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The in-vivo effect of sodium-potassium citrate on the crystal growth rate of calcium oxalate and other parameters in human urine

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Summary. In this study, an efficient microtechnique (gel crystallization method) was used to investigate the in-vivo effect of sodium-potassium citrate on the crystal growth rate of calcium oxalate (Vcr) in human urine samples of 6 healthy volunteers. With a daily dose of 3×11 mmol of alkali citrate, Vcr decreased by 70%. This could have been due to the decrease of calcium excretion, which caused 50–60% of the total change, and to the increase of citrate and pH, each contributing about 20–25% to the decline of Vcr. The findings explain the clinical advantages of alkali citrates in the prevention of recurrent calcium oxalate stone formation.

Key words: Alkali citrate – Calcium oxalate – Crystal growth – Human urine – Prophylactic treatment – Urolithiasis

Alkali citrates have been used as an efficient therapy in uric acid lithiasis, hypocitraturic calcium nephrolithiasis and in renal tubular acidosis [9, 11–13].

The main physiological effects during therapy have been significant increases in urinary pH, citrate and potassium, and a decrease in calcium excretion [11–13, 10].

We have developed a new, highly efficient microtechnique for the determination of crystal growth kinetics in gel matrices (Gel Crystallization Method; GCM) [1, 2]. By this method, the total effect of thermodynamic and kinetic factors on the crystal formation rate of calcium oxalate hydrates (Vcr) can be determined [4, 8].

The parameter Vcr is therefore more related to the risk of calcium oxalate (Caox) stone formation than corresponding calculated supersaturation, which is often used as a physicochemical marker [5].

It was the aim of this study to evaluate the in-vivo effect of sodium-potassium citrate on the crystal growth rate of Caox as measured by the GCM and to estimate the contribution of the different urinary parameters related to the total change of Vcr.

Material and methods

Normal subjects and treatment schedule. 6 healthy male normal volunteers (age: 22–47 years; average: 29 years) participated in the study on the basis of the experimentally determined crystal growth rates of Caox (Vcr) in their 24-h urines. As a rule, $Vcr > 0.5$ was accepted to be high enough to observe a potential decreasing effect during treatment.

The schedule of the study is demonstrated in Fig. 1. During the first period (A; without treatment) the subjects were taking usual diet which was explored in detail using a special questionnaire. At the 2. and 3. day of this period they collected a total of 10 3-h and 2 9-h urinary fractions corresponding to the time intervalls given in Fig. 1.

Subsequently, a dose of 3×2.9 g of sodium potassium citrate was given per day up to the end of period B.

In this period (9. to 11. day) the subjects kept to the same diet in quality and quantity of nutrition and fluid intake as in period A. and followed the same normal habits. Corresponding urinary fractions in B. were collected as mentioned before.

Preparation. One packaged dose of the drug preparation (Oxalyt C®; Dr. Madaus & Co.) contained 2.9 g powdered sodium potassium hydrogen citrate corresponding to 13.1 mmol K, 13.1 mmol Na, and 10.9 mmol citrate. The powder was dissolved in appropriate liquids and given orally. One portion was taken with breakfast and two portions were taken with dinner.

Sample handling and laboratory measurements. Urinary volumes were registered and pH-values were electrometrically measured by pocket pH-meters just after voiding. After that, two 20-ml samples of each fraction were frozen at −20 to −30 °C and stored at −80 °C up to further laboratory investigation.

24-h urines were composed by pipetting of corresponding aliquots of the single fractions immediately after thawing.

The relative crystal growth rate of Caox (Vcr) was determined in all urinary fractions and 24-h urines. In order to avoid unreliable results by potential precipation of calcium phosphate, especially at high pH values, Vcr was measured after acidifying and adjusting the pH of all solutions to 6.0.

Corresponding values of Vcr at original pH were derived from the results of measurements in artificial and native urines using a corresponding mathematical relationsship (see below).

Relative crystal growth rates of Caox (Vcr) were determined using the automated Gel Crystallization Method (GCM) [1, 2]. Measuring device: automated microphotometric system for trans-

Therapy	none		Na-K citrate		
Dosage			3×2.9 g per day		
Diet	free, documented		free		corresponding to period A
Periods		A			B
Time (days)	1.	3.	4.	8.	9. 11.

Fig. 1. Treatment schedule of in-vivo test of sodium potassium citrate with respect to its effects on parameters of crystal formation in urine of healthy probands. A and B = collection of 12 urine samples during 2 days. Time periods = 7–10, 10–13, 13–16, 16–19, 19–22, and 22–7 h

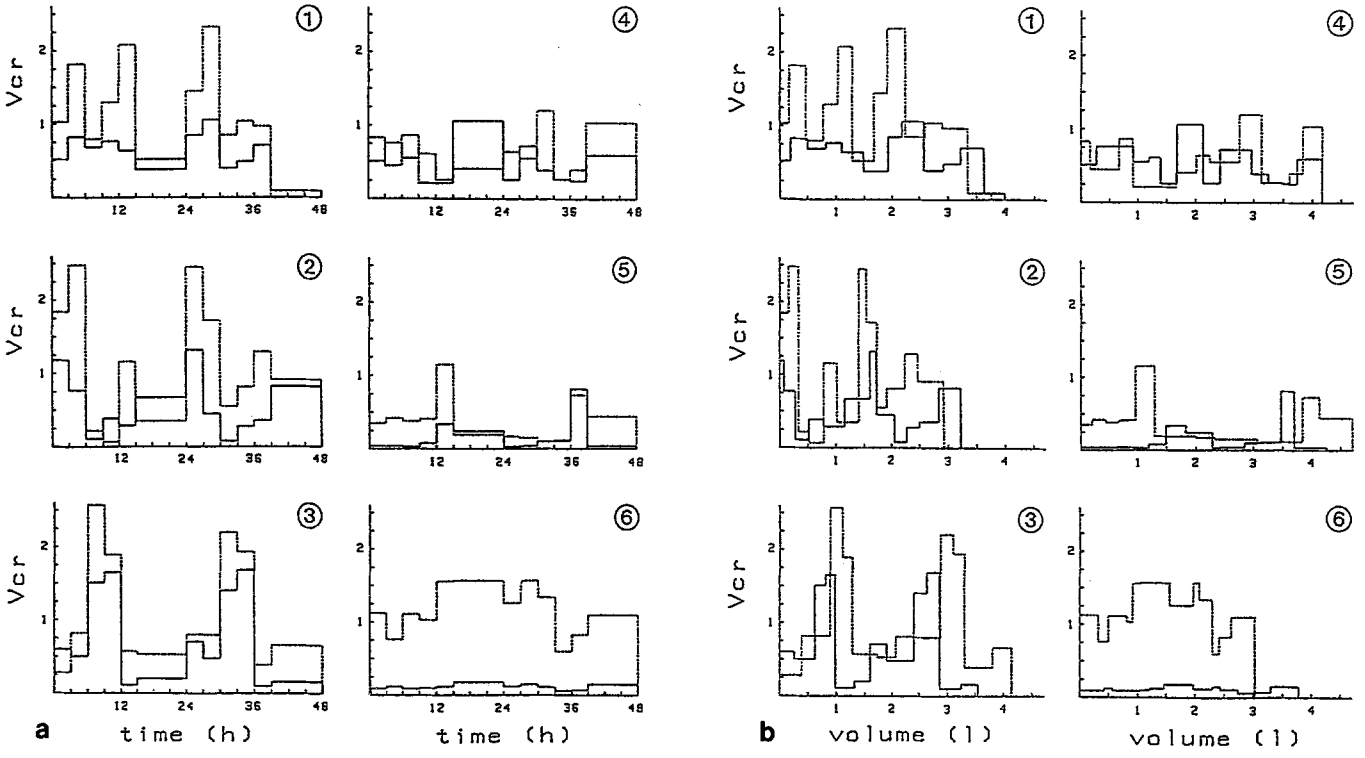

Fig. 2 a and b. Crystal growth rate of Caox (Vcr) at pH 6.0 as a function of time (**a**) and voided volume (**b**) in fractional 3- and 9-h urines of 6 healthy probands before (broken curves) and during application (full curves) of sodium potassium citrate

mitted light, equipped with rapid scanning stage adapted to 96-well microtiter plates, electronic control unit MPC 64, and on-line computer HP 9816S (Zeiss, Oberkochen, FRGermany: Hewlett-Packard). Mode of measurement: dark field. Gel matrix: 0.5% (w/w) agar-agar, 2 mmol/l sodium oxalate, and approximately 0.1 mmol/l seed crystals of Caox. Measuring standard solution (total concentrations in parentheses given in mmol/l): Na (131), K (40), NH4 (25), Ca (4.0), Mg (3.0), phosphate (20), sulfate (15), citrate (2.0), chloride (149), urea (250), pH 6.0.

In addition to pH and Vcr, the following parameters were determined in 24-h urines: total concentrations of Ca, Mg, Na, K, phosphate, and sulfate by ICP-coupled atomic emission spectroscopy (simultaneous spectrometer JY 32P; Instruments S.A.); citrate, isocitrate, creatinine, urate, and oxalate by enzymatic microphotometric analysis in 96-well microplates (automated pipetting station TECAN 505; microplate reader MR 600, Dynatech; commercially available kits from Boehringer, Mannheim, FRG [3]).

Saturation ratios of calcium oxalate, uric acid and brushite were calculated using a computer program for the calculation of complex chemical equilibria written in HP-BASIC 2.0 [7]. They represent the ratios of the activity products of corresponding counterions divided by their thermodynamic solubility products. The following solubility products were used (given in mol^2/l^2): Ksp (Caox) $= 3.63 \cdot 10^{-9}$, Ksp (brushite) $= 2.49 \cdot 10^{-7}$, Ksp (uric acid) $= 9.86 \cdot 10^{-10}$.

Probability of significance of differences in measured or calculated values between pretreatment and treatment periods was assessed by appropriate statistical tests for paired data. Principally, distributions of sample data were evaluated using the Shapiro Wilk test. For normal distribution the paired t-test was applied and checked by the Wilcoxon test. Otherwise the sign test was used. Calculations were carried out using the Statistics Library HP 98820A (Hewlett-Packard).

Table 1. Effect of sodium potassium citrate therapy on urinary crystal growth parameters (at pH 6) from 48-h profiles of 6 healthy volunteers corresponding to Fig. 2

Variable ($n=6$)	1. and 2. day of collection (48-h profiles)		
	before therapy mean ± SD	during therapy mean ± SD	p*
Σ Vcr · Δ time (h)	41.3 ±14.7	21.0 ± 11.2	0.016
Σ Vcr · Δ volume (l)	3.08 ± 0.99	1.63 ± 0.91	0.010

* one-sided statistical test

Table 2. Parameters of crystal growth of Caox in 24-h urine samples of 6 volunteers before and during therapy with sodium potassium citrate

Pos		Mean values from 1. and 2. day of collection			
		before therapy	during therapy	Δ (abs.)	Δ (%)
1	pH, exp.	6.08	6.98	+0.90	
2	Vcr, exp. (pH 6.0)	0.91	0.42	−0.49	−54%
3	Vcr, calc. (pH 6.0)	1.45	0.74	−0.71	−49%
4	Vcr, calc. (pH, exp.)	1.44	0.55	−0.89	−62%
5	Vcr, corr. (pH, exp.)	0.90	0.23	−0.67	−74%

Results

Effect of sodium potassium citrate therapy on the crystal growth rate of Caox in urinary fractions (Fig. 2 and Table 1)

Figure 2 shows the relative crystal growth rate of Caox (Vcr) at pH 6.0 in the 3- and 9-h urinary fractions of the 6 subjects under consideration. Vcr is plotted vs. time of collection (Fig. 2a) and vs. voided volume (Fig. 2b) as 48-hour profiles before (broken curves) and during treatment (full curves).

As may be seen from both figures, Vcr was significantly reduced during treatment with Na-K-citrate in most of the urinary fractions of 5 subjects. Temporary peaks of Vcr seen in the periods without therapy were diminished in all probands.

At constant oxalate concentration, the crystal growth risk of Caox should be mainly determined by Σ Vcr · Δ time or Σ Vcr · Δ Vol represented by the areas under the corresponding profiles in Fig. 2. As demonstrated in Table 1, a significant reduction of about 50% of each of these parameters occurred during treatment.

It may further be derived from Fig. 2 that there was a differential response of the subjects to the therapy in terms of the crystal growth parameter measured.

Measurements of Vcr were carried out at pH 6.0 because potential precipitation of calcium phosphates in single fractions could have lead to artifacts. Therefore, the results presented in Fig. 2 and Table 1 do not take into account the additional Vcr-reducing effect of pH. This will be regarded with respect to 24-h urines in the next section.

Effect of sodium potassium citrate therapy on crystal growth parameters in 24-h urines

Apart from the measurements in fractional urinary samples, Vcr was experimentally determined in all 24-h urines at pH 6.0 (Tables 2 and 3). In order to estimate the crystal growth parameter at original pH, the dependence of Vcr on pH was determined by separate experiments.

From multiparametric variations of pH and total concentrations of calcium, citrate and magnesium in artificial urine, the following relationship between Vcr and these parameters could be derived (Equation 1) [6].

$$\mathrm{Vcr} = \frac{1 + P_{101}\left(\frac{Ca_T}{Ca_N} - 1\right) + P_{201}\left(\frac{Cit_T}{Cit_N} - 1\right)}{1 + P_{102}\left(\frac{Ca_T}{Ca_N} - 1\right) + P_{202}\left(\frac{Cit_T}{Cit_N} - 1\right)} \cdots$$

$$\cdots \frac{+ P_{301}\left(\frac{pH}{pH_N} - 1\right) + P_{401}\left(\frac{Mg_T}{Mg_N} - 1\right)}{+ P_{302}\left(\frac{pH}{pH_N} - 1\right) + P_{402}\left(\frac{Mg_T}{Mg_N} - 1\right)} \cdots \quad \text{(Eq. 1)}$$

$$\cdots \frac{+ P_{231}\left(\frac{Cit_T}{Cit_N} - 1\right)\left(\frac{pH}{pH_N} - 1\right)}{+ P_{232}\left(\frac{Cit_T}{Cit_N} - 1\right)\left(\frac{pH}{pH_N} - 1\right)} \cdots$$

$$\cdots \frac{+ P_{241}\left(\frac{Cit_T}{Cit_N} - 1\right)\left(\frac{Mg_T}{Mg_N} - 1\right) + P_{441}\left(\frac{Mg_T}{Mg_N} - 1\right)^2}{+ P_{242}\left(\frac{Cit_T}{Cit_N} - 1\right)\left(\frac{Mg_T}{Mg_N} - 1\right)}$$

$P_{101} = 1.780$; $P_{201} = -0.247$; $P_{301} = -0.655$; $P_{401} = -0.041$;
$P_{231} = -0.543$; $P_{241} = 0.041$; $P_{441} = -0.021$
$P_{102} = -0.125$; $P_{202} = 0.201$; $P_{302} = 0.792$; $P_{402} = 0.151$;
$P_{232} = 0.123$; $P_{242} = -0.036$
$Ca_N = 4$ mmol/l; $Cit_N = 2$ mmol/l; $pH_N = 6.0$;
$Mg_N = 3.0$ mmol/l

Inserting repective mean values of the variables into the equation, "theoretical" values, Vcr, calc., could be calculated at pH 6.0 and mean original pH before and during therapy (Table 2; line 3 and 4). Therefrom, a value for Δ Vcr/Δ pH = 0.20 was derived and used to correct the experimental Vcr at pH 6.0 (line 2) with respect to the additional influence of pH (line 5).

Additionally, the dependence of Vcr on pH was estimated in 42 24-h urines in the following way. Samples were adjusted to pH 7.0 and, after centrifugation of possible precipitates, acidified to pH 6.5, 6.0, 5.5, and 5.0

Table 3. Effect of sodium potassium citrate therapy on parameters in 24-h urines of 6 healthy volunteers

Variable	1. day of collection			2. day of collection		
	before therapy mean ± SD	during therapy mean ± SD	p	before therapy mean ± SD	during therapy mean ± SD	p
Volume (ml)	1,786 ± 274	1,915 ± 274	ns.	2,000 ± 461	1,909 ± 172	ns.
pH	5.96 ± 0.34	6.99 ± 0.25	***	6.21 ± 0.23	6.98 ± 0.26	***
Calcium	4.95 ± 1.29	3.65 ± 1.02	ns.	4.38 ± 1.39	3.43 ± 0.77	ns.
Magnesium	3.07 ± 1.05	2.76 ± 1.01	ns.	2.81 ± 0.90	2.63 ± 0.51	ns.
Sodium	114 ± 26	114 ± 33	ns.	112 ± 37	116 ± 35	ns.
Potassium	43.7 ± 15.0	64.3 ± 17.9	**	40.3 ± 16.0	57.7 ± 11.3	*
Oxalate	0.12 ± 0.04	0.12 ± 0.05	ns.	0.11 ± 0.03	0.11 ± 0.02	ns.
Phosphate	24.8 ± 7.8	23.3 ± 7.6	ns.	23.4 ± 7.8	20.8 ± 7.2	ns.
Citrate	1.57 ± 0.41	2.31 ± 0.91	*	1.53 ± 0.52	2.33 ± 0.50	**
Isocitrate	0.21 ± 0.06	0.21 ± 0.05	ns.	0.22 ± 0.06	0.23 ± 0.03	ns.
Sulphate	16.6 ± 5.4	15.4 ± 6.9	ns.	14.7 ± 4.5	14.7 ± 4.8	ns.
Uric acid	2,09 ± 0.58	1.78 ± 0.59	ns.	1.68 ± 0.53	1.86 ± 0.52	ns.
Creatinine	9.94 ± 3.02	9.18 ± 2.92	ns.	8.49 ± 2.37	8.68 ± 2.16	ns.
Vcr (pH 6.0)	0.88 ± 0.31	0.37 ± 0.19	**	0.94 ± 0.43	0.46 ± 0.28	**
Saturation ratio:						
S(Caox)	2.64 ± 0.91	1.77 ± 0.91	*	2.11 ± 0.85	1.61 ± 0.47	ns.
S(UA)	1.30 ± 0.89	0.17 ± 0.16	**	0.62 ± 0.24	0.18 ± 0.16	**
S(brushite)	3.10 ± 1.85	4.85 ± 1.95	ns.	3.67 ± 2.17	4.08 ± 1.63	ns.

*$p<0.05$; **$p<0.01$; ***$p<0.001$ corresponding to appropriate statistical test of paired data before and during therapy. Tests were one-sided for pH, Ca, K, citrate, Vcr, S(Caox) and S(UA), and two-sided for the remaining parameters

by 1 M HCl. Subsequently, Vcr was determined in these fractions. A mean value of $\Delta Vcr/\Delta pH = -0.23$ resulted from linear regression analysis of the data. It agreed fairly well with that derived from the relationship mentioned above.

Taking into account these results, the (corrected) mean crystal growth rate of Caox in 24-h urines at original urinary pH is decreased from 0.90 before therapy to 0.23 during treatment with sodium potassium citrate. This corresponds to a relative decline of Vcr of about 74%.

Effect of sodium potassium citrate therapy on other urinary parameters

Apart from the crystal growth rate of Caox, a series of other parameters was determined in the 24-h urines before and during treatment. The results are presented in Table 3. The two days of investigation in both periods were regarded separately.

Application of Na-K-citrate caused significant increases in urinary pH, citrate and potassium. Total calcium concentration was decreased by about 25%. The 95% level of significance for this difference was just missed (P = 0.07) perhaps due to the small number of subjects included in the study.

Isocitrate, which has not been considered hitherto in similar studies, remained unchanged during treatment with alkali citrate.

From the experimental data shown in the upper part of Table 3, the relative saturation ratios of calcium oxalate, brushite (DCPD) and uric acid were calculated [7]. During treatment, S(Caox) decreased by about 30% and S(UA) by more than 80%. Though there was a mean increase of S(brushite) by approximately 24%, the difference could not be shown significant.

Contribution of individual parameters to the alteration of crystal growth of calcium oxalate

It is known that the crystal growth of Caox is affected by those urinary parameters which are predominantly altered during treatment with alkali citrate, i.e., calcium, citrate and pH (Table 3).

As an example, Fig. 3 shows the crystal growth parameter Vcr measured by the GCM as a function of normalized concentrations of Ca_T, Cit_T, Mg_T and pH in artificial urine. Along each curve an individual variable was altered while keeping all others at their normal values. The section point of all curves (Vcr = 1; all normalized concentrations = 1) corresponds to the "normal" state.

From those multiple variations in artificial urine, equation 1 was derived by nonlinear regression analysis.

It was used to calculate Vcr from the respective means of experimentally determined Ca_T, Mg_T, Cit_T and pH in the 24-h urines before and during treatment with alkali citrate. As shown in Table 2, calculated values of Vcr (Vcr, calc.) are higher than their experimental counterparts. This may be accounted for by the presence of additional inhibitors in native urine compared to artificial solutions. However, the relative differences of calculated and experimental Vcr before and during treatment were comparable.

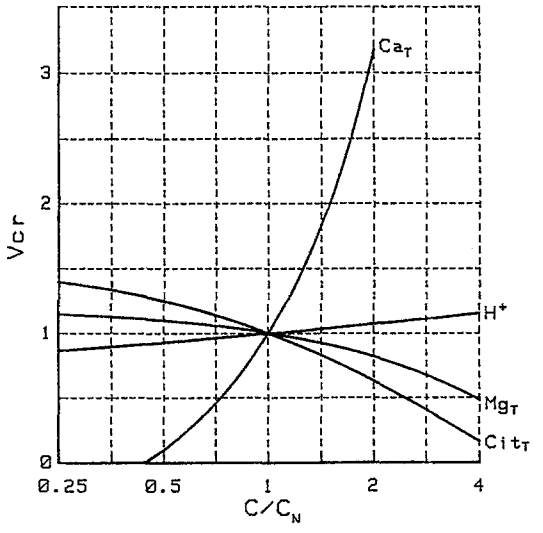

Fig. 3. Dependence of the crystal growth rate of calcium oxalate (Vcr) on normalized total concentrations of calcium (Ca_T), citrate (Cit_T), magnesium (Mg_T), and hydrogen ion (H^+) in artificial urine. Method: gel crystallization method (2 mmol/l oxalate; 0.5% agar-agar). Normal concentrations (at $c/c_N = 1$): $Ca_T = 4$ mmol/l, $Cit_T = 2$ mmol/l, $Mg_T = 3$ mmol/l, $H^+ = 10^{-6}$ mol/l (pH = 6.0). At $c/c_N = 0.25$ and 4 pH corresponds to 6.6 and 5.4, respectively

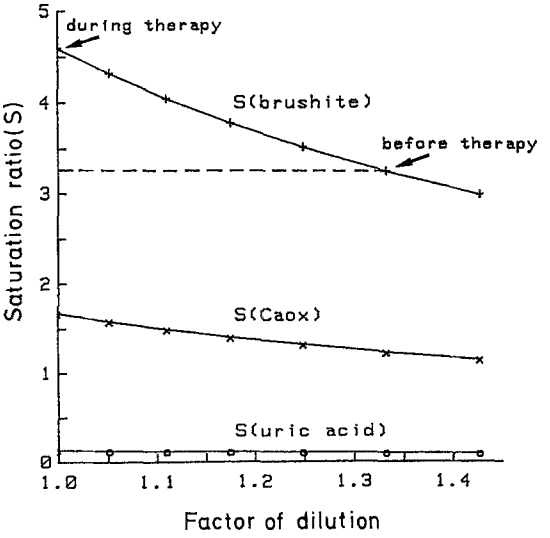

Fig. 4. Calculated saturation ratios of brushite, calcium oxalate and uric acid as a function of urine dilution starting from mean values of 24-h urines of the 6 probands during therapy with sodium potassium citrate (computer simulation of supplementary fluid intake during treatment)

The following partial contributions of Ca_T, Cit_T and pH to the total decrease of Vcr could be estimated by stepwise mathematical variation of these parameters along their axis of coordinates from the level before therapy to that during therapy. According to this, about 57% of the total decline of Vcr is due to the decrease of calcium excretion, 20% to the increase of urinary citrate, and about 23% should be caused by the elevation of pH.

Discussion

In this study, an highly efficient microtechnique (gel crystallization method) was used to measure the in-vivo effect of sodium potassium citrate on the crystal growth rate of calcium oxalate in urine of 6 healthy male volunteers.

Applying a daily dose of 3×11 mmol, a mean decrease of the crystal growth parameter Vcr of more than 70% was caused by the preparation.

Regarding the individual parameters calcium, citrate, pH and potassium, our data agree in principle with other results on the physiological and physicochemical effects of alkali citrate treatment in human urine [10, 11].

Though a significant decrease of urinary calcium seems to be detectable only under a standardized or strictly controlled diet in the periods before and during treatment, from our study, calcium was most effective with respect to the reduction of the crystal growth rate. It caused more than 50% of the total decline of Vcr during therapy while corresponding increasing citrate and pH each accounted for 20–25% of the effect.

Since the specific alterations of all three parameters observed affect the crystal growth of calcium oxalate in the same direction, the change of Vcr is most pronounced compared to all other experimental values.

Furthermore, the parameter Vcr is sensitive to both thermodynamic and kinetic effectors of the crystal growth process. This explains the decrease in Vcr of more than 70% compared to a lesser reduction of the urinary saturation ratio of calcium oxalate (S(Caox)) of only 30% during treatment with Na-K-citrate.

The direct kinetic effect of citrate and a corresponding indirect contribution of pH (via deprotonation of other urinary constituents) to the inhibition of Caox crystal growth could also be demonstrated by crystallization in a gel matrix [4, 8].

In contrast to the significant change of urinary citrate during treatment, no alteration of isocitrate could be found in the study. This demonstrates that the metabolism and renal handling of isoctrate should be unaffected by alkali citrate therapy.

The relative saturation ratios for calcium oxalate, uric acid and brushite (Table 3) may be regarded as the "thermodynamic risks" for these crystal phases under consideration.

S(Caox) is decreased as described above. S(UA) is reduced drastically (by 80%) as a consequence of increased pH, which corresponds to the well known effect of alkali citrate in uric acid lithiasis.

Because treatment with alkali citrate causes a considerable increase of pH, S(brushite) is elevated. However, the increase could not be proven to be significant, which must be due to the simultaneous decline in urinary calcium and the increase in citrate. The result is in agreement with the findings described by Pak et al. [11].

Because of the importance of potential calcium phosphate formation as an undesirable side effect in alkalini-

zing therapy, the following should be emphasized. In order to determine the "pure" in-vivo effect of Na-K-citrate, the volunteers involved in this study were advised to avoid any additional fluid intake during medication, i.e., they kept strictly to the same diet in both periods of collection. This, however, is in contrast to the usual recommendations given with alkali citrate therapy in patients with urolithiasis. Additional fluid intake reduces the risk of all crystal phases [7, 14] and should be an indispensable primary measure.

In order to obtain an estimation of that amount of fluid which would be necessary to compensate for the increased saturation of calcium phosphate during therapy, we carried out the following computer simulation (Fig. 4). Starting from the mean composition of the 24-h urines during treatment, fluid excretion or intake was simulated by stepwise reduction of all urinary constituents, except pH value. The relative saturation ratios of brushite, Caox and uric acid were plotted as a function of the hypothetical fluid increase. As may be derived from Fig. 4, an elevation of the 24-h excretion volume by a factor of 1.33 (corresponding to a supplement of about 600 ml) would reduce the saturation ratio for brushite to the amount before therapy. Thereby, S(Caox) and S(uric acid) are dimished nearly by the same percentage. Thus, an intake of one portion (= 11 mmol) of sodium potassium citrate dissolved in an extra 200 ml of fluid should avoid any potential complications from calcium phosphate formation during treatment and would cause a further decrease in the crystal growth rate of Caox.

As may be seen from Fig. 2, the response of individual subjects to the dose of alkali citrate applied may be different. While subject no. 6 was an ideal responder to the therapy, practically no effect could be observed in subject no. 4. Thus, considering the well-established indications [11], an individual dose/response test should be useful before treating a patient on a long-term basis with alkali citrate.

With this respect, the crystal growth rate of Caox as measured by the GCM is a suitable diagnostic parameter in order to control the efficacy of therapeutic measures in patients suffering from calcium oxalate urolithiasis.

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