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Erik Fjellstedt · Torsten Denneberg
Jan-Olof Jeppsson · Hans-Göran Tiselius

A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria

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Abstract For many years, urine alkalinization has been one of the cornerstones in the treatment of homozygous cystinuria. Because of the relationship found between the excretion of urinary sodium and cystine, potassium citrate has emerged as the preferred sodium-free alkalizing agent. To evaluate the usefulness of potassium citrate for urine alkalization in cystinuric patients, sodium bicarbonate and potassium citrate were compared in 14 patients (10 on tiopronin treatment and four without treatment with sulfhydryl compounds). The study started with 1 week without the use of any alkalizing agents (*Period 0*) followed by 2 weeks with sodium bicarbonate (*Period 1*) and 2 weeks with potassium citrate (*Period 2*). Urinary pH, volume, excretion of sodium, potassium, citrate and free cystine, as well as the plasma potassium concentration, were recorded. Potassium citrate was shown to be effective as an alkalizing agent and, in this respect, not significantly different from sodium bicarbonate. Even though a normal diet was used, a significant increase in urinary sodium excretion was observed with sodium bicarbonate (*Period 1*). Urinary potassium and citrate excretion increased with potassium citrate (*Period 2*). A significant correlation was found between urinary sodium and cystine in the tiopronin-treated patients. No significant differences in cystine excretion were recorded in *Periods 0, 1* and *2*. Plasma potassium was significantly higher during *Period 2*, but only one patient developed a mild hyperkalemia (5.0 mmol/l). The use of potassium citrate for urine alkalization in homozygous cystinuria is effective and can be recommended in the absence of severe renal impairment.

Keywords Cystinuria · Cystine · Urinary pH · Sodium bicarbonate · Potassium citrate

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E. Fjellstedt (✉)
Department of Nephrology and Transplantation,
Malmö University Hospital, 205 02 Malmö, Sweden
E-mail: erik.fjellstedt@swipnet.se

E. Fjellstedt
Department of Internal Medicine, Motala Hospital,
Motala, Sweden

T. Denneberg
Department of Urology, University Hospital, Linköping,
Sweden

J.-O. Jeppsson
Department of Clinical Chemistry, Malmö University Hospital,
Malmö, Sweden

H.-G. Tiselius
University Hospital Malmö and Department of Urology,
Huddinge University Hospital Stockholm, Sweden

Introduction

Stone formation in homozygous cystinuria constitutes approximately 1% of urinary calculi [1]. The basis of urinary cystine crystallization is an autosomal, recessive defect in proximal tubular cells, which causes an increased excretion of cystine and dibasic amino acids. Urinary stone formation occurs because of the low solubility of cystine. Treatment of this disease is two-fold: lowering the concentration of free cystine and increasing cystine solubility.

Maintaining a high fluid intake reduces the concentration of urinary cystine. The introduction of the sulfhydryl compounds D-penicillamine and tiopronin (2-mercaptopropionylglycine) made it possible to reduce free urinary cystine by forming soluble disulfide complexes between cystine and tiopronin or cystine and D-penicillamine [7, 8, 9, 10, 17, 19, 31].

Dent and Senior showed in 1955 that urinary cystine solubility was pH-dependent and that an increased urinary pH resulted in an increased solubility of cystine [11]. The traditional way to alkalinize urine has been to give sodium bicarbonate [11, 12]. A number of in vitro studies have suggested, however, that amino acid transport across tubular epithelial cells is coupled with a

parallel transport of sodium [37, 38, 43]. Moreover, a reduction of sodium intake in cystinuric patients resulted in a diminished cystine excretion [14, 24, 33]. Lindell et al. confimed the relationship between sodium intake and urinary cystine excretion[20]. They found a reduction in mean cystine excretion after withdrawal of sodium bicarbonate while on a daily sodium intake of 50 mmol.

Consistent use of pronounced dietary sodium restriction in clinical practice is, however, limited by patient compliance, and our general recommendation, therefore, has been to reduce the dietary intake of sodium (unpublished data). To accomplish alkalinization, without a sodium load, potassium citrate is theoretically a more attractive compound.

To our knowledge, no study has been carried out that compares the effects of sodium bicarbonate and potassium citrate in patients with cystinuria, and the recommendation of using potassium citrate seems to be based on the disadvantage of sodium administration rather than on studies of potassium citrate itself. The aim of the present study, therefore, was to investigate the biochemical effects of sodium bicarbonate and potassium citrate in cystinuric patients with and without tiopronin treatment.

Patients and methods

Patients

Table 1 summarizes the clinical characteristics of the 14 patients who concluded the study. The diagnosis of homozygous cystinuria had, in all cases, been established by determination of the urinary excretion of cystine and dibasic amino acids [16]. Eight of the patients were men, and six were women. The mean age was 49 years (range 33–74 years). The mean age at clinical presentation was 21 years (range 12–34 years), and the mean duration of the disease when the study started was 29.5 years (range 17–54 years). Ten patients were on long-term treatment with tiopronin (2-mercaptopropionylglycine, Thiola, Santen Pharmaceutical, Osaka, Japan), and four were treated with urinary alkalinization and high fluid intake. All of the tiopronin-treated patients received the drug twice daily (in the morning and at bedtime) with the daily doses of tiopronin as shown in Table 1. The Swedish National Board of Health and Welfare licensed the prescription of Thiola for each patient.

Thirteen of the patients were treated with with potassium citrate (Urocit-K, Swedish Orphan) for up to 18 months, and one of the patients (patient no. 3) was treated with sodium bicarbonate due to dyspeptic symptoms when potassium citrate was given. All patients were encouraged to maintain a high fluid intake. Three patients were also treated with other drugs, all of which were taken once daily. Patient no. 1 was treated with aspirin 75 mg, patient no. 2 with trimethoprime 100 mg as well as folacine 5 mg and patient no. 7 with amlodipine 10 mg and bendroflumethiazide 5 mg.

All of the patients had a history of active stone formation. Since the clinical onset of the disease, 12 patients had had stone surgery, and seven had been treated with extracorporeal shockwave lithotripsy (ESWL) prior to the study. Six of the patients had urinary stones visible at the latest radiographic examination, although none of the patients exhibited any symptoms of either urinary obstruction or renal colic during the study period. Glomerular filtration rates are shown in Table 1, and, as is evident, four patients had a value below the normal range [13]. Three of the patients had only one kidney, two of whom had been nephrectomized because of stone formation (patient nos. 3 and 13), and one patient had a right-sided renal aplasia (patient no. 8). The patients were usually seen at intervals of 6 months.

Study design

The study was performed during 5 weeks, according to the schedule outlined in Fig. 1. The patients started with a period of 1 week during which all alkalinizing agents were discontinued (*Period 0*). At the end of this period, patients collected a 24-h urine sample, and blood samples were drawn at the outpatient clinic (Department of Urology, Linköping University hospital). The analyses of the urine included free cystine, sodium, potassium, citrate, pH and measurement of urine volume. Blood samples were analyzed for serum concentrations of sodium, potassium, creatinine and bicarbonate. During this visit, each patient received thorough information about the study, and a detailed, individualized study guide

Table 1 Clinical characteristics of 14 patients with homozygous cystinuria. *GFR* glomerular filtration rate

Patient no	Sex	Age (years)	Duration of clinical disease (years)	Daily tiopronin dose (mg)	History of stone surgery	History of ESWL	Known renal stones at study start	GFR[a] (ml/min/1.73m^2)
1	M	48	23	3,000	Yes	No	No	111 [d]
2	F	37	24	3,000	Yes	Yes	Yes	100 [b]
3	M	67	54	2,750	Yes	No	No	**59** [b]
4	F	41	23	2,750	Yes	No	Yes	**77** [c]
5	M	57	33	2,500	Yes	Yes	Yes	110 [e]
6	F	42	24	2,500	Yes	Yes	No	101 [b]
7	M	74	42	2,250	Yes	Yes	No	79 [b]
8	M	57	39	2,250	Yes	No	No	**59** [b]
9	F	63	29	1,750	Yes	No	No	**45** [b]
10	M	44	29	1,250	No	Yes	No	100 [d]
11	F	43	28	0	No	No	No	110 [b]
12	M	42	20	0	Yes	No	Yes	113 [b]
13	F	40	28	0	Yes	Yes	Yes	93 [b]
14	M	33	17	0	Yes	Yes	Yes	101 [b]

[a] Values in bold type faces are below normal range for the method with respect to the patient's age
[b] ^{51}CrEDTA-plasma clearance
[c] ^{99m}Tc DTPA-plasma clearance
[d] ^{99m}Tc DTPA-plasma clearance estimated from external gamma-camera measurements of ^{99m}Tc- MAG III [13]
[e] 24-h endogenous creatinine clearance

Fig. 1 Design of the study

was handed out. During *Period 1* the patients were given sodium bicarbonate with a starting dose of 47.6–107 mmol based on earlier treatment with sodium bicarbonate. After 1 week, urine pH was recorded, and, if necessary, the bicarbonate dose was adjusted, aiming at a urinary pH of 7 at the end of the following week. Final doses of sodium bicarbonate are given in Table 2.

At the end of *Period 1* two 24-h urine samples were collected and analyzed as above. One set of blood samples were also drawn at this time for analyses as above. The patients were then switched to treatment with potassium citrate (*Period 2*) with a starting dose of 40–70 mmol based on earlier treatment with potassium citrate. Urinary pH was measured after 1 week, and, if necessary, the dose was adjusted, aiming at a urinary pH of 7 at the end of the following week. Final doses of potassium citrate are given in Table 2.

At the end of *Period 2*, two 24-h urinary samples were collected and blood samples drawn and analyzed in the same way as above. These steps terminated the study.

Patients were instructed to keep a uniform diet during the study periods and to continue to maintain a low-sodium intake. For practical reasons, no other dietary restrictions were given.

Two additional patients, not on tiopronin treatment, refused to take part in the study and one more patient, on tiopronin treatment, dropped out during the study for practical reasons.

Informed consent was obtained from each patient, and the study was approved by the local ethics committee.

Analytical methods

Urinary pH was measured in fresh morning urine with a glass electrode at the departments of clinical chemistry in each local hospital. The blood samples were also analyzed there. The patients measured the urinary volume of each collection, and a 10 ml aliquot of each collection was sent as a frozen sample to the Department of Clinical Chemistry at Malmö University Hospital. Cystine was analyzed with an ion-exchange chromatographic technique [10,16]. Prior to chromatography, an internal standard of amino-ethylcysteine was added to the samples, and urinary proteins were precipitated with sulfosalicylic acid. Separation and detection of analyzed constituents were carried out with an amino acid analyzer (Biochrom 20, Pharmacia Amersham Biotech, Uppsala, Sweden). The ninhydrin complexes were detected spectrophotometrically at 570 nm, and concentrations were calculated with EZChrom integration software (Scientific Software Inc., USA). Urinary sodium and potassium were analyzed with atomic absorption spectrophotometry.

The analysis of urine citrate was performed by the use of an enzymatic method [42]. Plasma and urine analyses of potassium and sodium was performed with ion selective electrodes.

Statistics

Friedman's two-way analysis of variance and Wilcoxon's signed rank test were used for statistical analysis of the results, and a P value of < 0.05 was considered statistically significant. In the cases where more than one comparison was made, P values have been corrected accordingly (Bonferroni). The relationship between sodium, potassium and cystine was evaluated by linear regression.

Results

Individual data for the 14 cystinuric patients concerning urinary pH, volume, excretion of sodium, potassium, citrate and free cystine, urinary concentration of free

Table 2 Effects of alkali treatment on urine and plasma composition in 14 patients with homozygous cystinuria (Department of Clinical Chemistry, Malmö University Hospital). *nm* no measurement available

Measurement period [a]	Pat. no	1 [b]	2 [b]	3 [b]	4 [b]	5 [b]	6 [b]	7 [b]	8 [b]	9 [b]	10 [b]	11 [c]	12 [c]	13 [c]	14 [c]	Median	25th percentile	75th percentile
Urinary pH	0	6.45	6.20	6.20	6.40	6.00	6.90	nm	5.20	6.00	5.80	7.20	6.55	6.85	6.55	6.40	6.00	6.62
	1	6.10	7.40	7.34	7.08	7.00	6.91	7.20	6.80	7.38	6.80	7.30	7.65	7.90	7.90	7.25	6.91	7.40
	2	5.50	7.40	6.70	7.09	7.30	7.10	6.85	6.50	7.48	6.90	7.00	7.50	7.50	7.20	7.10	6.85	7.40
Urinary volume (ml/24 h)	0	1.500	1.710	2.530	1.460	2.280	2.670	1.850	1.340	2.240	2.590	1.540	3.545	3.130	2.070	2.155	1.540	2.590
	1	1.230	1.510	2.470	1.640	2.350	2.310	2.450	2.320	2.250	3.400	1.850	2.700	4.290	3.100	2.335	1.850	2.700
	2	1.260	1.790	2.230	1.790	2.350	2.540	1.890	1.880	2.000	3.280	1.100	2.500	3.770	3.300	2.115	1.790	2.540
Urinary sodium (mmol/24 h)	0	243	108	147	156	315	107	139	72	141	179	234	181	122	141	144	122	181
	1	151	180	195	146	244	176	274	246	182	371	414	273	245	164	220	176	273
	2	256	111	98	143	310	147	89	141	48	279	176	72	170	208	145	98	208
Urinary potassium (mmol/24 h)	0	64	62	61	73	48	93	44	40	65	54	77	74	88	52	63	52	74
	1	66	50	22	84	118	60	47	88	40	68	117	68	107	46	67	47	88
	2	69	57	83	91	169	86	49	113	52	157	109	98	121	142	94	69	121
Urinary citrate (mmol/24 h)	0	3.88	4.74	2.91	2.54	4.47	4.03	4.05	1.11	3.74	1.71	3.10	2.91	1.00	1.86	3.00	1.86	4.03
	1	4.39	4.51	3.81	3.68	5.66	6.75	3.33	3.04	4.46	3.43	nm	2.08	1.69	1.16	3.68	2.80	4.47
	2	3.53	5.86	2.66	4.14	4.84	3.14	5.35	3.42	4.22	3.46	4.54	2.21	2.00	3.57	3.55	3.14	4.54
Urinary excretion of free cystine (μmol/24 h)	0	2.385	1.017	1.961	942	2.257	1.509	1.166	918	1.187	2.318	3.296	3.829	2.285	3.643	1.348 [b] (3.469 [c])	1.017 [b] (2.790 [c])	2.257 [b] (3.736 [c])
	1	1.365	1.253	1.618	1.041	1.927	1.502	1.556	1.322	968	2.652	2.923	3.551	2.763	3.906	1.433 [b] (3.237 [c])	1.253 [b] (2.843 [c])	1.618 [b] (3.728 [c])
	2	1.959	1.441	1.594	1.325	2.562	1.765	1.285	1.072	830	3.296	5.104	3.700	3.487	5.016	1.518 [b] (4.358 [c])	1.285 [b] (3.594 [c])	1.959 [b] (5.060 [c])
Urinary concentration of free cystine [d] (μmol/l)	0	1.590	595	775	645	990	565	630	685	530	895	2.140	1.080	730	1.760	665 [b] (1.420 [c])	595 [b] (905 [c])	895 [b] (1.950 [c])
	1	1.110	830	655	635	820	650	635	570	430	780	1.580	1.315	644	1.260	652 [b] (1.288 [c])	635 [b] (952 [c])	820 [b] (1.448 [c])
	2	1.555	805	715	740	1.090	695	680	570	415	1.005	4.640	1.480	925	1.520	728 [b] (1.584 [c])	680 [b] (1.182 [c])	1.005 [b] (2.796 [c])
Plasma potassium (mmol/l)	0	3.7	3.3	4.5	3.9	nm	3.6	3.2	4.4	3.6	3.6	3.5	3.8	4.1	3.8	3.6	3.6	4.0
	1	3.7	4.1	4.9	4.2	4.1	4.1	3.0	4.9	4.0	4.1	4.2	4.1	3.8	3.8	3.8	3.8	4.2
	2	3.8	3.9	4.4	4.4	4.4	4.1	3.5	5.0	4.3	4.4	4.2	4.3	4.3	4.2	4.1	4.1	4.4
Dose of sodium bicarbonate (mmol/day)	1	71.4	71.4	71.4	47.6	71.4	71.4	107	71.4	71.4	107	95.2	71.4	107	107	71.4	71.4	107
Dose of potassium citrate (mmol/day)	2	60	70	40	60	60	60	70	70	60	80	70	60	60	70	60	60	70

[a] Definition of periods: *Period 0*: No alkali; *Period 1*: Sodium bicarbonate; *Period 2*; Potassium citrate
[b] Tiopronin treatment
[c] No tiopronin treatment
[d] Normal concentration of urinary cystine in adults: < 88 μmol/l

cystine as well as plasma potassium and administered doses of sodium bicarbonate and potassium citrate are shown in Table 2.

As shown in Fig. 2, there was a significant increase in urinary pH during treatment with sodium bicarbonate (*Period 1*), as well as with potassium citrate (*Period 2*), with medians of 7.25 ($P < 0.01$) and 7.10 ($P < 0.05$), respectively. The corresponding pH value during *Period 0* was 6.40. There was no statistically significant difference in urinary pH between *Periods 1* and *2*. The median daily dose of sodium bicarbonate was 71.4 mmol, and the daily dose of potassium citrate was 60 mmol.

The urinary excretion of sodium was significantly increased during intake of sodium bicarbonate ($P < 0.05$) also in the absence of a strictly controlled diet (Fig. 3). The median 24-h sodium excretion during *Period 1* was 220 mmol as compared with 144 mmol during *Period 0*. Similarly, the 24-h median excretion of potassium during treatment with potassium citrate was 94 mmol and 63 mmol, respectively, $P < 0.01$ (Fig. 4) There were no significant differences in urinary cystine excretion or urine volume in the three periods (data not shown). Neither were there any significant correlations between sodium or potassium and urine volume. Administration of potassium citrate resulted in a significantly higher citrate excretion than during *Period 0* (Fig. 5). Sodium bicarbonate also was associated with higher levels of citrate, but the difference did not reach statistical significance ($P = 0.1$ when using Bonferroni's correction). There was no statistical difference between potassium citrate and sodium bicarbonate in terms of citrate excretion.

Plasma levels of potassium during treatment with potassium citrate increased significantly ($P < 0.01$; Fig. 6), but only one patient with impaired renal function (patient no. 8, GFR 59 ml/min/1.73m^2) exceeded the upper normal level of plasma potassium and developed a mild hyperkalemia of 5.0 mmol/l (normal range 3.3–4.6 mmol/l).

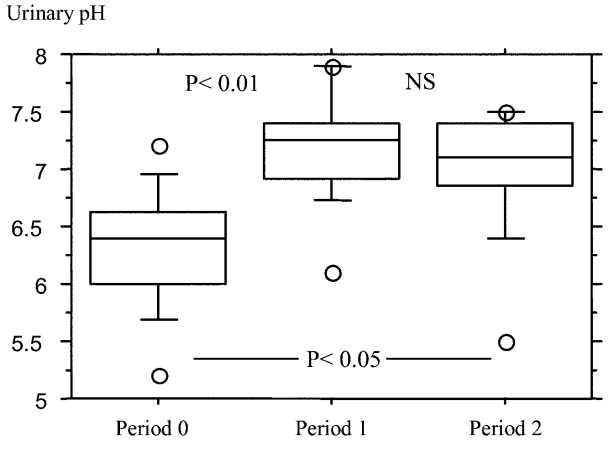

Fig. 2 Box plot of urinary pH during *Periods 0, 1 and 2* Box plot: *Lines* represent 10th–25th–50th–75th and 90th percentiles, respectively. *Circles* represent values below the 10th and above the 90th percentile

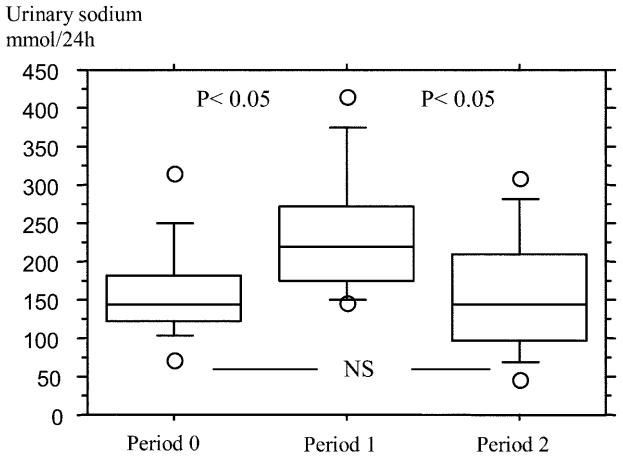

Fig. 3 Box plot of urinary sodium excretion. *NS* Not significant

In the ten patients treated with tiopronin, a significant correlation between sodium and cystine excretion was recorded based on the ten measurements of urinary sodium and cystine during *Periods 0* and *1* ($P < 0.001$; Fig. 7). There was no significant correlation between sodium and cystine in the patients not treated with tiopronin, but it should be noted that this group was small ($n = 4$).

Discussion

Our results showed that potassium citrate was effective in increasing urinary pH in cystinuric patients.

The pH-dependent solubility of cystine in urine provides the basis for one of the major principles in the clinical management of patients with cystinuria and stone formation. The common use of sodium bicarbonate to achieve sufficient alkalinization has been questioned because of the relationship between the tubular re-absorption of amino acids, such as cystine, and sodium [37, 38, 43]. Lindell et al. [20] showed, however, that the

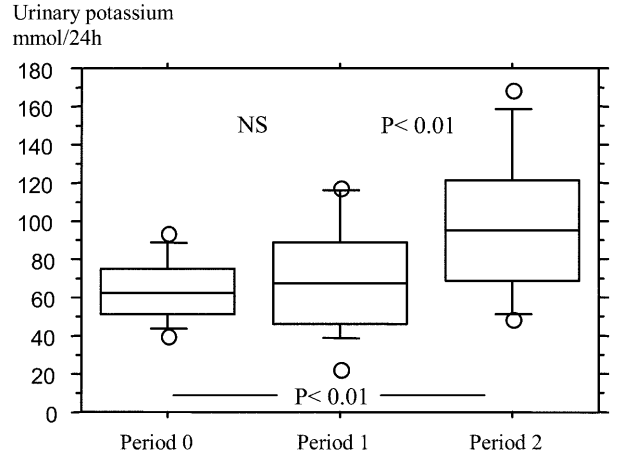

Fig. 4 Box plot of urinary potassium excretion

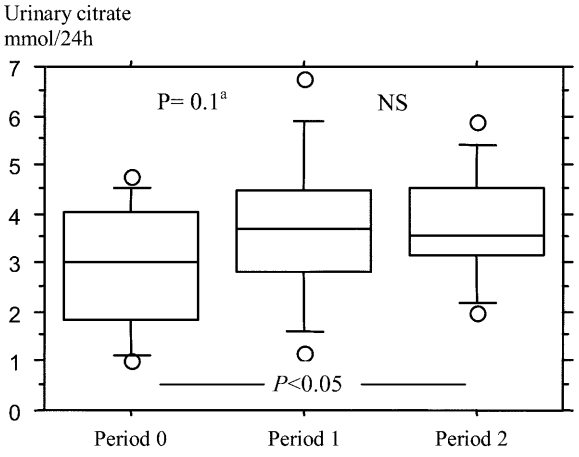

Fig. 5 Box plot of urinary citrate excretion. *a* Bonferroni's correction

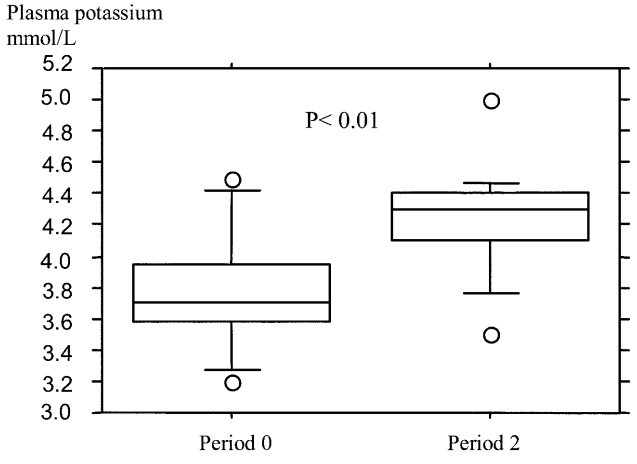

Fig. 6 Box plot of plasma potassium

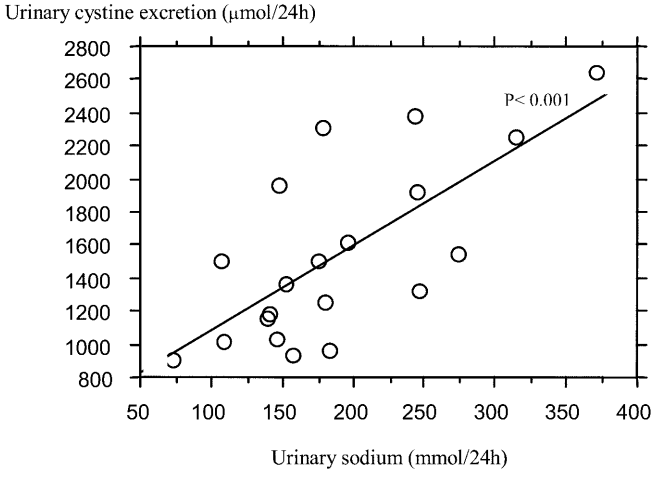

Fig. 7 Relationship between excretion of sodium and free cystine in tiopronin-treated patients. Cystine excretion = $577 + 5 \times$ U–Na ($r^2 = 0.50$)

decreased cystine excretion following withdrawal of sodium bicarbonate did not compensate for the ensuing decrease in urinary pH and, accordingly, in cystine solubility. Because potassium citrate is a sodium-free compound, it has been put forward as the alkalinizing agent of choice in the treatment of cystinuria [25, 35]. The therapeutic use of potassium citrate, however, is mainly based on studies performed on calcium and uric acid stones [2, 5, 6, 15, 29, 35, 36]. Potassium citrate thus has been recommended for prevention of recurrent stone formation in patients with distal renal tubular acidosis [34], enteric hyperoxaluria [29], thiazide-induced hypocitraturia [30], hyperuricosuric calcium nephrolithiasis [28], idiopathic hypocitraturia [27], and gouty diathesis [32].

Citrate decreases the saturation of uric acid by an increased dissociation and reduces the risk of uric acid precipitation [26]. In vitro studies of citrate in the case of calcium stones have shown that citrate inhibits spontaneous nucleation of calcium oxalate [23] and counteracts growth and agglomeration of pre-formed calcium oxalate crystals [3, 18, 41]. Citrate also has been shown to be a potent inhibitor of the growth of calcium phosphate crystals [4, 21]. Moreover, citrate prevents heterogeneous nucleation of calcium oxalate by monosodium urate [26], and an increased citrate excretion also counteracts the increased risk of CaP-crystallization caused by an increased pH [26].

In cystine stone formation, as far as we know, the only expected effect of treatment with potassium citrate is increased urinary pH and the associated increment in cystine solubility. The findings mentioned above are of importance when considering the fact that mixed stones might form in up to 50% of patients with cystinuria [40].

During the short course of this study, potassium citrate was well tolerated, causing adverse reactions (dyspepsia) in only one patient (patient no. 3). The tolerance of potassium citrate in the clinical management of these patients was good, as shown by the fact that prior to the study, 13 of the 14 patients were on long-term treatment with potassium citrate already.

It appears, however, that patient no. 1 and patient no. 5 were non-compliant. In patients 1 and 5, a reduction in urinary sodium during treatment with sodium bicarbonate and an increase during treatment with potassium citrate was observed. Furthermore, in patient no. 1, there were no changes in urinary pH in either period.

As can be seen in Fig. 5, potassium citrate and sodium bicarbonate both resulted in higher urinary citrate excretion, even though this change did not reach the level of statistical significance during *Period 1*. Both potassium bicarbonate and potassium citrate administered orally have been shown by Sakhaee et al. to increase urinary citrate excretion, an effect that appeared to be related to the provision of alkali [36]. No statistical difference in the citrate excretion between orally administered bicarbonate and citrate was found either in our investigation or in the study by Sakhaee et al.

In the present study, a correlation between urinary sodium and cystine was observed in the tiopronin-

treated patients (Fig. 7), although no such correlation was found in the small group of four patients not treated with tiopronin. A correlation between urinary sodium and cystine excretion, as well as a reduction in urinary cystine excretion due to a decreased dietary sodium intake have been observed by several authors [14, 20, 24, 33]. This has lead to the proposal of using dietary sodium restriction in the treatment of cystinuria.

In clinical practice, however, it has been our experience that consistent use of a more pronounced sodium-restricted diet in the long-term treatment of cystinuria is limited by poor patient compliance (unpublished data). This study was conducted under clinical circumstances, whereby the patients had been advised to maintain a low-sodium intake, but no specific diet was prescribed. Although patients thus continued to eat a normal diet, a significant increase in urinary sodium excretion occurred during *Period 1*, and the same was true for urinary potassium excretion during *Period 2*.

There was, however, no significant difference in the cystine excretion between *Period 0* (no alkali), *Period 1* (sodium bicarbonate) and *Period 2* (potassium citrate), which would have been expected due to the increased sodium load associated with *Period 1*.

Jaeger et al. observed that, in one patient, higher amounts of cystine were excreted into urine while the patient was on a diet containing 300 mmol of sodium per day, as compared with a diet containing 150 mmol of sodium per day. This was also true for another patient in the same study when diets of 150 mmol and 50 mmol sodium per day were compared [14].

A reduction in urinary cystine excretion also was observed by Peces et al. comparing diets with a sodium intake of 50–230 mmol in three patients [33]. However, in these two studies, the urinary excretion of sodium was expressed per gram of creatinine, and the total 24-h sodium excretion was not reported.

Lindell et al. followed 13 patients during four different levels of sodium intake and found that the average 24-h excretion of cystine was increased by 3.1 μmol for each mmol increase in urinary sodium [20]. In the same study, while on a diet of 50 mmol of sodium per day, withdrawal of sodium bicarbonate was associated with a significant reduction in cystine excretion. The effect of withdrawal of sodium bicarbonate on cystine excretion was, however, not studied at higher levels of sodium intake.

In the paper by Norman and Manette [24], an unrestricted sodium intake was compared with a diet containing 87 mmol sodium per day in five patients. The 24-h mean excretion of urinary sodium in their patients was reduced from 100 to 50 mmol. This reduction in 24-h urinary sodium excretion was associated with a significant decrease in urinary cystine.

One explanation for the absence of an increased cystine excretion due to the higher sodium load during *Period 1* in our patients could be that the resulting increase in 24-h urinary sodium excretion was not sufficient to cause a significant increase in cystine excretion when the patients were on a normal diet.

One of the drawbacks of treatment with potassium citrate is the risk of hyperkalemia, especially in patients with a glomerular filtration rate below 40 ml/min [26].

A significant increase in the serum concentration of potassium was noted (Fig. 6). In spite of the fact that four patients had impaired renal function (Table 1), only one patient with a GFR of 59 ml/min/1.73m^2 got a slightly elevated plasma potassium concentration of 5.0 mmol/l (normal range 3.3–4.6 mmol/l). On the other hand, the patient with the lowest recorded GFR did not develop hyperkalemia (patient no. 9, GFR 45 ml/min). Apart from the obvious risk in patients with reduced renal function, an increased risk of hyperkalemia has been reported in patients with type IV renal tubular acidosis [26]. Treatment with potassium-sparing agents is also associated with an increased risk of hyperkalemia.

In conclusion, the use of potassium citrate for treatment of patients with cystinuria and stone formation resulted in a significantly elevated urinary pH, comparable to that achieved with sodium bicarbonate. The load of sodium caused by administration of sodium bicarbonate resulted in an increased urinary excretion of sodium. In the case of tiopronin-treated patients, a significant correlation between urinary sodium and cystine excretion was observed. Potassium citrate did not result in any cases of severe hyperkalemia, although careful monitoring of serum potassium levels is advisable.

The use of potassium citrate for urine alkalization in homozygous cystinuria is thus effective and can be recommended in the absence of severe renal impairment.

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