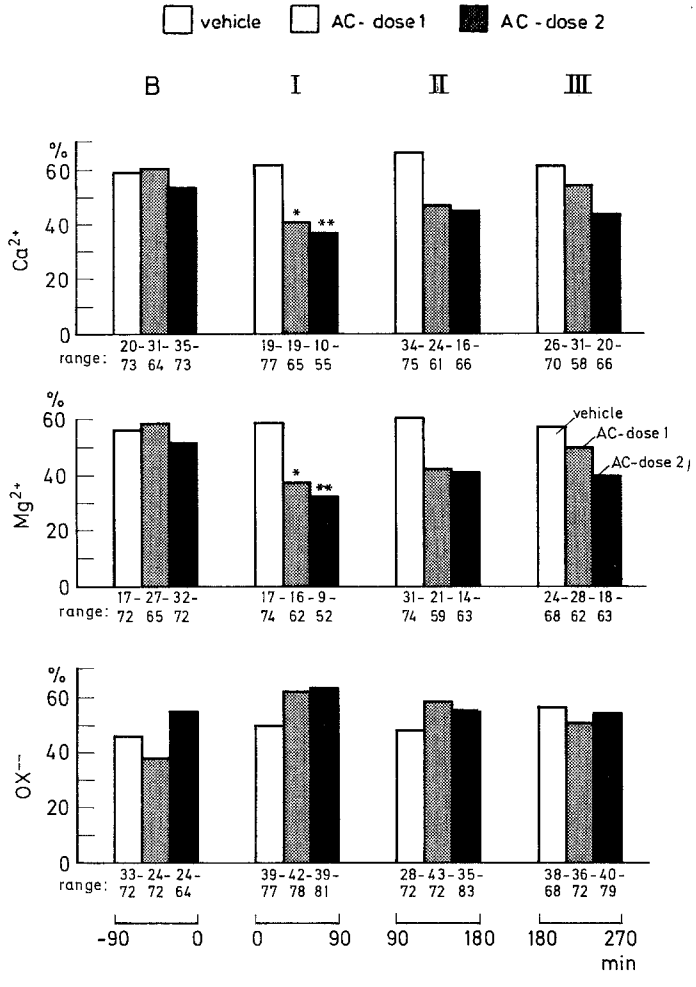

Fig. 3. Percentage of free ion activities of calcium (Ca^{2+}), magnesium (Mg^{2+}), oxalate (OX^{--}) in urine before (B) and following (I, II, III) a breakfast without (Vehicle), and with, two doses of alkali citrate. Medians, range (below). ·: $p < 0.05$, ··: $p < 0.01$ versus Vehicle

d) Degree of Supersaturation (Table 3). The median values of the relative supersaturation (RS; see [36]) with respect to brushite were always negative (vehicle; AC doses 1, 2) i.e. they were obtained from urines which were undersaturated. With two exceptions (period B before AC dose 1; period III after dose 2) similar observations were made for sodium acid urate. Conversely, the median RS with respect to CaOx was positive with three exceptions (period I, AC dose 1; period B, period III, AC dose 2), and the RS with respect to HAP was positive with one exception (period I, vehicle). This confirmed earlier observations that urine from healthy subjects is generally supersaturated with HAP [18]. In the postprandial periods the RS was not uniform: there was a tendency for the RS to increase with HAP, while in the case of CaOx the RS was stable, and the pre-existing undersaturation with respect to brushite and sodium acid urate increased. With AC (both doses) the supersaturation with HAP increased, but the difference is significant only between vehicle load and AC dose 2.

The AC-mediated changes in brushite and CaOx were not significant when compared with vehicle; sodium acid urate showed significantly less undersaturation in period I (dose 1). A marked increase in supersaturation with respect to sodium acid urate and HAP under AC was seen when the sum of all the values of the postprandial periods (period I, II, III) was compared with the sum of the values under vehicle. Sodium acid urate (median/range): vehicle $-171/-5.11-1.62$, dose 1 $-0.49/-4.27-3.13$ ($p < 0.05$), dose 2 $-0.27/-3.71-3.25$ ($p < 0.01$), respectively, versus vehicle; HAP: vehicle $-1.95/-3.86-5.21$, dose 2 $3.76/-2.16-7.07$ ($p < 0.001$). Here, too, CaOx and brushite were not significantly changed.

e) Crystalluria (Table 3). 116 filters were evaluated from the ten participants under the three loads. With the

Table 3. Supersaturation (I) of crystal-forming phases, and crystalluria (II) in the pooled (♂ + ♀) study participants (see section on Methods). Median/range. HAP: Hydroxyapatite; CaOx: Calcium oxalate; NaHU: Sodium acid urate

	B	I	II	III
I. Supersaturation				
Vehicle; $n = 10$				
Brushite	−3.58/−7.02 – −1.32	−4.43/−7.16 – −2.81	−3.56/−7.19 – −1.93	−2.94/−7.51 – −1.18
HAP	1.57/−2.6 – 7.34	−0.29/−2.74 – 4.82	2.0/ −3.28 – 5.21	2.15/−3.86 – 3.75
NaHU	−1.23/−2.17 – 3.47	−2.16/−5.11 – 0.59	−1.41/−3.07 – 1.62	−1.35/−2.85 – 1.50
CaOx	0.35/−2.97 – 2.67	0.39/−2.95 – 1.41	0.87/−17.2 – 1.77	0/−1.45 – 3.07
AC Dose 1; $n = 10$				
Brushite	−2.18/−6.11 – 0.79	−4.3/−7.05 – −2.15	−3.84/−6.45 – −0.7	−3.48/−5.98 – −1.82
HAP	1.71/−1.39 – 6.91	1.33/−5.36 – 6.62	2.39/−2.91 – 6.58	1.46/−1.46 – 5.17
NaHU	1.39/−2.09 – 3.42	−0.14/−1.8 – 3.04[a]	−1.05/−4.27 – 3.13	−0.34/−2.69 – 1.93
CaOx	1.33/−2.46 – 2.27	−0.30/−2.37 – 1.48	0.26/−1.93 – 1.98	0.31/−1.94 – 2.43
AC Dose 2; $n = 10$				
Brushite	−3.25/−4.19 – −0.20	−3.12/−6.05 – −0.73	−2.68/−7.03 – −1.51	−2.17/−6.02 – −1.32
HAP	2.17/−0.62 – 7.77	4.05/−0.18 – 7.07[a]	4.72/0.68 – 6.38[a]	2.59/−2.16 – 5.01
NaHU	−0.35/−3.13 – 3.85	−0.73/−1.43 – 3.25	−0.27/−2.56 – 2.87	0.06/−3.71 – 2.41
CaOx	−0.24/−1.65 – 3.12	0.10/−2.13 – 2.20	0.46/−2.75 – 2.01	−0.20/−2.55 – 3.25
II. Crystalluria Score				
Vehicle; $n = 9$	0.375/0 – 0.75	0.250/0 – 0.50	0.250/0 – 0.50	0.250/0 – 0.75
AC Dose 1; $n = 10$	0.313/0 – 0.75	0.250/0 – 0.75	0.250/0.125 – 0.50	0.250/0.125 – 0.625
AC Dose 2; $n = 10$	0.375/0 – 1.0	0.250/0.125 – 0.625	0.250/0.125 – 0.50	0.313/0.125 – 0.75

[a] $p < 0.05$ versus Vehicle

Negative values (< 0): undersaturation; 0: Saturation; Positive values (> 0): Pressure to crystallization (for details see ref. [36])

technique, only a few crystals are generally found per filter. Also with Nucleopore filters the postprandial crystalluria of healthy subjects is low compared with stone patients [31]. No sex difference in the degree of crystalluria is detectable (data not shown). The pooled data (♂ + ♀) before and after loading demonstrate that the values B were roughly identical, and that postprandially (periods I, II, III) a tendency towards lower values prevails (Table 3; II).

After the vehicle load the minimal values are 0, while after AC load in the dose 1 group two out of three, in the dose 2 group all three, values were above 0. This indicates that under AC a tendency towards a relatively more marked CaP-crystalluria might develop. Therefore, the differences between the postprandial (periods I, II, III) and the respective basal score (period B) were calculated in addition and the pooled differences (I − B plus II − B plus III − B) compared. With less negative median values a tendency towards a more pronounced crystalluria under the AC loads was recognized (median/range): vehicle −0.125/−0.5 − 0, $n = 27$; dose 1 −0.06/0.25 − 0.5, $n = 30$; dose 2 0.125/−0.75 − 0.25, $n = 30$. The differences (dose 1 vs. vehicle, and dose 2 vs. vehicle respectively) were only of marginal significance ($p < 0.10$).

f) Correlations. When the differences between the postprandial and the respective basal periods are calculated for both crystalluria (= Y) and the saturation products of HAP (= X), and when these differences are correlated, the following coefficients of correlation result: vehicle, $n = 30, r = 0.326$, $p < 0.07$; AC dose 1, $n = 30$, $r = 0.113$, n.s.; AC dose 2, $n = 30, r = 0.085$, n.s..

Discussion

Oral administration of AC induces a dose-dependent rise in serum citrate (approximately 30–60% above basal) within 45 min. This observation suggests citrate absorption in the small intestine, which, on the basis of the serum levels of the present and another [21] study, should be in the range of 1–2% of the oral dose. A concomitant decrease in the ionized calcium cannot be documented unequivocally, in contrast to situations of extremely high serum citrate due to massive administration of citrate into the systemic circulation [1]. The small changes in serum total calcium, PTH and urinary cAMP, lead to the assumption that during short-term loading AC at the chosen doses does not stimulate the parathyroid glands.

Approximately identical urinary citrate excretion following the two AC doses is, at first, surprising, since the serum levels of citrate are different, and citrate is mostly unbound to serum macromolecules and thus is freely filterable through the glomerular membrane [26]. Up to 30 μmol · min^{-1} or of filtered citrate 75% is reabsorbed in the proximal tubule; at higher values reabsorption attains a

plateau. In the present study, with the highest serum level observed (dose 2, sample II; Table 1) approx. 18 μmol citrate · min^{-1} per 100 ml of creatinine clearance are filtered, as a result of which urinary citrate should reflect mainly non-reabsorbed citrate. In contrast, administered potassium and metabolic alkalosis lead to enhanced intracellular synthesis of citrate and citrate secretion [29]. Although we were unable to demonstrate extracellular alkalosis, we cannot exlude the possibility that intracellular alkalosis develops with AC. This would indicate that urinary citrate originates mainly from tubular secretion in response to the enhanced synthesis of citrate. The origin of urinary citrate is of interest; we observed a twofold increase in citrate excretion following an oral dose of AC. Whether this could be achieved with a pre-existing citrate deficit and how long the rise in citrate might last, and what doses of AC would be necessary are important questions. A doubling of citrate in the 24 h urine in idiopathic uric acid lithiasis by means of potassium citrate [23], and a rise by a factor of 3 in hypocitraturic calcium lithiasis induced by the AC preparation used in this study [6] have been reported. Our data from healthy subjects (Table 2) suggest that a doubling of urinary citrate in diurnal urine by AC dose 1 taken three times a day is not practicable. This is supported by the observation that normocitraturic stone patients develop less than a 50% rise in urinary citrate with AC [6]. This discrepancy cannot be explained at present. In the normocalciuric variant of calcium lithiasis we found signs of hypokaliuria [20] and hypokalemia [25]. Correction of a latent potassium deficit in these patients by administration of AC might lead to enhanced citrate synthesis and secretion, whereas in healthy and in normocitraturic stone patients administration of potassium remains ineffective.

As the AC preparation used also supplies sodium, a rise in urinary sodium and calcium, and, to some extent, also of magnesium and phosphate, was expected [14]. The absence of a rise in urinary calcium would therefore indicate a reduction in calcium level if it were related to the concomitant sodium level. This finding cannot be explained by metabolic alkalosis, during which a decrease of urinary calcium is well documented [32], nor by changes in calcitonin (Table 1) which exerts a calciuric action in man [3]. With identical loads of sodium delivered by vehicle and by AC, the calcium/creatinine ratio in the urine is lowered by the latter, by 40% by AC (P. O. Schwille, unpublished data). This may indicate that AC interferes with intestinal calcium absorption, probably by enhanced complexing of free calcium ions by citrate ions.

In the postprandial period, a higher supersaturation of the urine with respect to HAP, brushite and CaOx [31, 27, 28] as well as crystalluria [31, 28] have been observed. Contributing factors are the higher urinary pH and oxalate, a deficit of inhibitors for the respective phase [31], or a combination of these factors. The combination of food and AC, which has been used as an alkalizing principle in idiopathic uric acid lithiasis, increases the relative supersaturation with HAP (Table 3) in healthy subjects. Since the concomitant crystalluria does not follow pari passu, it may be assumed that the rise in urinary citrate with AC has an inhibitory effect on the HAP system. The tendency towards nucleation and crystallization due to increased supersaturation with this phase would be partially neutralized. An accurate and final interpretation is prevented by the absence of a method to measure directly the inhibitory effects in the urine, and by the small number of crystals found per filter in the present study. In contrast, the decreasing correlations of supersaturation with HAP and phosphate crystalluria during the whole postprandial exposure period of 270 min occurring with AC suggest the dual effect of AC in this system (Results: section 2, f). For potassium citrate, but not for sodium citrate, other authors arrived at similar conclusions [23]. Two disadvantages of the administration of AC, a combination of potassium and sodium citrate, exist. The first is the approximate parallel reduction in the percentage of free ions of both magnesium and calcium (Fig. 3), i.e. there is a resulting decreased competition of magnesium and calcium for the binding sites of the oxalate ions. However, if in spite of decreased free magnesium and a tendency towards an increase in free oxalate ions (Fig. 3), the relative supersaturation with respect to CaOx does not exceed the values seen during the vehicle load (AC dose 1; Table 3), or only to a small degree (AC dose 2; Table 3), it may be concluded that under these physicochemical conditions the effect of calcium dominates that of oxalate, and that the risk of homogenous nucleation of CaOx does not increase. The other disadvantage is the rise in the RS with respect to sodium acid urate with AC dose 1 (Table 3). The median value of this change is, however, within the region of undersaturation of the urine with this phase (values < 0). Thus the risk of heterogenous nucleation of CaOx by sodium acid urate [19] due to alkalization, enhanced uric acid dissociation and natriuresis (due to the sodium supplied by AC) should not be important. Therefore, on the basis of our data, in the AC preparations used, several principles can be recognized which counteract key mechanisms in the pathophysiology of calcium urolithiasis.

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