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Clinical course and cystine stone formation during tiopronin treatment

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Abstract The formation of stones in patients with cystinuria can be counteracted by reducing the urinary concentration of cystine and by increasing its solubility. Thirty-one patients with homozygous cystinuria and treated with tiopronin (2-mercaptopropionylglycine) were followed for between 0.4 and 12 years (median 8.8). With the aim of avoiding cystine concentrations above 1200 μmol/l, the daily dose varied between 500 and 3000 mg (median 1500). The therapeutic effect was evaluated from the clinical symptoms and repeated radiographic examinations. The rate of stone formation during the treatment period was reduced by 60% in comparison with the pretreatment period ($P < 0.001$). The frequency of active stone removal was reduced by 72% ($P < 0.05$). The formation of new stones was associated with a higher cystine concentration than was the case during periods when stone formation and stone growth were excluded ($P < 0.05$). The probability of new stone formation increased with increasing concentrations of cystine up to 1100 μmol/l, but stone formation was not accentuated above 1200 μmol/l. There was no significant relationship between the 24 h excretion of cystine and stone formation.

It is concluded that the formation of cystine stones can be efficiently counteracted during treatment with tiopronin, guided by analysis of the concentration of urinary cystine.

Key words Cystinuria · Cystine · Tiopronin · 2-Mercaptopropionylglycine · Renal stone formation

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Introduction

Cystinuria is characterized by an excessive urinary excretion of the poorly soluble amino acid cystine. The disorder is inherited as an autosomal recessive trait and accounts for 1–2% of the patients with renal stones [18]. Because of the strong, lifelong tendency for stone formation in patients with homozygous cystinuria, they are highly susceptible to the complication of renal stone disease. In a follow-up study of 66 patients in 1958 Boström found that 8 patients had died of renal causes [4]. Of 23 patients followed by Crawhall and 49 by Linari and coworkers one and two patients, respectively, required maintenance hemodialysis [8, 23]. The problems with frequent, repeated open renal stone surgery are well recognized. Despite the fact that ESWL (Extracorporeal shock wave lithotripsy) has rendered the removal of cystine stones a less traumatic procedure [2], it is, nevertheless, essential to reduce the formation of renal stones in this group of patients to avoid renal complications. This calls for long-term prophylactic management.

Stone-preventive measures in patients with cystinuria aim at a decreased concentration and an increased solubility of cystine in urine. The conventional management of cystinuria with a high fluid intake and alkalinization of urine was introduced by Dent and Senior in 1955 and thoroughly evaluated 10 years later [12, 13]. Even with such a regimen some patients continue to form cystine stones. In 1963 Crawhall and coworkers introduced a new approach with which the urinary excretion of cystine was reduced by the administration of a sulfhydryl compound, D-penicillamine

[9]. A major drawback with this treatment was, however, the high frequency of adverse effects [10, 15, 19, 28]. Later another sulfhydryl compound, tiopronin (2-mercaptopropionylglycine), with less pronounced side effects came into clinical use [11, 17, 21–23, 26, 28, 29]. Recently the pharmacokinetics of tiopronin and of its metabolite 2-mercaptopropionic acid was elucidated [5–7].

The effect of treatment can be followed by either the biochemical effect on urinary cystine, or by the effect on stone formation. In a recent study of 31 cystinuric patients we found that tiopronin effectively reduced the urinary excretion of cystine, and that monitoring of urinary cystine was required because of considerable individual variations in dose requirements (in preparation). Little is known, however, about the relationship between changes in the urinary content of cystine and the formation of cystine stones.

In this investigation we followed the same group of 31 patients during long-term treatment with tiopronin while the urinary cystine was monitored regularly. The aim was to evaluate the effect of tiopronin on the formation of stones and the relationship between urinary cystine and stone formation.

Patients and methods

Thirty-one patients with homozygous cystinuria were treated with tiopronin (Thiola, Santen Pharmaceutical, Osaka, Japan) during an average period of 7.8 years (range 0.4–12). The diagnosis of cystinuria was established by determination of the urinary excretion of cystine and the dibasic amino acids [20]. All patients who started a long-term treatment with tiopronin between 1979 and 1992 were included in the study. The indications for starting treatment with tiopronin were a urinary concentration of cystine exceeding 1200 μmol/l in a 24-h urine sample, or active stone formation in spite of traditional management comprising administration of sodium bicarbonate and a high fluid intake or both. The aim of the treatment was the prevention of cystine stone formation. The prescription of Thiola was licensed for each individual patient by the Swedish National Board of Health and Welfare. Fifteen of the patients were women, 16 were men. The mean age at the time of the first symptoms of renal stone disease was 23 years (range 3–48 years) and the mean age at the start of tiopronin treatment 42 years (range 17–70 years). The mean glomerular filtration rate was 82 ml/min/1.73 m^3 (range 45–113). Nine of the 31 patients had glomerular filtration rates below the age-related normal range. The pretreatment time, defined as the period from the first symptoms of renal stone disease to the start of treatment with tiopronin, was on average 15 years (range 0.9–41 years).

Eight patients suffered from mild to moderate hypertensive disease. Five of them were treated with beta-blockers, three in combination with vasodilators. Only one patient was treated with diuretics (bendroflumethazide) and no patient received ACE inhibitors. One patient took allopurinol for gout, and another glipizide (non-insulin dependent diabetes mellitus) and levothyroxine (hypothyreosis).

Sixteen of the 31 patients had previously been treated with D-penicillamine during an average of 3.1 years (range 0.04–11 years), and this therapy was included in the pretreatment periods. Ten of the 16 patients had adverse reactions to D-penicillamine, and 3 of the female patients were changed to tiopronin when they planned to become pregnant. During their D-penicillamine treatment, 11 of the patients were followed by us [14], whereas the remaining 5 patients attended other clinics without regular monitoring of urinary cystine.

Twenty-four of the 31 patients had undergone active stone removal (open stone surgery, PCN (percutaneous nephrolithotomy), ESWL or loop extraction) prior to treatment with tiopronin. Three of the patients were unilaterally nephrectomized and one patient had a left-sided congenital renal agenesia. Thirteen of the 31 patients had renal stones at the start of tiopronin treatment, 5 of whom had bilateral concrements and two staghorn stones. Twenty-three patients could be closely followed by the authors during the whole treatment period. In 1985 eight of the patients were retransferred to their respective home clinics, but the same therapeutic principles were applied and the cystine concentration was analyzed at the same laboratory during the following years. All patients were encouraged to maintain a high fluid intake. Sodium bicarbonate was given in daily doses of 3–10 g aiming at a urinary pH of between 7.0 and 8.0. Since 1986 pH was measured with a glass electrode. In four of the patients sodium bicarbonate had to be withdrawn because of gastrointestinal complaints.

During treatment with tiopronin the urinary excretion of cystine was measured by ion-exchange chromatography at least every 6 months, more often during the adjustment of dosage at the beginning of the treatment [11, 20]. The between-day imprecision of cystine determinations was 7.3%. The total number of cystine measurements was 709. The aim of the combined treatment with tiopronin and increased fluid intake was to keep the urinary cystine concentration beneath the assumed stone-forming level of 1200 μmol/l [12]. Urinary cystine concentrations above 1200 μmol/l in repeated 24-h urine collections or continuous formation of stones prompted an increased dose of tiopronin. The highest individual daily doses ranged from 500 to 3000 mg (mean 1540 mg). Daily doses up to 1000 mg were given in the evening whereas higher doses were given twice a day [11]. Measurements of the urinary mixed tiopronin-cysteine disulfide served as a non-quantitative control of medication. To include the influence of urinary pH on the solubility of cystine the ion activity product of cystine was calculated as described by Tiselius [30]:

$$\frac{(10^{-pH})^2 \times \text{Conc}_{\text{cystine}} \times 0.155}{\{1 + (0.39 \times 10^{10} \times 10^{-pH}) + [(10^{-pH})^2 \times 3.51 \times 10^{16}]\}}$$

The frequency of cystine stone formation was estimated from information in patient records. Typical symptoms of renal colic, stone passages and active stone formation were classified as "renal stone episodes." Renal colic occurring at an interval of less than 3 months was not regarded as a new stone episode unless the first symptoms were followed by a stone passage, or the patient proved to be free of stones at a radiographic examination between the episodes.

Information about all radiographic examinations of the urinary tract (plain radiograms, excretion urographies) from the pretreatment and treatment periods were compiled. Of 382 radiographic examinations 342 were available for reexamination. In general, radiograms older than 10 years could not be recovered. In such cases information from the original description was used for conclusions on stone formation. All radiographs were reexamined by one radiologist (E.H.), who had no information of the urinary cystine levels. All radiographs of a single patient were examined on the same occasion to allow for adequate comparisons. The number and location of the stones were recorded, and the smallest (d_1) and largest (d_2) diameter of each stone measured. A decision was made by the radiologist whether there had been an increase or reduction of total stone mass between consecutive radiographic examinations. An approximate stone volume was calculated by the formula proposed by Ackerman et al. [1]: $0.6 \times (\pi \times d_1/2 \times d_2/2)^{1.17}$. For evaluating the relationship to urinary cystine each stone volume was assigned to the preceding cystine measurement. Stone passages and surgical procedures between consecutive examinations were taken into account in the estimation of changes in stone volume.

The number of newly formed urinary tract stones was assessed by considering new stones appearing on the radiogram and reported stone passages. Conclusions on the passage of a stone were drawn from the combined information of the medical history and of repeated

radiographic examinations. The registration of a new stone, or a stone episode was related to the latest preceding measurement of the urinary cystine concentration.

Statistical analysis

Linear regression analysis, Student's *t*-test and Wilcoxon's signed rank test were used for statistical analysis. Values of probability of less than 0.05 were considered to be statistically significant.

Results

During treatment with tiopronin 13 of the 31 patients were free of new stone formation and stone growth. There were no staghorn stones formed. On five occasions partial dissolution of stones was observed. Nineteen surgical procedures were performed on nine patients, six of whom were treated with ESWL. Five of the surgical procedures were carried out within 6 months from the start of tiopronin treatment. At the final dose there were no signs of stone activity in 19 of the 31 patients. Table 1 shows the average annual rates of "renal stone episodes," new stone formation and active stone removal during the pretreatment and treatment periods. There was a 69% decrease in the frequency of "renal stone episodes," a 60% decrease in the frequency of new stone formation and a 72% decrease in the need for surgical procedures.

Figure 1 shows the cumulative sum of "renal stone episodes" and new stone formation before and during treatment with tiopronin. For each patient a pretreatment period of equal length to the treatment time was chosen for comparison. The 12 months immediately preceeding the start of treatment as well as the first 12 months of treatment were excluded in order to avoid an overestimation of the rates of stone formation. The activity of the stone disease was clearly reduced during treatment with tiopronin, in terms of both clinical symptoms and verified formation of new stones.

Figure 2 shows the relationships between the annual rate of new stone formation, and the 24-h urinary cystine excretion and the urinary concentration of cystine before treatment and at the final dose of tiopronin. The numbers were calculated as averages of individual means. Urinary cystine measurements at the start of treatment were used as pretreatment values. The average (SD) of the urinary cystine concentration was lower during treatment with the final dose of tiopronin than that at the start of treatment – 862 (228) μmol/l compared with 1382 (526) μmol/l ($P < 0.001$). This change in cystine concentration was influenced by the fluid intake as well as by the administration of tiopronin. The change in average (SD) 24-h urinary excretion of cystine, which is a direct effect of tiopronin treatment, was 1619 (524) μmol at the final dose of tiopronin compared with 2355 (917) μmol at the start of treatment ($P < 0.001$). At the final dose an average urinary

Table 1 Annual rates of "renal stone episodes," new stone formation and active stone removal before and during treatment with tiopronin

	Pretreatment period Median (range)[a] Mean (SD)	Treatment period Median (range) Mean (SD)	Significance of difference[b]
Renal stone episodes	0.40 (0–3.0) 0.71 (0.77)	0.09 (0–1.0) 0.22 (0.29)	$P < 0.001$
Formation of new stones	0.42 (0–3.4) 0.68 (0.82)	0.08 (0–2.3) 0.27 (0.50)	$P < 0.001$
Active stone removal	0.08 (0–1.1) 0.20 (0.28)	0.0 (0–0.51) 0.06 (0.12)	$P < 0.05$

[a] In one partient without previous stone formation the indication for tiopronin treatment was high urinary cystine concentrations
[b] Wilcoxon's signed rank test

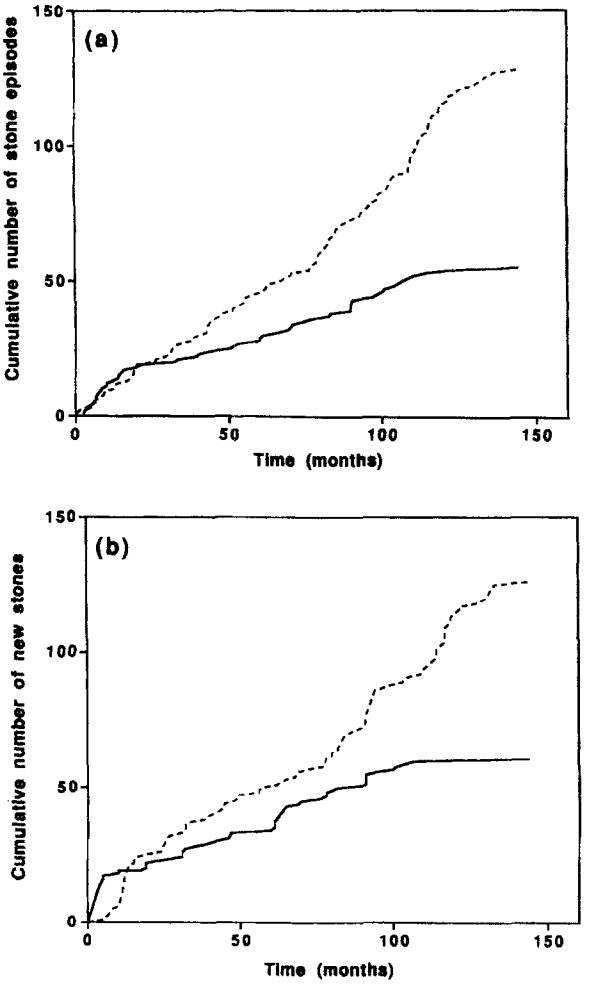

Fig. 1a,b The cumulative sum of number of renal stones episodes (**a**) and number of new stones (**b**) during treatment with tiopronin (*continous lines*) and before treatment (*broken lines*)

concentration of cystine of less than 1200 μmol/l was achieved in 28 of the 31 patients.

The average (SD) urinary cystine concentrations were higher in association with the formation of new stones than when stone formation and stone growth had been radiographically excluded – 1278 (569) μmol/l compared with 1007 (584) μmol/l ($P < 0.05$). No significant differences were obtained when the concentration of cystine was replaced by the 24-h excretion or the ion activity product of cystine. The average urinary concentrations of cystine assigned to "renal stone episodes', were compared with urinary cystine measurements not associated with such signs or symptoms. No significant differences were revealed.

The relationship between the urinary concentration of cystine and changes in renal stone volume calculated from measurements on the radiographs was evaluated. No significant association was recorded. Stone growth was related to an increased concentration of cystine in only 3 of 16 patients (data not shown).

In Fig. 3 the individual means of urinary concentration of cystine during treatment with tiopronin have been plotted against the annual rate of "renal stone episodes" and the annual rate of new stone formation. There appeared to be a higher frequency of "stone episodes" and new stone formation at higher cystine concentrations, but the slopes of the regression lines were not statistically different from zero ($P = 0.051$ and 0.22, respectively). There was also a tendency to higher annual rates of new stone formation at higher levels of 24-h urinary excretion of cystine and at higher levels of ion activity product of cystine, but these associations were not statistically significant.

Figure 4 illustrates the relationship between the urinary concentration of cystine and the probability of forming new stones. The number of cystine concentrations associated with new stone formation was

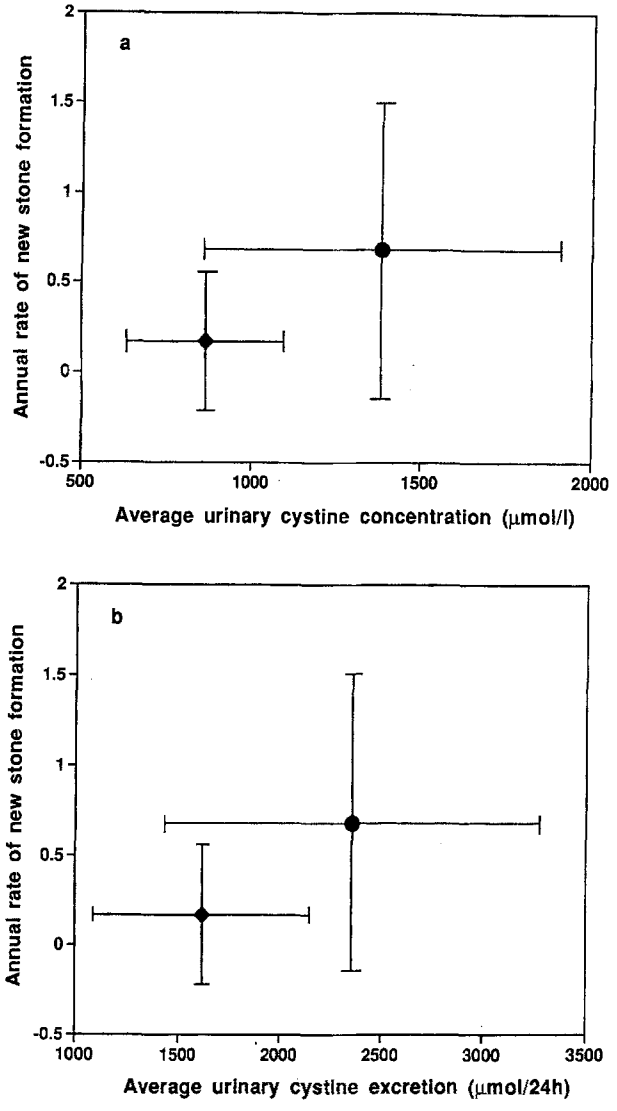

Fig. 2a,b The relationship between the rate of new stone formation, the 24-h urinary excretion (**a**) and the urinary cystine concentration (**b**). The average during pretreatment period (●) and at the final dose of tiopronin (◆) is shown. *Bars* represent one standard deviation from the mean

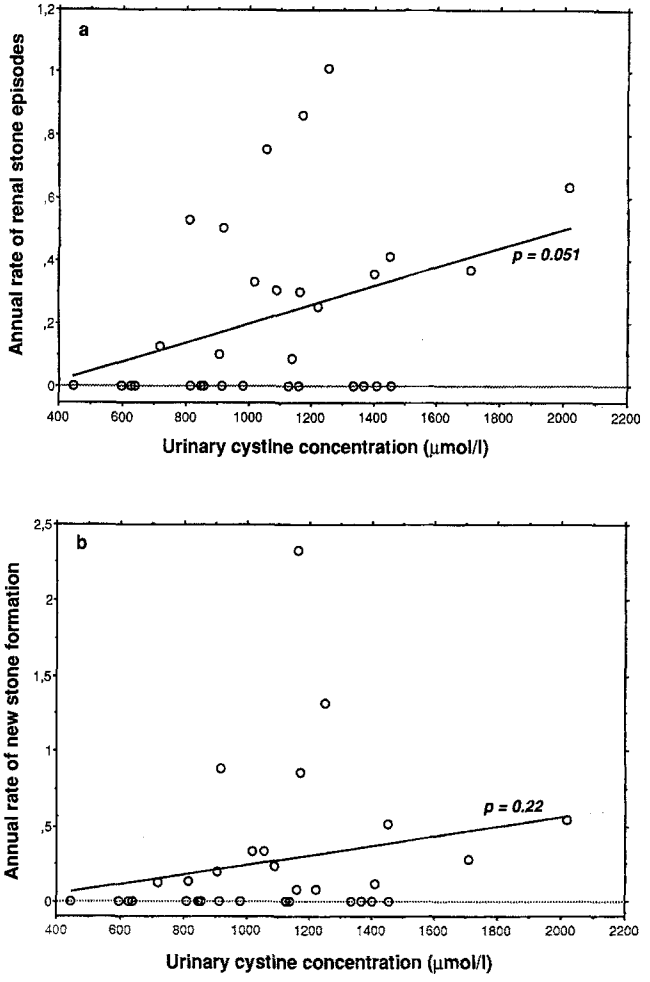

Fig. 3a,b Relationship between the urinary cystine concentration, the rate of renal stone episodes (**a**) and the rate of new stone formation (**b**) during treatment with tiopronin in the 31 patients

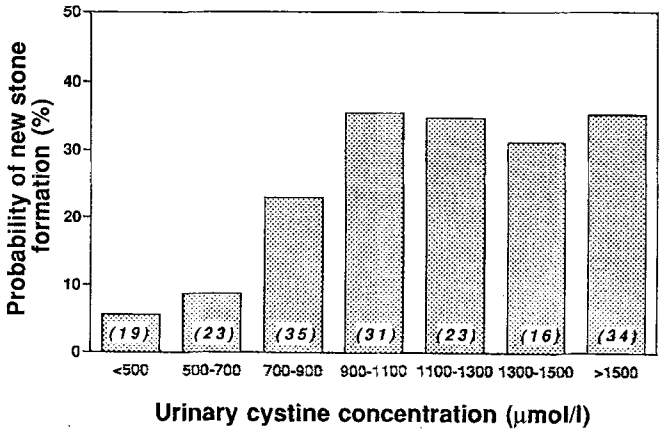

Fig. 4 Probability of new stone formation at different levels of urinary cystine concentration. The probabilities were calculated as the percentage of urinary cystine measurements associated with new stones within each range of concentration. The range limits were chosen to avoid groups with very few observations (*numbers within brackets*)

compared with the number when stone formation and stone growth had been radiographically excluded. There was an increasing risk of renal stone formation with increasing cystine concentrations up to approximately 1100 μmol /l, but there was no further increase in the risk of stone formation above that level.

There was no significant change in urinary volumes during the treatment with tiopronin. The average (SD, range) of individual means of urinary volumes recorded during the first months of treatment with tiopronin was 2034 (1200, 870–5963) ml compared with 2174 (1084, 917–5900) during the last year of the observation period ($P > 0.05$). The average of individual means (SD) of urinary pH during tiopronin treatment was 6.9 (0.6).

In four patients tiopronin was withdrawn because of proteinuria. In three of these patients renal biopsy revealed a membranous glomerulonephritis [24]. One patient with a previous history of adverse effects of D-penicillamine had to stop medication because of an SLE-like syndrome without renal involvement. The symptoms were reversible in all five cases. In one patient tiopronin was changed to D-penicillamine because of general discomfort, but the association with tiopronin treatment was doubtful.

Discussion

The dosage of tiopronin used in this study was guided by regular determinations of the urinary cystine concentration, and the aim was to keep the concentration below the assumed risk level of 1200 μmol/l. Our results show that the activity of the disease was significantly reduced by this regimen whether clinical symptoms, formation of new stones or the need for active stone removal was chosen as a reflection of stone activity (Table 1, Fig. 1). It is of interest that the reduction of the rate of active stone removal was similar to the reduction of the other signs of stone activity. The need for surgical intervention indicates more serious complications of renal stone disease.

The administration of tiopronin was combined with a high fluid intake and urinary alkalinization. The patients had, however, been subjected to this conventional management before the start of the tiopronin treatment. To our knowledge only one clinical evaluation of sodium bicarbonate treatment in cystinuria has been published. In this report the treatment was considered as being of doubtful value [13]. The 24-h urinary volumes showed no increase during the period of tiopronin treatment. It is thus reasonable to assume that the treatment with tiopronin was the major cause of the improved control of stone formation. Treatment with D-penicillamine made up a considerable part of the pretreatment periods in some of the patients, and this was the main reason for the inclusion of periods with D-penicillamine treatment. It may have influenced our results unfavorably with respect to the effect of tiopronin, but the stone activity during the administration of D-penicillamine was not significantly different from the stone activity during the rest of the pretreatment period (data not shown).

The evaluation of the effects of stone-preventing treatment in renal stone diseases in general is associated with several problems because of the difficulties of finding reliable estimates of stone formation and growth. The activity in most forms of stone disease varies over time. It is usually extremely difficult to assess the time course of the formation of stones and relate it to the therapeutic procedures. The risk of overestimating the pretreatment stone-forming activity and the problem of finding a representative observation period has been addressed by Bek-Jensen and Tiselius [3]. In cystinuria the evaluation is further complicated by the limited radiodensity of the stones which may impair the accuracy of the radiographic examination [16]. In the literature information about temporary variations in the metabolic activity of cystinuria is scanty [4]. It can be assumed, however, that the initiation of a more intensive treatment tends to occur in periods with a high activity in stone formation. In the cumulative diagrams (Fig. 1) we excluded the 12 months preceding the start of tiopronin treatment, and a period of equal length after start of the treatment, to improve the comparability of pretreatment and treatment periods. The exclusion of the 12 month's intervals had, however, only minor effects on the shape of the cumulative curves.

Other authors have also reported a considerable reduction in the activity of cystine stone formation during treatment with tiopronin [17, 22, 23, 26, 28] or D-penicillamine [8, 10, 25, 28]. The different approaches in recording stone formation and evaluating the effects of therapy render comparison with other studies difficult. Several investigators have based the

dosage of the SH compounds on urinary cystine, but a majority of them used the 24-h excretion [10, 17, 23, 28]. In some studies the purpose of the treatment was stone dissolution, with lower levels of urinary cystine than in our patients [10, 22, 26]. During treatment with tiopronin Linari and coworkers recorded 0.21 stone episodes/year in 36 patients observed during 3.5 years [23], which is similar to our results. Pak and coworkers found a reduction of the annual rate of stone formation from 5.3 to 1.8 in 14 patients during 1.6 years of treatment [28]. This comparably high rate of stone formation illustrates the problem of patient selection in group comparisons. The individual tendency towards the formation of cystine stones differs considerably, something we have observed in our 31 patients (Fig. 3). The results of treatment may depend on the patient's compliance, a topic discussed by Pak and coworkers [28]. A regimen with three or four doses a day, often used in the treatment with D-penicillamine [8, 9, 25] and tiopronin [26, 28], tends to increase the problem with compliance. Determinations of the tiopronin-cysteine disulfide served as a non-quantitative control of medication and such measurements supported our conclusion that noncompliance was a minor problem in our patients.

The initial event of cystine stone formation is the precipitation of cystine from a supersaturated urine, and the principal objective of stone-preventing therapy therefore is to maintain the cystine concentration below the level of saturation. Dent and Senior determined the solubility of cystine in human urine, and described the pronounced pH dependence of cystine solubility [12]. Later Pak and Fuller observed interindividual variations in urinary cystine solubility [27]. In our study the aim was to keep the urinary cystine concentration below 1200 μmol/l and the urinary pH between 7.0 and 8.0. We attempted to relate the urinary content of cystine to the activity of the renal stone disease. Whether urinary cystine was expressed as the individual means of concentration, the 24-h excretion or the ion activity product, a tendency towards increased stone formation at higher cystine levels was found ($P > 0.05$; Fig. 3). Some patients did not form any stones in spite of high levels of cystine concentration. A possible explanation is that there are probably individual differences in the disposition for cystine stone formation depending on variations in urine composition [27] or minor aberrations in the morphology of the urinary tract. The ion activity product of cystine was expected to give a better reflection of the actual solubility since it incorporates the pH. The association with stone formation was, however, not stronger than what we obtained by only considering the concentration of cystine. Urinary pH varies considerably over the day, and one explanation for the lack of relationship may be that samples of fresh morning urine were not available from many of the patients living a distance from our outpatient clinic.

It is important to emphasize that the average urinary cystine concentration associated with new stone formation was significantly higher than the cystine concentration during the periods when stone formation or stone growth was excluded. There was, however, no obvious relationship between stone growth and urinary cystine concentration. Precipitation of cystine on a preexisting crystal surface is likely to occur at a lower cystine concentration than that required for new stone formation. This explains why it is easier to demonstrate an association between urinary cystine concentration and new stone formation than between urinary cystine and stone growth. Nor did we find any statistically significant association between "renal stone episodes", and urinary cystine concentration. The interpretation of clinical symptoms in the estimation of stone activity tends to be precarious, and the number of verified new stones is superior in reflecting the activity of stone formation.

There was an increased probability of new stone formation when the urinary cystine concentration was increased from below 500 μmol/l to about 900–1100 μmol/l (Fig. 4). At higher concentrations of cystine the probability of stone formation, however, remained stable at around 30–35% when the problem is considered in this way. This might indicate that a cystine concentration of approximately 1000 μmol/l reflects the formation product of cystine. This can be compared with the experimentally determined solubility of 1250 μmol/l previously reported by Dent and Senior [12]. It needs to be emphasized that our long-term results indicate that there is a risk of stone formation even when the average cystine concentration was as low as 500 μmol/l. One important explanation for this is that urinary cystine concentration varies considerably with the urinary flow. The cystine concentration in 24-h urine samples therefore gives little information of any peak concentration that occurs during the 24-h period. Particularly high concentrations can be expected during the night, and during such periods there might be a risk of stone formation. This issue is of importance for optimizing the treatment with tiopronin, and further studies with fractional sampling of urinary cystine are in progress.

Our study revealed no significant associations between the 24-h cystine excretion and the formation of new stones. The problem in the determination of the 24-h excretion is that the accuracy depends on representative urinary volumes. In spite of its rather limited ability to reflect the stone activity the concentration of cystine correlated better with stone formation, and therefore seems to be the best alternative for monitoring the treatment. The fact that the concentration reflects the degree of saturation of urinary cystine, and that the concentration also incorporates the influence of urine flow, further supports the use of the concentration of cystine as the preferred analysis.

We conclude that with our principles of long-term management of patients with cystine stone disease

a substantial reduction of renal stone formation can be achieved. The drug was well tolerated in 80% of the patients, and side effects were in all cases reversible. The treatment with tiopronin requires monitoring of urinary cystine to individualize the treatment and avoid unnecessarily high doses. A urinary concentration of cystine not exceeding 1200 μmol/l appeared to be sufficient for two thirds of our patients in whom stone formation was stopped. The remaining patients continued to form stones in spite of cystine concentrations below that level. It therefore seems appropriate to individualize the therapeutic concentration of cystine in view of the clinical response.

For the long-term prevention of stone formation in patients with cystinuria we recommend the combination of tiopronin treatment, urinary alkalinization and a high fluid intake. When stone removal is required ESWL is preferred [2].

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References

1. Ackermann D, Griffith DP, Dunthorn M, Newman RC, Finlayson B (1989) Calculation of stone volume and urinary stone staging with computer assistance. J Endourol 3:355
2. Ahlstrand C, Tiselius H-G (1993) Treatment of cystine urolithiasis by a combination of extracorporeal shock wave lithotripsy and chemolysis. J Stone Dis 5:32
3. Bek-Jensen H, Tiselius H-G (1989) Stone formation and urine composition in calcium stone formers without medical treatment. Eur Urol 16:144
4. Boström H (1959) Cystinuria in Sweden. III. Prognosis of homozygous cystinuria. Acta Chir Scand 116:287
5. Carlsson MS, Denneberg T, Emanuelsson B-M, Kågedal B, Lindgren S (1993) Pharmacokinetics of oral tiopronin. Eur J Clin Pharmacol 45:79
6. Carlsson MS, Denneberg T, Emanuelsson B-M, Kågedal B, Lindgren S (1994) Steady state pharmacokinetics of 2-mercaptopropionyl-glycine (tiopronin) in healthy volunteers and patients with cystinuria. Drug Invest 7:41
7. Carlsson MS, Denneberg T, Emanuelsson B-M, Kågedal B, Lindgren S (1994) Pharmacokinetics of 2-mercaptopropionyl-glycine (tiopronin) in patients with impaired renal function. Drug Invest 7:74
8. Crawhall JC (1987) Cystinuria – an experience in management over 18 years. Miner Electrolyte Metab 13:286
9. Crawhall JC, Scowen EF, Watts RWE (1963) Effect of penicillamine on cystinuria. B M J 1:588.
10. Dahlberg PJ, Berg CJ van den, Kurtz SB, Wilson DM, Smith LH (1977) Clinical features and management of cystinuria. Mayo Clin Proc 52:533
11. Denneberg T, Jeppsson J-O, Stenberg P (1983) Alternative treatment of cystinuria with alpha-mercaptopropionylglycine, Thiola®. Proc EDTA 20:427
12. Dent CE, Senior B (1955) Studies on the treatment of cystinuria. Br J Urol 27:317
13. Dent CE, Friedman M, Green H, Watson LCA (1965) Treatment of cystinuria. B M J 1:403
14. Ekberg M, Jeppsson J-O, Denneberg T (1974) Penicillamine treatment of cystinuria. Acta Med Scand 19:415
15. Halperin EC, Thier SO, Rosenberg LE (1981) The use of D-penicillamine in cystinuria: efficiacy and untoward reactions. Yale J Biol Med 54:439
16. Hambraeus L, Lagergren C (1962) Biophysical and roentgenological studies of urinary calculi from cystinurics. Cystinuria in Sweden, part VI. J Urol 88:826
17. Hautmann RE (1981) Cystine-stone therapy with alpha-mercaptopropionyl-glycine – ten years experience with forty-two patients. In: Smith LH, Robertson WG, Finlayson B (eds) Urolithiasis: clinical and basic research. Plenum Press, New York, p 139
18. Herring LC (1962) Observations on the analysis of ten thousand urinary calculi. J Urol 88:545
19. Jaffe IA (1986) Adverse effects profile of sulfhydryl compounds in man. Am J Med 80:471
20. Jeppsson J-O, Karlsson IM (1972) Ion-exchange chromatography of physiological sulphur amino acids on a highly crosslinked resin. J Chromat 72:93
21. Kallistratos G, Timmerman A (1968) Über die Wirkung von Thiola. Naturwissenschaften 55:648
22. Koide T, Kinoshita K, Takemoto M, Yachiku S, Sonoda T (1982) Conservative treatment of cystine calculi: effect of oral alpha-mercaptopropionylglycine on cystine stone dissolution and on prevention of stone recurrence. J Urol 128:513
23. Linari F, Marangella M, Fruttero B, Bruno M (1981) The natural history of cystinuria: a 15 year follow up in 106 patients. In: Smith LH, Robertson WG, Finlayson B (eds) Urolithiasis: clinical and basic research. Plenum Press, New York, p 145
24. Lindell Å, Denneberg T, Eneström S, Fich C, Skogh T (1990) Membranous glomerulonephritis induced by 2-mercaptopropionylglycine (Thiola®). Clin Nephrol 34:108
25. Lotz M, Potts JT, Holland JM, Kiser WS, Bartter FC (1966) D-Penicillamine therapy in cystinuria. J Urol 95:257
26. Miano L, Gallucci M, Petta S (1979) Results of medical treatment of cystine lithiasis. Tratto da Eur Urol 5:265
27. Pak CYC, Fuller C (1983) Assessment of cystine solubility in urine and of heterogeneous nucleation. J Urol 129:1066
28. Pak CYC, Fuller C, Sahaee K, Zerwekh JE, Adams BV (1986) Management of cystine nephrolithiasis with alpha-mercaptopropionyl-glycine. J Urol 136:1003
29. Remien A, Kallistratos G, Burchardt P (1975) Treatment of cystinuria with Thiola (alpha-mercaptopropionylglycine). Eur J Urol 1:227
30. Tiselius H-G (in press) Solution chemistry of supersaturation. In: Coe F, Favus M, Pak C, Parks J, Preminger G (eds) Kidney stones: medical and surgical management. Raven Press, New York