ALTERNATIVE TREATMENT OF CYSTINURIA WITH 
α-MERKAPTOPROPIONYLGLYCINE, THIOLA®

T Denneberg, J-O Jeppsson, P Stenberg

University Hospital, Malmö, Sweden

Summary

Sixteen patients with cystinuria have been treated with Thiola for 0.5—4 years. Only two of the patients had recurrence of stones because of initial inadequate dose. The excretion of free cystine and the mixed Thiola-cysteine disulphide in the urine has been measured on an automatic amino acid analyser. Thiola has less side effects than D-penicillamine with respect to bone marrow, kidney, liver, gastrointestinal tract and skin. No chelating properties on urinary excretion of copper and zinc were observed during Thiola treatment. We conclude that successful treatment will depend on determining an individual dose of Thiola for every patient and from monitoring free cystine and Thiola-cysteine disulphide in the urine.

Introduction

Cystinuria is an inherited metabolic disease which is characterised by the urinary excretion of abnormally high amounts of the amino acids cystine, arginine, lysine and ornithine. The aim of management in cystinuria is to keep the urinary cystine concentration less than supersaturation thereby preventing cystine precipitation and subsequent stone formation. This may be accomplished by reducing the concentration of cystine in the urine and/or by increasing its solubility. In severe cases specific treatment is necessary to prevent formation of cystine stones and the most common form of therapy is changing cystine to a chemically more soluble form, the mixed disulphide, with D-penicillamine.

Since Crawhall et al [1] introduced D-penicillamine treatment, several reports have confirmed this concept. However, as many as 50 per cent of patients develop one or more complication such as hypersensitivity reactions, haematological changes, abnormalities of taste and smell, nephrotoxicity, formation of abnormal antibodies, dermatopathy and connective tissue changes, as well as an antipyradoxine effect and chelating properties [2–4]. The signs of renal damage are described with slight to severe proteinuria, clinically as a nephrotic
syndrome and ‘penicillamine nephropathy’, and immune-complex glomerulonephritis [5]. Thus clinical experience with D-penicillamine has shown that the drug has serious side effects which limits its application. For this reason new potential drugs, other than thiol derivatives, with better tolerance have been developed. Among the new compounds, α-merkapropionylglycine* has been selected because of its advantages compared with other thiols [6,7].

This report records our experience of Thiola and the value of cystine and Thiola-cysteine disulphide analysis in the urine. The determination of free cystine and its mixed disulphide makes it possible to determine individual treatment for cysinuric patients using Thiola as a safe and effective drug in preventing stone formation.

Material and methods

Of sixteen patients with homozygote cystinuria treated with Thiola, seven were female and nine male, aged 18–70. The observation period at treatment was 0.5–4 years. The cases were selected postoperatively for prophylactic purposes because of stone recurrence. The diagnosis of cystinuria was made by chemical analysis of the stones.

As a screening procedure cyanide-nitroprusside reaction (Brand’s test) was used with a sensitivity for urine cystine >300μmol/L. All positive urines were run on high voltage electrophoresis at pH 1.9 and 6.4. Final quantitations of cystine, arginine, lysine and ornithine were performed on a Kontron Liquimat III amino acid analyser. During the Thiola treatment quantitative determinations of cystine and Thiola-cysteine disulphide were routinely made by an automatic 40 minutes programme of ion-exchange chromatography developed for this purpose (Figure 1).

Treatment with Thiola was started in hospital with a dose of 250–500mg given at night. After a few days the dose was increased to 750–1000mg. The patient was hospitalised for a 10-day period and was then followed up monthly or every second month as an outpatient. As the patients were treated conservatively prior to surgery with hydration and alkalisation they were instructed to drink adequately, especially in the evening, to achieve an output of 2L/day or more. Previous sodium bicarbonate medication of 15–20g daily was reduced (3–6g) to maintain a urinary pH at approximately 6.5–7.0.

Results

Figure 2 summarises the clinical results of the sixteen patients treated with Thiola. The bars show 24-hour urine cystine excretion before treatment with Thiola and Thiola-cysteine disulphide during treatment with Thiola. The excretion of cystine before treatment varies between 1500–3800μmol/24 hours, and the excretion of Thiola-cysteine disulphide between 1000–5000μmol/24 hours. The dose of Thiola required (0.5–2.5g) was adjusted to achieve a urinary cystine excretion of less than 1200μmol/24 hours.

*Thiola, Santen Pharmaceutical Co Ltd., Osaka, Japan
Figure 1. Analysis of cystine and related compounds on a Kontron Liquimat III amino acid analyser equipped with a Durrum DC-6A resin. The ninhydrin amino acid complexes were monitored at 570 nm.
Only two of the patients (case AG and LA) had stone recurrence during treatment. All the other fourteen patients had no recurrence of stones or signs of further growth. Case AG was given a dose which was too low at the start of treatment and case LA had gastrointestinal side effects (gastritis). None of the other patients had side effects of skin rash or fever, but some of them had registered soft faeces and could accept the sulphurous smell of Thiola in the urine and faeces.

There was no evidence of bone marrow depression (granulocytopenia, thrombocytopenia or anaemia). The liver enzymes were normal and no proteinuria was found. No increased urinary excretion of copper or zinc, due to chelation, were observed during Thiola treatment which was in contrast with the massive excretion of copper and zinc in D-penicillamine treated patients.

Discussion

We have employed the Brand’s test as a screening method for the early diagnosis of cystinuria and found it to be simple, rapid and reliable. The occurrence of a positive Brand’s test in the urine and a radiopaque calculus was however not diagnostic of cystinuria. There is a need for further investigation before treatment with Thiola is started. The sensitivity limit of the Brand test is 300µmol/L and it is also positive in cases of heterozygote cystinolysisinuria, isolated cystinuria, homocystinuria, β-merkaptolactatecysteine-disulfiduria and general aminoaciduria.

High voltage electrophoresis is a suitable medium for the identification of cystine and the other three dibasic amino acids. If the patient is homozygous, all four amino acids are represented in high concentration. The amount of cystine in a 24-hour urine should, if possible, be quantified by ion-exchange chromatography before treatment with Thiola. A specially designed programme on an amino acid analyser is of great value for sequentially following urinary cystine excretion. On our chromatography system the free cystine is eluted with the free Thiola and the Thiola-cysteine disulphide. Thus therapy could be monitored by periodic quantitation of free cystine and the Thiola-cysteine disulphide. The determination of the mixed Thiola-cysteine disulphide is a therapeutic control of the co-operation of the patient during the life-long treatment.

Our results are in agreement with other investigators [8–10] but we recommend the quantitation of Thiola and the Thiola-cysteine disulphide for careful follow-up of these high-risk patients. The results of the present study confirm the efficiency of Thiola in the prophylaxis of cystine stone formation. Only two of the sixteen patients had stone recurrence during treatment. Furthermore therapy with Thiola was not associated with any serious side effects and appears to be well tolerated, making it acceptable long-term therapy. This is a distinct advantage of Thiola over D-penicillamine which produces side effects of such severity necessitating that withdrawal is necessary in some patients.

References

2 Lulle RG. Postgrad Med J Suppl 1968; 44: 21
Open Discussion

HALDIMAN (Sierre, Switzerland) An escape phenomenon to the effect of D-penicillamine has been observed in patients with cystinuria. Have you observed the same escape phenomenon to the effect of Thiola? Secondly, how many months of therapy are needed until the effect of D-penicillamine can be seen again?

DENNEBERG The first question about the value of Thiola and penicillamine is difficult to answer but we can’t say as we have only a short experience of Thiola in comparison to penicillamine in dissolving stones, but we can say that it is a very good drug for the prophylaxis. From the literature we were a little ambivalent about the dose at which we should begin. I would say that you can start with a dose of 500mgs and increase very quickly and don’t wait as we did in the beginning. We start treatment in hospital for 10 to 12 days because if you have side effects they will be manifest during this time.

HALDIMAN My question has not been completely answered. The escape phenomenon I am referring to is the fact that the patients will have an increase in the 24 hour urinary excretion of cystine and this has been described after a few months or a year of treatment. Have you seen this effect?

DENNEBERG No.

HALDIMAN Does anybody know how many months of therapy are needed until the full effect can be seen again?

CAMERON (Chairman) I don’t know either.

MARANGELLA (Turin, Italy) This is just to confirm your results. We have presented in Williamsburg some data about patients with cystinuria who had been treated with 2HPG for a mean of 36 months. We haven’t observed any escape phenomenon.

DENNEBERG Yes, I know of your work from Italy. There are, in fact three groups in Europe who have used this drug*. Some papers come from Japan† where this drug comes from.

PAK (Dallas, USA) We have been conducting a multi-centre trial in the United States concerned with the question of whether penicillamine is more toxic than Thiola, or conversely whether Thiola is safer to use than penicillamine. To test this hypothesis we have taken patients who had developed clear cut toxicity to penicillamine and offered them instead Thiola. To date 45 per cent of the patients developed toxicity to Thiola suggesting that there is at least an element of cross reactivity of side effects.

CAMERON That's a very important comment.

GOLDSMITH (Liverpool) It may be impossible in a hot climate to procure the necessary high urine volumes to deal successfully with cystinuria in people with established stones. I have the impression that at least in this country most nephrologists simply use a very high fluid intake and adequate amounts of bicarbonate. Certainly this is true of one or two colleagues with whom I have discussed this. In my own practice, and in view of the toxicity of these drugs I would have thought that this should be the first line of approach.

CAMERON Would you like to comment on that Dr Denneberg, because I think the custom in Britain, which has been heavily influenced by the late Dr Giles Dent, was to exploit the physical chemistry of cystine in the urine to educate patients very carefully and very thoroughly with alkalinisation giving them pH papers. We use, for example, the British Drug Houses medium range pH paper to test their early morning urine. In addition to ensure a high fluid intake, and with this regime, as Dr Goldsmith said, one can achieve a great deal that one can achieve with either of the chelating drugs. You mention that you only use moderate diuresis and I wonder if you could tell us before the patients reach the Thiola and penicillamine treatment how intensively was diuresis or alkalinisation exploited, or was it not at all?

DENNEBERG I'm situated in the south of Sweden and the patients are coming from the urologists so they are operated on and sent to me afterwards. They are instructed to drink as much as four to five litres daily and with about 15 to 20 grams bicarbonate. So I reduce their drinking and reduce also their bicarbonate to about three to six grams daily.

ROBERTSON (Leeds) Just to come back on this question of giving bicarbonate for cystine stone formation. One of the problems is that you have to give fairly high doses of bicarbonate. The urine pH must go up well into the sevens to have any significant effect on the solubility of cystine. I think if you look in the literature on this form of therapy you will find several reports of calcium phosphate that precipitates being overlayers on the top of cystine stones. It is not entirely effective in every individual in preventing stone formation.

DENNEBERG Yes, this is described in the literature and is also our experience.