

The Management of Cystinuria in 1976

by Dr A D Stephens
(Department of Haematology,
St Bartholomew's Hospital,
London EC1A 7BE)

Introduction

Cystinuria is an inherited condition associated with the formation of renal stones composed of the amino-acid cystine. These stones may cause severe abdominal pain which can mimic acute appendicitis or occasionally a more chronic loin discomfort. They may also promote urinary tract infection and may cause acute renal failure due to ureteric obstruction.

Cystinuria is an uncommon disease, but not a rare one, and it is found in approximately 1 in 20000 of the population. The condition commonly presents in children and adolescents, 75% of cases presenting before the age of 20 years. Once the first symptom has occurred it is common for symptoms to be recurrent every few months for the remainder of the patient's life. No treatment has been shown to affect the basic biochemical defect, but the clinical symptoms can be successfully prevented if stone formation can be controlled. However, since the condition is inherited, treatment must be suitable for the patient to continue for the remainder of his life.

Principles of Treatment

The patient with cystinuria has one great advantage over most patients with renal stone disease: not only can cystine stone formation be prevented, but stones already present can also be dissolved. Successful treatment of cystinuria involves reducing the urinary concentration of cystine sufficiently to keep it below the critical concentration at which precipitation occurs. This reduction in concentration must be consistently maintained throughout the day and night, through weekdays, weekends, schooldays and holidays. The night time is the most critical period, since the urine gets more concentrated and the pH falls during sleep, both events making stone formation more likely at night (the maximum solubility of cystine being about 300 mg per litre of urine). All the persuasive skill of the doctor must be directed to convincing the patient of the necessity of maintaining a regular regime.

Only two forms of treatment have stood the test of time: the first, introduced by Dent & Senior in 1955 (see also Dent *et al.* 1965), is the high fluid regime in which sufficient water is drunk to dilute the urinary cystine. The second is penicillamine, which was suggested on theoretical

grounds by Walshe in 1958, but whose introduction had to wait for the work of Crawhall *et al* (1963).

Penicillamine works in two ways. It both increases the solubility of cystine and also reduces the amount of total cyst(e)ine excreted (Crawhall & Thompson 1965, Bartter *et al.* 1965, Perrett *et al.* 1976). It makes cystine more soluble by undergoing thiol exchange with the cysteine radicals to produce the mixed disulphide cysteine-penicillamine disulphide which is 50 times more soluble than cystine (Lotz *et al.* 1966). Penicillamine reduces the 'total cyst(e)ine' excreted (cysteine+cystine+cysteine-penicillamine disulphide) to about one-third of the pretreatment level. The basic mechanism of this change in cysteine-cystine metabolism is unknown but is discussed more fully by Perrett (*see p 61*).

Further information on cystinuria can be obtained from the reviews by Crawhall & Watts (1968) and Scriver & Rosenberg (1973).

Experience at St Bartholomew's Hospital

Our experience at St Bartholomew's in the use of penicillamine for the treatment of cystinuria began in December 1962 when our first patient began regular treatment. At that time she was an 11-year-old schoolgirl, and she has been taking penicillamine regularly ever since. The treatment of this patient followed both *in vitro* and *in vivo* experiments by Crawhall and his colleagues at St Bartholomew's Hospital.

In the last 13 years a total of 34 patients have been treated with penicillamine; this may seem a very small number compared to the patients treated with penicillamine for rheumatoid arthritis, but by comparison cystinuria is an uncommon disease. From our experience I believe that penicillamine now has a definite place in the treatment of cystinuria, just as it has in Wilson's disease. Our results may be of interest to workers in other fields, since prolonged treatment has allowed some adverse reactions to appear and their effects to be assessed.

Of the 34 patients, 22 were treated for four years or more and 10 for ten years or more; the remaining 12 have been treated for less than four years. At the start of treatment their ages varied from 5 to 65 years. The penicillamine used was semisynthetic D-penicillamine (Distamine) prepared by hydrolysis of penicillin. Initially the hydrochloride was used (150 mg capsules = to 120 mg of base), but many patients preferred to change to the 250 mg tablets of D-penicillamine free base when they became available, since there were fewer tablets to swallow. In this paper all dosages are given as if they were D-penicillamine free base.

In almost all cases penicillamine is given three times each day and spaced as evenly as possible: this usually means with breakfast, with tea and at bedtime. In all cases the urinary cystine has been monitored by amino-acid column chromatography (Purdie *et al.* 1968), which is the only practical method for measuring cystine in the presence of penicillamine and cysteine-penicillamine disulphide. Dosage was adjusted in order to keep the urinary cystine well below the concentration at which precipitation occurs. Initially it was kept below 300 mg/24 h and later below 200 mg/litre, the patients being advised to drink sufficient to produce a urine volume of 1½-2 litres/24 h.

It has been our practice to introduce penicillamine gradually over a period of 2-3 weeks, by which time they are usually taking 500-750 mg three times a day, though some patients require 1000 mg three times a day and a few, especially children, require less.

Treatment is considered successful if stones are dissolved or if recurrent stone formation is prevented in patients suffering from recurrent stones or gravel. Stones were dissolved in 6 patients and prevented in 25.

However, treatment failed in 7 patients. In 5 of these it was because they failed to take their penicillamine regularly, and this was particularly common in the late teens and early twenties, the ages of these patients varying from 15 to 27 years. This is very similar to Walshe's experience in Wilson's disease. The patients will often say that they are taking the recommended dose, and in this situation an amino-acid analyser can be invaluable, as it allows not only the cystine to be monitored, but the penicillamine as well.

Treatment also failed to dissolve stones in 2 patients with persistent urinary tract infections. One of these had surgical clearance of the stones, and it is interesting that analysis showed the residual stones to be composed of 'triple phosphates', typical of infective stones, and there was no evidence of any cystine in the stones. The cystinuria had therefore been adequately controlled, but the stone disease had not. In the eight years since the operation the patient has continued on penicillamine and no more stones have developed.

Treatment had to be withdrawn in 5 patients: in 4 because of heavy proteinuria (>5 g/24 h with or without the nephrotic syndrome) and in one patient because of severe anorexia and nausea. In all cases the proteinuria disappeared on stopping the penicillamine, and in one patient it was possible to reintroduce penicillamine, at first in low dosage (375 mg/24 h), and later in high dosage (3000 mg/24 h). The reintroduction of penicillamine was considered justifiable in this

patient since he had severe stone disease, and no other adequate treatment was available since his stones had increased in size while he was off penicillamine and attempting to maintain a high fluid intake. He has now been treated for three years on the high dose and the stones have disappeared.

Side-effects

Side-effects are common in patients treated with penicillamine. They may cause the patient little or no discomfort, they may be warning signs to be watched very carefully, or they may demand immediate withdrawal of treatment. In our cases the common side-effects are those affecting the skin and kidney. An early rash occurs in nearly half the patients, usually around the tenth day of treatment. It is often transitory, and occasionally accompanied by slight itching and/or pyrexia; in these cases no alteration in treatment is necessary. Occasionally the rash and fever are more persistent and accompanied by general malaise and sometimes even generalized lymphadenopathy is seen; in these cases we found it necessary to reduce or even withdraw treatment temporarily. However, in all cases it has been possible to reintroduce penicillamine with or without steroid cover. We have seen a late rash similar to that which has been called epidermolysis bullosa in several of the patients. These patients have had penicillamine for between two and 12 years, and were taking 1.5-2.0 g/24 h at the time the rash was noticed. It has not been necessary to alter their penicillamine dosage.

Proteinuria is also common, occurring in 14 of the 34 patients. In cystinuria the patients may have pre-existing renal damage and they may also have stones or urinary tract infection. I therefore find it useful to subdivide the patients with proteinuria into three groups: those with less than 1 g/24 h, those with 1-5 g/24 h, and those with more than 5 g/24 h. Less than 1 g/24 h has been found in 5 patients, and these patients often have urinary tract infection or stones. Moderate proteinuria of 1-5 g/24 h has also been found in 5 patients and may be persistent over many years, but does not seem to do the patients any harm. With these patients we continue treatment, but monitor the protein excretion at regular intervals.

Severe proteinuria (more than 5 g/24 h) has been found in 4 patients (11-19 g/24 h) at intervals of 2 months to 4½ years after starting treatment. The proteinuria was of sudden onset in all 4 patients, and was accompanied by the nephrotic syndrome in 2 of the patients. Penicillamine was stopped in all 4 patients and steroids were given in the 2 with the nephrotic syndrome. In all cases the proteinuria gradually disappeared over a

period of one year. As already mentioned, penicillamine was reintroduced in one patient. In this patient there was a temporary recurrence of proteinuria after three months' high-dose treatment (3 g/24 h), but this disappeared after reducing the dose to 2.25 g/24 h for three months, and his urine has remained protein-free for a further three years on 2.25 g/24 h. It is of interest that in our small group of patients proteinuria of less than 5 g/24 h has never progressed to severe proteinuria or the nephrotic syndrome.

Other side-effects have been rare in our cystinuric patients. Loss of taste occurred in one patient, but this gradually returned to normal during one year's treatment at the same dosage. Severe anorexia and nausea also occurred in one patient, and necessitated withdrawing treatment on two occasions. Thrombocytopenia, neutropenia and aplastic anaemia have not yet been seen. There has been no evidence of delayed wound healing in patients undergoing renal operations during treatment.

Discussion

Although penicillamine is useful it does have disadvantages: it has to be taken three times a day for the rest of the patient's life, some patients complain that it has a nasty taste, it has toxic side-effects that must be looked for in all patients, and in a few patients immediate action is necessary. Last, but to some patients most important, it is expensive, though comparison with the price of cigarettes is revealing (80p-£1.60 per day=40-80 cigarettes per day). What of the future? Low-dose regimes and a single bedtime dose are being investigated in the hope of reducing side-effects. A long-acting or depot preparation would be welcomed by many patients, but might be a disadvantage if side-effects occurred.

Conclusions

(1) Penicillamine has a definite place in the treatment of cystinuria and it can transform the life of some patients. It can dissolve stones already present and is helpful in preventing new stone formation if a high fluid regime fails.

(2) Dose: 500-750 mg three times in 24 h is adequate for most patients. A few may need 1000 mg three times in 24 h.

Urinary amino-acid analysis is helpful in controlling the dose in all patients and may be invaluable in difficult cases.

(3) Toxic side-effects occur in some patients. In cystinuria the main ones are those that affect the skin and kidney.

(4) Treatment failures are usually due to failure to take penicillamine regularly (especially found in adolescents) or to the presence of infected stones.

(5) Because cystinuria is an uncommon disease and because difficulties can arise both with dosage and side-effects it is probably advisable to treat most patients at centres accustomed to using penicillamine and with ready access to quantitative amino-acid analysis.

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DISCUSSION

Dr H F H Hill (Stoke Mandeville): Did Dr Stephens' patients with a rash complain of itching when asked about it?

Dr Stephens: Some of them did, but not all.

Dr Hill: I wonder whether Dr Marsden could comment on the rash.

Dr R A Marsden (Oxford): The scarred lesions are similar to those in epidermolysis bullosa dystrophica. Such lesions and a tendency to bruise have both been described following penicillamine therapy and are probably due to the drug's lathyrogenic action on dermal collagen.

Dr I H Scheinberg (New York): When we have seen this rash in Wilson's disease it has never been reported as itching.

Dr Stephens: I may have misunderstood the question about itching. The rash which we find itches is the early one, not the late epidermolysis bullosa. This late rash has never itched; it is the rash occurring early, at about ten days, which sometimes itches.

Dr J Golding (Harrogate): I was extremely interested in the effect on the kidney described by Dr Stephens. He could put these patients into three separate groups. We have had experience in the treatment of rheumatoid arthritis with penicillamine. We generally find that a trace of albumin appears in the urine, which may well increase to unacceptable amounts if the penicillamine is continued. We are unable to segregate rheumatoid patients into three groups.