Urol Res (1992) 20:145–155

Urological Research

Citrate and recurrent idiopathic calcium urolithiasis

A longitudinal pilot study on the metabolic effects of oral potassium citrate administered over the short-, medium- and long-term medication of male stone patients

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Accepted: August 1, 1991

Summary. In idiopathic recurrent calcium urolithiasis (RCU) in men ($n = 37$) the metabolic effects of oral tripotassium citrate (PC) were investigated in a longitudinal field study. The patients were either normo- ($n = 22$) or hypocitraturic ($n = 15$). Laboratory examinations were performed before, and after 3, 6, and more than 12 months of medication. Acceptance of PC was poor, mainly because of the salty taste of the tablet preparation chosen, and a number of participants dropped out of the study. In the remaining participants, compliance was acceptable when evaluated on the basis of urinary potassium and undesired side effects did not occur. In the short term (up to 3 months), PC evoked compensated metabolic alkalosis (pH and citrate in urine increased; blood gases remained normal), a drop in urinary calcium, together with increasing oxaluria, hydroxyapatite supersaturation, and calcium phosphate crystalluria. In the long term (> 12 months) PC urinary pH and citrate "dissociated", in that pH returned to pretreatment baseline values, whereas citrate stayed at high levels. In normocitraturics but not in hypocitraturics, urinary urea and sodium increased with PC. Hypocitraturics appeared to be less sensitive to the effects of PC, as reflected by the relatively small rise in urinary pH and citrate, and they maintained higher mean levels of indicators of bone metabolism (osteocalcin, alkaline phosphatase, hydroxyproline) despite continuous administration of PC. It was concluded that although the PC tablet preparation was effective it may not be an ideal anti-stone drug treatment in the long term and that, especially in hypocitraturics, the intrinsic metabolic defect of RCU may not be sufficiently well controlled.

Key words: Oral potassium citrate, calcium urolithiasis, acid-base metabolism, mineral metabolism, supersaturation of urine, crystalluria

Over the last 10 years alkali citrates have been used for the treatment of recurrent idiopathic calcium urolithiasis (RCU). In use are neutral potassium citrate (PC) [30, 32] and the slightly acidic complex salt potassium sodium citrate [5, 49]. Oral alkali citrates exert an alkalinizing effect on the metabolism, since, owing to the degradation of triply charged citrate to three base milli-equivalents, there is a rise in urinary pH and citrate [5, 30, 32, 49] and, during the acute load, also of capillary pH and total carbon dioxide [46, 48]. The institution of alkali citrates as anti-stone drugs was based on the following factors: (1) hypocitraturia, frequently associated with RCU [5, 19, 43, 59], (2) the results of long-standing research into causes of the latter and associated anomalies of metabolism in RCU [23, 35, 41, 44] (3) the complexing effects of citrate on calcium ions, and (4) the direct action of citrate as an inhibitor of nucleation, growth and aggregation of calcium oxalate and calcium phosphates both in vitro and in vivo [7, 15, 21, 27, 42].

Whereas in middle Europe there is a preference for potassium sodium citrate, in North America (US, Canada) PC is the preferred preparation. This is a result of the criticism levelled against potassium sodium citrate by US authors, to the effect that its sodium moiety causes increased calciuria. More specifically, sodium may abolish the decrease in calciuria, one of the beneficial effects possibly exhibited by PC [39]. However, during the long-term administration of potassium, accumulation of potassium may occur in the blood, heart, and gastrointestinal mucosa, with the risk of cardiotoxicity, diarrhea, and mucosal lesions [29]. These unwanted side effects limit the amount of bases that can safely be delivered by PC.

In RCU, citraturia can attain a low level [19, 43, 44]. It has not yet been adequately clarified whether, with maximal doses of alkali citrate, e.g. 6 g PC per day [32], normocitraturia, an acceptable increase in urinary pH, and systemic metabolic alkalosis can be achieved. This also applies to the type and degree of crystalluria and the accompanying supersaturation of urine with stone-forming constituents. Both citrate and metabolic alkalosis inhibit intestinal calcium absorption in humans and in the rat [36, 37], and effects of alkalosis on bone metabolism have been reported [1, 2]. Interestingly, in the published

studies on PC, data on the state of calcium and bone metabolism are scarce.

In the present work, RCU patients not previously classified in terms of the degree of calciuria were investigated. The aims were: (1) assessment of the effects of short-, medium- and long-term PC medication, regarding acid-base, mineral and bone metabolism, physicochemical activity products of stone-forming substances in urine, and crystalluria, which suggests microlithiasis [10, 11]; and (2) elucidation of possible differences in these effects, depending on whether the patients exhibit pre-existent normo- or hypocitraturia. We were able to show that PC effects may be not confined to acid-base metabolism, but may include the metabolism of calcium, sodium, oxalate and bone. There are additional indications that the alkalinizing effects of PC on urinary pH and on the stimulation of urinary citrate may diminish during long-term medication.

Materials and methods

1. Design of the cohort pilot study

Although a controlled intervention study of the effect of PC[1] (dosage see below) would have been desirable, as no study on PC had yet been done in Europe the present study was designed as a field trial. We expect the data obtained in this study and in another independent but identically designed trial on potassium sodium citrate [52] to yield improved insight, especially into the more critical variables, such as urinary pH and citrate. The combined data from the two trials may serve as a basis for a future controlled and blind comparative study on the effects of several alkali citrate preparations.

RCU patients were informed about the purpose and duration of the study, and their consent to take part was obtained. The overall group (no breakdown by degree of citraturia) is referred to below as N-Cit + H-Cit. For urinary citrate the lower limit of normalcy in this laboratory was taken to be 300 mg per day [44], and on this basis the two subgroups were broken down into normocitraturia (N-Cit) and hypocitraturia (H-Cit).

2. Patients and investigations

The study comprised 37 male RCU subjects. Female subjects were excluded because of the unspecific influence the menstrual cycle might exert on citrate metabolism [4]. A spectrum of individual characteristics is listed in Table 1. Subjects had in common the absence of (1) anti-stone medication (thiazides, allopurinol, phosphates, etc.); (2) disorders with renal stone formation as one of the symptoms (primary hyperparathyroidism, oxalosis, renal tubular acidosis, enteric hyperoxaluria); (3) associated disorders (hypertension, diabetes, gout, urinary tract infection etc.); (4) drug-induced stones (vitamin D overdosage, acetazolamide). Current medication with life-saving drugs was not considered grounds for exclusion, however.

The duration or RCU was 1–33 years. The metabolic activity was scored [8], but showed marked scatter (score 0–62; Table 1). On initial presentation in our laboratory, 62% of the patients had one stone or more (Table 1). The subgroups N-Cit and H-Cit did not differ statistically with respect to age, anthropometric data, duration of stone disease, time elapsed between last stone episode and first laboratory examination, number of patients with stone(s) on that occassion, number of patients with hypercalciuria. The mean metabolic activity in H-Cit was 44% higher than in N-Cit. Also in H-Cit, apart from decreased citraturia, the mean endogenous creatinine clearance was lower, but with individual values falling within the normal range (>60 ml/min; Table 1) and unremarkable serum creatinine (<1.4 mg/dl; data not shown).

3. Study performance and duration, nature and dosage of PC, drop-outs

Four examinations in the laboratory were scheduled: before treatment, and after short-term (3 months), medium-term (6 months), and long-term (>1 year) PC treatment. Except for the days on which they had to attend the laboratory, all the patients went about their usual daily activities and took their usual home diet and liquids. The study was carried out on an outpatient basis, but within the framework of our standardized laboratory program, which included ingestion of a calcium-rich synthetic test meal (see [40]). On the days of the three examinations done under the influence of PC, the morning dose of the drug (see below) was taken together with the meal; also, in several participants, the meal was supplemented by 10 μCi ^{14}C-oxalic acid (Amersham, Braunschweig; FRG), in order to assess intestinal ^{14}C-oxalate absorption in terms of the radioactivity appearing in the 3-h postprandial urine [45].

The dosage of PC was twelve beeswax tablets (so-called slow-release preparation) per day, i.e. 6 g, delivering 18.6 mmol citrate, corresponding to 55.8 base mEq; this dose was scheduled to be taken fractionated as 3 × 2 g. Up to 3 months, acceptance of the preparation was adequate (1 drop-out). At this point patients unwilling to continue PC intake over a longer period, and those with complaints as to its palatability, etc., were excluded from the trial (21 drop-outs). The remaining 16 were examined after the following 3-month period, i.e afer PC intake for 6 months. Of these last, 11 presented for the last examination, i.e., approximately 18 months after start of PC. These 11 patients recorded the times they took PC during this 18-month period. From this information it was possible to identify drug-free intervals of a maximum of 2–3 weeks' duration each, and also to calculate a total period on PC of over 1 year's PC administration. They also faithfully adhered to continuous PC intake during the 2 weeks preceding the final laboratory examination.

In order to document the effects of PC in the prevention of stones (not a major aim of the study) the stone disease history, spanning an 18-month period before PC medication and another of the same duration commencing at the start of PC medication, was recorded for the 11 patients who had taken PC over more than 1 year. Stone events were evaluated as spontaneous passage (SP) and "surgery" (S; lithotripsia, loop, etc.). For N-Cit (H-Cit) the distribution was: before PC, SP 8 (2), S 3 (4); after initiation of PC SP 2 (1), S O (1).

The laboratory examinations were coded as follows: I, prior to PC ($n=37$); II, 3 months ($n=36$); III, 6 months ($n=16$); IV, >12 months ($n=11$).

4. Analyses

All estimations in capillary blood, serum, and urine followed established procedures: blood gases, creatinine, sodium, potassium, chloride, urea, total alkaline phosphatase and the bone isoenzyme, calcium, magnesium, phosphorus, uric acid, citrate, osteocalcin (using an assay detecting the C-terminal epitope), mid-regional parathyroid hormone, hydroxyproline, pyrophosphate, sulfate, ammonium, pH, cyclic AMP, ^{14}C radioactivity. Crystalluria measurement involved filtration of freshly voided urine [17, 50, 60],

[1] In tablet form, available from Mission Pharmacal Company, San Antonio, USA

Table 1. General inclusion criteria

	N-Cit + H-Cit $n = 37$	N-Cit $n = 22$	H-Cit $n = 15$
Age (years)	39.5 ± 1.9 21–59	41.1 ± 2.5 26–59	37.2 ± 2.8 21–58
Weight (kg)	76.5 ± 2.1 55–127	75.0 ± 2.2 55–94	79.1 ± 4.1 60–127
Ideal weight (%)	115.9 ± 3.1 87–191	114.6 ± 3.2 87–139	117.8 ± 6.1 95–191
Body mass index; $\frac{\text{kg}}{[\text{height (m)}]^2}$	25.4 ± 0.7 19–42	25.1 ± 0.7 19–30	25.9 ± 1.3 21–42
Lean body mass (kg)	58.3 ± 1.0 49–79	57.4 ± 1 43–67	59.6 ± 1.7 49–79
Blood pressure (mm Hg) Systolic Diastolic	129 ± 4 83 ± 2	131 ± 5 83 ± 2	126 ± 5 84 ± 4
Duration of stone disease (years)	10.92 ± 1.47 1–33	11.73 ± 2.02 1–33	8.33 ± 2.05 2–26
Last stone episode (<12/>12 months) patients	28/9	16/6	12/3
Stones present/absent	23/14	13/9	10/5
Metabolic activity (score)	18.9 ± 2 0–62	16.1 ± 3 0–42	23 ± 4 5–62
Normo-/hypercalciuria	28/9	16/6	12/3
Calcium (mg/g)[a,b]	177 ± 10	168 ± 11	191 ± 17
Oxalate (mg/g)[a,b]	16.3 ± 1	17.3 ± 1	15.0 ± 1
Citrate (mg/g)[a,b]	259 ± 19	327 ± 17	159 ± 19*
Creatinine clearance (ml/min)[b,c]	102 ± 5	109 ± 7	91 ± 6

[a] Per gram of creatinine in same 24-h urine
[b] Upper/lower limits of normal in this laboratory: calcium <230 mg, oxalate <31 mg, citrate >200 mg (all per g urinary creatinine); creatinine clearance >60 ml/min)
[c] In 2-h fasting urine
* $P \leq 0.05$ (difference from N-Cit group)

identification and scoring of crystals in retentates by polarization microscopy (for further details see [17]).

5. *Calculations, data presentation, statistics*

The renal phosphate threshold was read from the nomogram [58]. EQUIL software [10] was used for the estimation of relative supersaturation of urine with stone-forming sustances. Cumulative changes mean Σ (value during treatment − pre-treatment value). Except for the latter (given as median, second and third quartiles) and data on citrate metabolism (medians; Fig. 5), the arithmetic means ± 1 SEM are given in the tables and figures for the sake of simplicity, i.e. despite the sometimes non-Gaussian distribution.

The total variance over time of observation (dates I–IV) was assessed by the H-test (Kruskal-Wallis [38]). In the case of variables showing significance according to the H-test, the data from examinations II and I (short-term effects), and IV and III (medium- and long-term effects) were compared by the unpaired U- and *t*-tests, as appropriate; this procedure was chosen to prevent the imbalance in the number of participants becoming a major influential factor. N-Cit and H-Cit were compared by the unpaired U- or *t*-test at each examination date, the frequency of filters with detectable precipitates by the Chi-square test [38].

Results

1. *Acceptance of PC, side effects, urine volumes*

A number of patients refused to take PC continuously beyond 6 months, mainly due to poor palatability of the tablets. Although side effects were not reported spontaneously, the patients were nevertheless questioned on this point, but the answers were negative. The remaining study participants apparently accepted the medication, as confirmed by the changes in metabolism listed below.

PC did not statistically change urinary volume; the mean values at examination dates I–IV ranged between 1559 and 2202 ml (24-h urine), 144 and 289 ml (2-h urine), and 187 and 318 ml (3-h urine).

2. *Urine potassium, sodium, ammonium, urea*

In the N-Cit + H-Cit group, as well as in both subgroups (N-Cit, H-Cit), potassium rose under PC (II), and for the rest of the treatment period it remained higher by a factor

Table 2. Potassium, sodium, ammonium and urea (per gram of creatinine) in 24-h urine (means ± SEM)[a]

	n	K^+ mmol	Na^+ mmol	NH_4^+ mmol	Urea mmol
A. Pretreatment (I) versus 3 months treatment (II)					
N-Cit + H-Cit					
I	37	38 (2)	114 (6)	25 (3)	233 (11)
II	36	70 (5)[b]	121 (6)	9 (1)[b]	236 (7)
N-Cit					
I	22	40 (3)	105 (7)	22 (2)	228 (9)
II	21	73 (6)[b]	122 (7)	10 (1)[b]	250 (7)
H-Cit					
I	15	35 (3)	127 (11)	30 (5)	240 (23)
II	15	67 (7)[b]	121 (9)	9 (1)[b]	218 (13)
B. Treatment over 6 months (III) versus treatment over >12 months (IV)					
N-Cit + H-Cit					
III	16	71 (5)	122 (10)	13 (2)	266 (12)
IV	11	86 (8)	146 (12)	8 (2)	275 (18)
N-Cit					
III	9	68 (7)	127 (15)	10 (2)	267 (17)
IV	6	95 (9)[c]	167 (18)	7 (3)	288 (15)
H-Cit					
III	7	75 (7)	116 (13)	16 (5)	266 (18)
IV	5	77 (13)	121 (9)	9 (4)	260 (37)
C. H-test (over I–IV)					
N-Cit + H-Cit		$P<0.001$	ns	$P<0.001$	$P<0.05$
N-*Cit*		$P<0.001$	$P<0.05$	$P<0.001$	$P<0.05$
H-*Cit*		$P<0.001$	ns	$P<0.01$	ns

[a] Upper limits of normal in this laboratory (mmol): potassium <70, sodium <170, ammonium <70, urea <400;
[b] $P \leq 0.05$ (difference from I in same group); [c] $P<0.05$ (difference from III in same group); ns = not significant

of 1.5–2 (III, IV) than baseline values (I). Assuming a mean creatinine excretion of 1.3 g per day before PC (I), corresponding to approx. 50 mmol potassium, then at examination dates II–IV (PC over 3 to >12 months) between 80 and 100 per cent of the potassium supplied with PC (60 mmol per day) was excreted via the urine. Clearly, on this basis, compliance, that is the intake of PC, was adequate. In both N-Cit + H-Cit there developed a tendency towards high sodium (examination dates I–IV), and it became most prominent in N-Cit (I versus II, not tested). Ammonia decreased markedly (all groups; table 2), despite an associated drop in pH (dates III–IV; Table 3). Thus, the concordant pattern of urinary ammonia and pH that was expected from normal renal acid-base handling was not seen. Low ammonia was present after 3 months of PC (II), and the lowest values were observed in N–Cit after 12 months PC (IV). Conversely, with PC there was a clear tendency toward higher urea, which was most marked in N-Cit and in N-Cit + H-Cit (increase approx. 20%; comparisons I versus IV; not tested).

3. Urinary citrate, calcium, oxalate, pH, in N-Cit + H-Cit, magnesium

In 24-h urine, 3 months' PC treatment evoked an increase in citrate, oxalate, pH, whereas calcium was decreased (II). After more than 1 year on PC (IV) these variables were not changed as compared with the figures of examination date III; citrate, oxalate, pH, remained at the levels observed at examination II, but calcium rose and returned to the baseline values (I). Magnesium was statistically unchanged by PC; the mean values were 75 (I), 76 (II), 85 (III), 88 mg per g creatinine (IV).

In 2-h fasting urine, citrate and pH were elevated at date II, and the former tended to even higher values at examination date IV; whereas pH at this time was as low as at examination date I, despite continuing PC treatment.

In 3-h postprandial urine at examination dates II–IV, that is after intake of the test meal together with PC, citrate and pH were elevated above baseline values, i.e. before PC (I), but after more than 1 year PC (IV) the pH was again as low as in I, while citrate reached a peak value. The ^{14}C radioactivity in the urine of subjects who had taken ^{14}C-oxalic acid with the meal was 2–3% of the oral dose; it remained unchanged by PC, indicating that intestinal oxalate absorption was also unchanged.

Table 3. Citrate, calcium, oxalate (per gram of creatinine) and pH in urine collected from all patients before (I) and during (II, III, IV) treatment (means ± SEM)

	n	Daily urine				Fasting urine				Postprandial urine			
		Citrate mg	Calcium mg	Oxalate mg	pH	Citrate mg	Calcium mg	Oxalate mg	pH	Citrate mg	Calcium mg	Oxalate mg	pH
A. Pre-treatment (I) versus 3 months treatment (II)													
N-Cit + H-Cit													
I	37	259 (19)	177 (10)	16.3 (0.7)	6.10 (0.07)	328 (22)	113 (7)	14.1 (0.8)	6.50 (0.10)	265 (24)	274 (15)	13.9 (0.7)	5.88 (0.07)
II	36	404 (29)[a]	130 (8)[a]	20.3 (1.6)[a]	6.82 (0.07)[a]	414 (25)[a]	89 (7)	15.6 (1.1)	6.76 (0.14)[a]	419 (25)[a]	220 (14)	16.5 (2.0)	6.33 (0.10)[a]
Mean % change from I		56	-27	25	12	26	-21	11	4	58	-20	19	8
B. Treatment over 6 months (III) versus treatment > 12 months (IV)													
N-Cit + H-Cit													
III	16	412 (57)	168 (14)	22.6 (1.6)	6.52 (0.12)	443 (64)	103 (13)	14.2 (1.9)	6.94 (0.13)	440 (51)	237 (20)	17.7 (2.6)	6.27 (0.11)
IV	11	430 (71)	170 (16)	22.4 (1.8)	6.64 (0.13)	475 (53)	107 (16)	16.2 (1.3)	6.53 (0.14)[b]	451 (60)	244 (29)	15.2 (0.7)	5.89 (0.13)
Mean % change from III		4	1	-1	2	7	4	14	-6	3	3	-14	-6
C. H-test (over I–IV)		$P<0.001$	$P<0.01$	$P<0.001$	$P<0.0001$	$P<0.05$	ns	ns	$P<0.05$	$P<0.0001$	ns	ns	$P<0.001$

[a] $P < 0.05$ or smaller versus 1 in the same group; [b] $P < 0.05$ versus III in the same group; ns = not significant

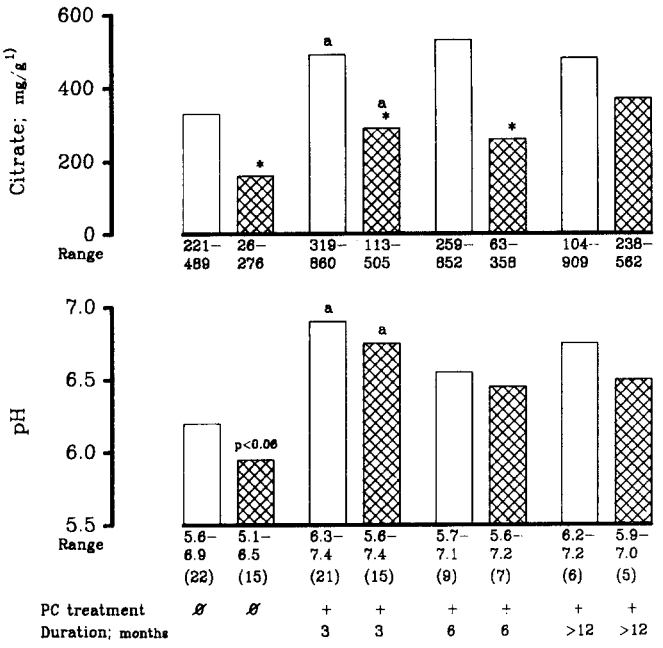

Fig. 1. Citrate and pH in 24-h urine of patients with recurrent calcium urolithiasis (RCU). *Light columns,* patients with normocitraturia; *dark columns,* patients with hypocitraturia. *Columns* represent mean values with the range of individual values beneath. *Figures* in *round brackets* show number of observations. The influence of the factor "duration of treatment (dates II–IV)" was significant (H-test; see Results). *1,* per gram of urinary creatinine; [a] $P<0.05$, versus I; *asterisk,* $P<0.05$, versus normocitraturia

4. Citrate, pH, calcium, and oxalate in 24-h urine of N-Cit and H-Cit

In both subgroups citrate and pH changed significantly (H-test) during the entire observation period (examination dates I–IV). At examination date II these two variables were increased. When N-Cit and H-Cit were compared directly, citrate and pH in H-Cit remained lower than in N-Cit, irrespective of PC treatment (II–IV), and this unexpected response could not be ascribed to inadequate compliance (see above).

Calcium remained statistically unchanged. The mean calcium excretion rates (mg per g creatinine) were: N-Cit – 168 (I), 127 (II), 177 (III), 173 (IV); H-Cit – 191 (I), 133 (II), 157 (III), 166 (IV). Oxalate also remained the same in N-Cit, but in H-Cit it was increased at examination date II ($P<0.01$). The mean oxalate excretion rates (mg per g creatinine) were: N-Cit –17 (I), 18 (II), 22 (III), 21 (IV); H-Cit –15 (I), 24 (II), 23 (III), 24 (IV).

5. Supersaturation and crystalluria in 3-h postprandial urine

In N-Cit + H-Cit, PC medication led to increasing transient (examination dates I–III) supersaturation products of hydroxyapatite, but not of brushite and calcium oxalate. Also, the mean supersaturation with hydroxyapatite, brushite, calcium oxalate, was higher in H-Cit than

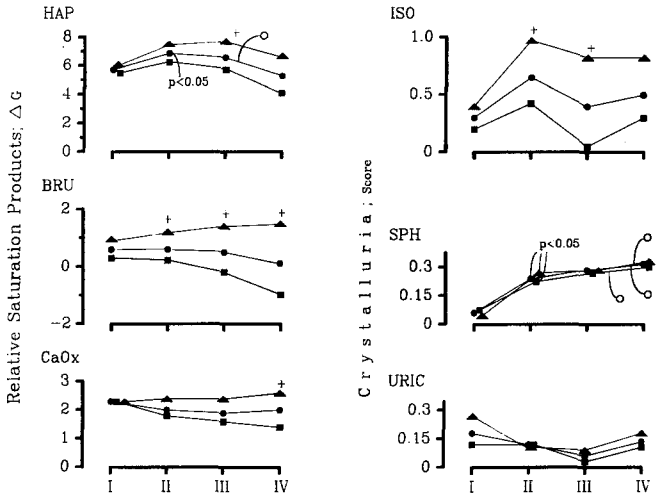

Fig. 2. Relative supersaturation products of hydroxyapatite *(HAP)*, brushite *(BRU)*, calcium oxalate *(CaOx)* in 3-h postprandial urine, and the associated crystalluria score of isotropic *(ISO)*, the spheroids *(SPH)*, and uric (URIC) phases. Data shown are means (range of individual values can be requested from the corresponding author). ●, N-Cit + H-Cit; ■ normocitraturia; ▲, hypocitraturia. For other abbreviations and the numbers of patients at examination dates I, II, III, and IV, see Material and methods. *Open circles:* $P < 0.05$, H-test; $P < 0.05$: versus I; $^{+}P < 0.05$ or smaller versus normocitraturia. Upper limits of normal in this laboratory: supersaturation – hydroxyapatite <7.7, brushite <0.9, calcium oxalate <3.8; crystalluria score – isotropic phase <1.5, spheroids <0.5, uric phase <0.5

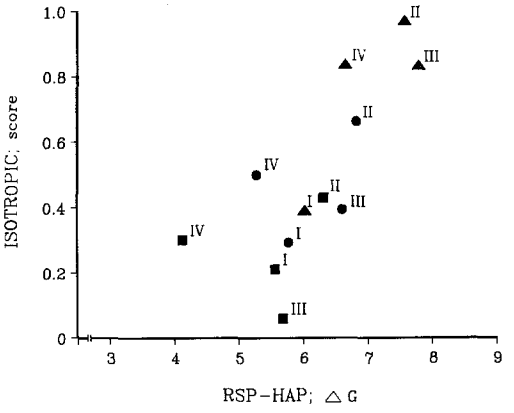

Fig. 3. Relationship in 3-h postprandial urine between supersaturation with hydroxyapatite (RSP-HAP) and the score for the isotropic phase *(ISO)*, the latter reflecting amorphous calcium phosphate. Symbols represent mean values for the three groups (●, N-Cit + H-Cit; ■, N-Cit; ▲, H-Cit) at the four dates of laboratory examination (I, II, III, IV). For further details see Materials and methods.

N-Cit subjects at examination dates II–IV, whereas calcium oxalate supersaturation at examination date I was comparable. Despite the strong dependence of hydroxyapatite supersaturation on urinary pH [10], in H-Cit the pH may not be the responsible factor, since in these individuals the rise in pH in response to PC is only slight. Also, the supersaturation with calcium oxalate and, within limits, brushite, is largely independent of pH [24]. Therefore, some combination of smaller deviations from normal, but with an influence on supersaturation data according to EQUIL, probably underlies the dissociating pattern of the latter in N-Cit and H-Cit (Fig. 2).

Particles in the urine of RCU, identifiable as crystals by microscopy, have been classified by us as follows: an isotropic phase, consistent with amorphous calcium phosphate (ISO), a lipid-like phase of spheroids (SPH), and a birefringent uric acid-containing phase (URIC) [17]. PC had no effect on the number of crystal-positive filters showing ISO and URIC. In N-Cit and H-Cit SPH was increased if the number of positive filters from examination dates II–IV were pooled and compared with those from examination date I [present/absent: N-Cit 25/8 (II–IV) versus 6/13 (I), $P < 0.01$; H-Cit 19/5 (II–IV) versus 2/12 (I), $P < 0.001$; χ^2-test]. The highest score, i.e. most crystals, was observed for the phase ISO in H-Cit (Fig. 2; right). Accordingly, in H-Cit the frequency of ISO resulting from pooling of the data from examination dates II–IV differed significantly from N-Cit [present/absent: H-Cit 18/6, N-Cit 12/21, $P < 0.01$; χ^2-test]. The development of ISO under PC roughly paralleled the hydroxyapatite supersaturation (see Fig. 2, left). Plotting the mean values of the groups revealed a direct relationship between the ISO score and hydroxyapatite supersaturation (Fig. 3), which was also the case when the individual date were plotted (now shown). Under PC the phases SPH and URIC tended towards higher and lower values, respectively, and both failed to show any relationship with any of the supersaturation products studied (uric acid was always in the undersaturation range).

6. Indicators of parathyroid gland function and bone metabolism

In N-Cit + H-Cit, serum total calcium, parathyroid hormone, phosphate threshold, urinary cyclic AMP, alkaline phosphatases, osteocalcin, were all statistically unchanged, while hydroxyproline increased (examination dates I–IV). In H-Cit, total alkaline phosphatase rose significantly, while in N-Cit all variables remained unchanged. When the two subgroups were compared directly, H-Cit had significantly higher total calcium, total alkaline phosphatase and hydroxyproline than N-Cit, all at examination date IV. In all three groups, the patterns of osteocalcin, the product of osteoblasts, and hydroxyproline "dissociated" during PC (II–IV), that is there was a tendency towards lower values of osteocalcin, which in general is considered as indicating bone formation [12], and a tendency toward higher values of hydroxyproline, reflecting bone resorption [12, 55]. It should be noted, however, that the number of subjects in this study was small.

7. Acid-base status, serum potassium, chloride, creatinine, osmolality, and blood pressure

In the case of these variables no significant changes were observed during treatment (H-test), neither in N-Cit + H-

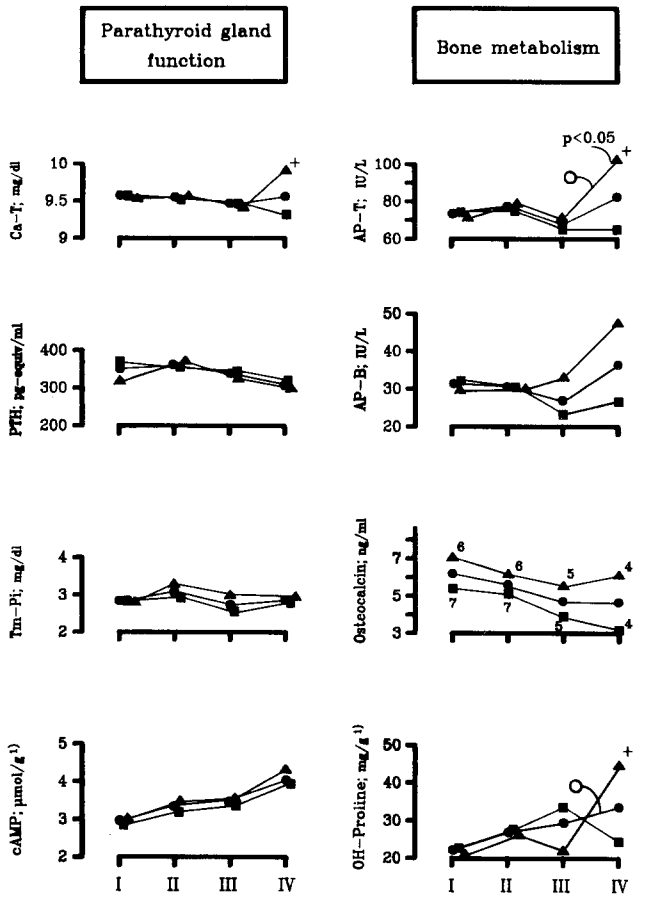

Fig. 4. Data on parathyroid function and bone metabolism, expressed in terms of serum concentration of total calcium *(Ca-T)*, parathyroid hormone *(PTH)*, total alkaline phosphatase *(AP-T)*, bone alkaline phosphatase *(AP-B)*, osteocalcin, urinary hydroxyproline *(OH-Proline)*, cyclic AMP *(cAMP)*, and renal phosphate threshold *(Tm-Pi)*. Data are mean values (standard deviations can be requested from the corresponding author). For the number of patients at the examination dates I–IV see Materials and methods, except for osteocalcin (see arabic numbers); for group symbols and other abbreviations see legend to Fig. 2. $P<0.05$: III versus IV. *l:* per gram of creatinine in 24-h urine. Upper limits of normal in this laboratory (same units as in graphs): Ca-T <10.5, PTH <1000, TmPi <3.6, cAMP <5.0, AP-T <105, AP-B <65, osteocalcin <8, OH-proline <47

Cit, nor in N-Cit and H-Cit. The mean values were between 7.34 and 7.41 (capillary pH), 23.3 and 25.0 mM/l (bicarbonate), 4.2 and 4.7 mM/l (potassium), 109–111 mM/l (chloride), 1.10–1.17 mg/dl (creatinine), 277–286 mosmol/l (osmolality), 117–138 (systolic) and 73–85 (diastolic) mm Hg (blood pressure). Since the latter data contrast with potassium-induced lowering of blood pressure in patients with mild hypertension [53], we incline to the assumption that blood pressure data in RCU patients in the present work were unremarkable from the beginning (Table 1).

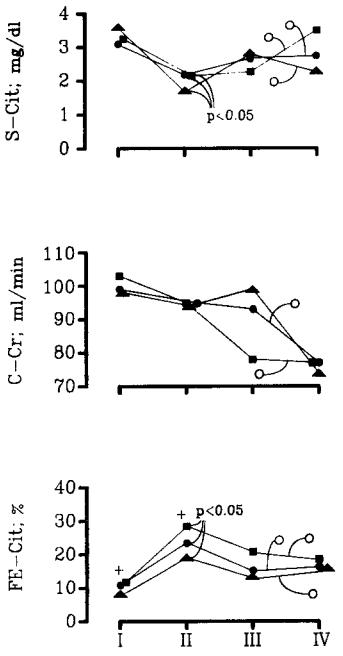

Fig. 5. Citrate metabolism, studied after a 12- to 15-h nocturnal fast, in terms of serum citrate *(S-Cit)*, creatinine clearance *(C-Cr)*, and fractional clearance of citrate *(FE-Cit)*. Data are medians (the range of individual values can be requested from the corresponding author). For the number of individual values at the examination dates I–IV, and for group symbols and other abbreviations, see Materials and methods and legend to Fig. 2. Upper limits of normal in this laboratory (same units as in graphs): S-Cit <2.9, C-Cr >60, FE-Cit <30

8. Fasting serum citrate, fasting urine creatinine clearance, fractional citrate clearance

Short-term PC evoked a drop in serum citrate in N-Cit + H-Cit, as well as in N-Cit and H-Cit, while the fractional citrate clearance increased (examination (date II). After over 1 year PC (examination date IV) serum citrate of N-Cit had returned to baseline, while in H-Cit and the total group (N-Cit + H-Cit) the mean concentration remained below the baseline. Generally, creatinine clearance also decreased (N-Cit + H-Cit, N-Cit); it should be noted that during PC there was some tendency towards low urinary creatinine (data not shown) for unknown reasons, meaning that in this presentation creatinine clearance may have been falsely too low and, in consequence, the fractional citrate clearance somewhat too high.

9. Cumulative response of N-Cit and H-Cit to long-term PC

Some variables in 3-h postprandial urine (pH, citrate, potassium, supersaturation) in 24-h urine (urea), and in serum (total calcium, bone alkaline phosphatase) were evaluated in those patients observed up to examination date IV (see methods). The aim was to clarify in the long term whether the same PC dosage (6 g per day) would lead to similar data in both groups or whether a different

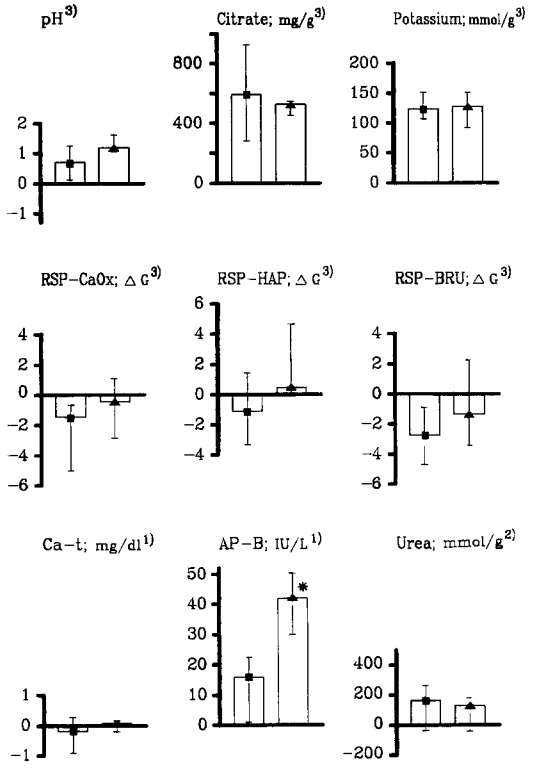

Fig. 6. Cumulative changes in nine variables, studied during PC treatment for up to over 1 year, in 6 patients with normocitraturia (■) and 5 patients with hypocitraturia (▲). Data are medians, 2nd and 3rd quartiles. RSP-CaOx, RSP-HAP, RSP-BRU are the relative supersaturation products of calcium oxalate, hydroxyapatite, brushite, respectively. *Ca-t* and *AP-B* are serum total calcium and bone alkaline phosphatase, respectively. For further explanations see Materials and methods. *1,* Fasting serum; *2,* per g creatinine in 24 h urine; *3, per gram of creatinine in 3-h postprandial urine;* $*P<0.05$ versus normocitraturia

responsiveness to PC of the two groups would be found. The selection of variables was based on changes in urine that are desirable in the drug metaphylaxis of RCU, changes in calcium and bone metabolism that are possibly associated with PC medication, but not necessarily desirable, and the (so far undocumented) modulation of urinary urea excretion by PC (see above; Table 2). Positive values were observed for pH, citrate, potassium, urea, phosphatase, negative values for the supersaturation products of calcium oxalate, brushite, hydroxyapatite (N-Cit), calcium (N-Cit). Except for the bone alkaline phosphatase, the differences between N-Cit and H-Cit were insignificant, but it should be noted that the number of patients was small. The general impression from Fig. 6, and from the above-mentioned on urinary citrate and pH, was that the responsiveness of H-Cit to PC was less than that of N-Cit.

Discussion

PC, contained in a beeswax matrix tablet (slow-release preparation [32]), tastes salty. It was this fact in particular that led numerous patients to reject continued intake of 4 tablets 3 times daily. Whether clinically inapparent PC-mediated changes, for instance gastrointestinal mucosal lesions [29], developed cannot be judged by us since we did not perform any endoscopic examinations.

Criticism of the study design

Studies on drug metaphylaxis of urolithiasis should ideally take account of recently established criteria [6]. Application of these criteria permits a reliable evaluation of stone recurrence; however, this was not the major goal of our work. Even with optimally designed protocols for such long-term observation factors as changes in dietary habits, life style, especially in terms of physical activity, and interference from other disorders, cannot be adequately controlled. Several shortcomings of earlier reports (see [6]) were shared by our study, such as the absence of a defined control group, the possibly too-short observation period, which prevented more conclusive evaluation of bone metabolism, possible unspecific factors, such as the occurrence of a stone clinic effect [18], and observer variation. Apart from these, however, there are advantages for our type of study. In consequence of earlier findings by us [49] and others [13] on a possible attenuation of alkali citrate effects with increasing duration of intake, we focused on acceptance and compliance, monitoring of citrate and acid-base metabolism, the composition of urine, and its proneness to form crystals, and the still unknown responsiveness to oral PC of N-Cit as opposed to H-Cit.

Response of N-Cit + H-Cit to PC

The increase in urinary citrate and pH (Table 3) was considered to result from the degradation of exogenous citrate to buffer bases (1 mmol triply charged citrate yields 3 mmol bicarbonate), which results in metabolic alkalosis [16]. Alkalosis per se enhances neoformation and decreases degradation of citrate, within cells [54]. According to our data obtained during PC medication up to examination date III, increasing citraturia may reflect not only the concomitant higher urinary pH with its inhibiting effect on passive back-diffusion of luminal citrate [9], but also a decrease in active reabsorption of deprotonated citrate by tubules; low serum citrate levels may at least partially reflect the latter (Fig. 5; see also below). A similar interpretation has been made for potassium sodium citrate [3, 46, 48]. The tendency towards maintenance of high urinary citrate at examination date IV, that is in the presence of falling urinary pH but rising serum citrate, was unexpected; it cannot be adequately explained by our present knowledge of renal citrate transport.

Low ammonia and simultaneously high urea in urine during PC ingestion (Table 2) were additional unexpected findings. These variables may reflect the current view of the role of the kidney in acid-base metabolism, according to which there is an interorgan flux of bicarbonate and ammonium between this organ and the liver. In essence, increasing the delivery of organic anions, like citrate, to

the kidney stimulates intrarenal bicarbonate production; simultaneously, the desamination of glutamine, an important renal energy substrate, is scaled down, thus resulting in a low ammonium supply to distal tubules and urine [22]. Renally formed excess bicarbonate is shifted towards the liver, specifically to urea synthesis. The latter process consumes bicarbonate and ammonium in stoichiometric amounts [16]. For the present study, this process, should it have occurred, might explain why there was no overt metabolic alkalosis during PC treatment, and also why the mean urinary pH did not attain higher values than about 6.9. The cause of high urinary sodium under PC is also unknow; however, citrate stimulates intestinal sodium absorption [34].

The spectrum of metabolic changes brought about by citrate and metabolic alkalosis apparently is broader than hitherto assumed [3]. For instance, with a calcium/citrate molar ratio <2.1 there was inhibition of net intestinal calcium absorption [36, 37], and stimulation of renal tubular calcium reabsorption during metabolic alkalosis has been documented [57]. Hence, the low urinary calcium (Table 3); examination date II) may be due to one of these actions, or may arise from a combination of the two. The percentage decrease in calcium corresponds roughly to the increase in oxalate in 24-h urine (Table 3; examination dates II versus I), suggesting at first glance that enhanced intestinal oxalate absorption, e.g. following intraluminal complexation of calcium citrate, has taken place, but what was not the case in the 3-h postprandial urine (see Results, Section 3). Moreover, in line with this would be the fact that increased oxaluria is absent from fasting and postprandial urine (Table 3), that is, under conditions under which by definition no oxalate had been present in the gut lumen. Against this are the urinary calcium at examination dates III and IV, when it had returned to baseline (examination date I, Table 3), and the fact that the concomitant urinary oxalate remained high. Thus, other, as yet unknown, factors may have contributed to the citrate-induced increase in oxaluria.

During treatment of RCU with potassium sodium citrate there was increasing urinary excretion of clusters of non-crystallized particles identified as amorphous calcium phosphate (in this study synonymous with the isotropic phase); the particle diameter was over 1 μm, and the urinary hydroxyapatite supersaturation was increased, as was urinary citrate [49]. These findings have been confirmed [3]. In the present study on PC similar observations were made with increase in pH, citrate, hydroxyapatite supersaturation, and isotropic phase crystalluria (Fig. 2), but no mature hydroxyapatite crystals were identified. The following interpretation is offered: the combination of high citrate, which is a strong complexor of calcium ions, and the average urine pH <7.0 at which the dissociation of calcium phosphate (into Ca^{2+} and HPO_4^{2-}) was still incomplete, led to some deficiency of these ions otherwise needed for the maturation of hydroxyapatite. Alternatively, considering that citrate is an inhibitor of the transition of amorphous calcium phosphate into hydroxyapatite [25], the presence of high urinary citrate may have prevented the development of hydroxyapatite. Accordingly, as hydroxyapatite can induce heterogeneous nucleation of calcium oxalate [33, 39], the virtual absence of both crystal types may reflect their interdependence. These facts may also be of interest for the clinical situation, in that PC medication was found to be highly effective in the prevention of stone recurrence [32].

In RCU there may be a kind of osteopathy, the origin and characteristic features of which are not completely understood (for details see [47, 56]). Also in RCU, the course of bone turnover as influenced by citrate medication has not yet been studied. This hampers the interpretation of the opposite development of osteocalcin and hydroxyproline seen in the present work with PC treatment (Fig. 4), since both are considered indicators of bone turnover [14, 20] (see also below). It has long been known that triply charged citrate increases the solubility of bone mineral [31], but some role for citrate in bone remodelling has also been suggested [26]. In untreated RCU, serum citrate was not low, but rather elevated [44] and with PC, serum citrate appears low (see Fig. 5). It is not known whether bone acted as a sink for serum citrate during PC ingestion in the present study. However, the possibility that PC may induce improvement in RCU osteopathy would be attractive. Some untoward effect could have been exerted by PC as well. Elevated serum 1,25-dihydroxyvitamin D is most probably frequent in RCU [51], as also is elevated total serum calcium, albeit still within the normal limit [47]. These facts, the uncertainty about PC effects on the D metabolite, and the observed tendency towards higher urinary hydroxyproline and higher bone alkaline phosphatase during the later PC treatment period, are reminiscent of osteoclast-induced increased bone resorption, possibly mediated by 1,25-dihydroxyvitamin D [55].

Pecularities of H-Cit during PC treatment

The mechanisms underlying hypocitraturia in RCU are insufficiently understood [19, 41]. Also, in the present work, a comparison of the responses of H-Cit and N-Cit fails to clarify details. Despite almost identical criteria in the members of both subgroups (Table 1), in the urine of H-Cit, citrate and pH were lower than in N-Cit (Fig. 1). This might be indicative of a more severely disturbed metabolism of unknown origin in H-Cit. Alternatively, because of equal compliance in N-Cit and H-Cit (Table 2), the latter may have exhibited a decreased responsiveness to PC. Pak [30] found a continuous increase in urinary citrate from pretreatment values over 36 months of PC treatment. In contrast to our patient population, with its predominance of normocalciuria (Table 1), hypercalciuria predominated in Pak's population. We earlier reported that hypocitraturia was more frequent in normo- than hypercalciuria [43, 44] (see also Table 1). Possibly, normocalciuric RCU is relatively resistant to PC. Development of intracellular acidosis leads to hypocitraturia [54], which is why a knowledge of intracellular pH as an important determinant of citraturia appears desirable in RCU. Another future area of research would be the interorgan flux of bicarbonate and ammonium, which proba-

bly accounts for the differences in urea excretion in N-Cit and H-Cit (Table 2) [16].

Concluding remarks and outlook

The introduction of alkali citrates into the metaphylaxis of RCU greatly stimulated comparative therapy research in this disorder. The knowledge that has since accrued on the regulation of citrate metabolism, especially in RCU [3, 41, 54], requires us to make more differentiated judgements as to the efficacy of these drugs. The results of our work make it appear likely that, in addition to those long documented, PC also exerts as yet unknown actions. These may include some modulation of liver, bone, oxalate, and sodium metabolism. Within the limits dictated by the study design it can be stated that the urinary pH-decreasing effect of PC diminishes, at least when medication lasts more than 6 months. This fact makes it worthwhile to study the utility of alkali citrates, with the aim of introducing medication-free intervals, as a possible means of preserving the sensitivity of those sites in the body that are responsible for bringing about a less acidic or neutral urinary pH under these agents.

Acknowledgements. We are grateful to the urologists who referred patients to our stone clinic. G. Hoffmann, B. Schreiber, and K. Schwille, provided technical assistance, I. Goldberg, secretarial work. Financial support was generously granted by the Division of Research and Development, Madaus, Ltd., Cologne, FRG.

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