The Use of D-Penicillamine in Cystinuria: Efficacy and Untoward Reactions

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A retrospective study was conducted to assess the efficacy of D-penicillamine in the management of cystinuria, as well as to define the frequency and nature of untoward reactions to this drug. Fifty-six individuals were identified who, by stone analysis and/or biochemical studies, met the accepted diagnostic criteria for phenotypic cystinuria. The majority of these patients presented in the second decade of life with evidence of stone formation: renal colic, hematuria, and/or stone passage. Thirty-five individuals were considered to have clinically advanced cystinuria because they had required at least one urinary tract lithotomy. In these advanced cases, frequency of subsequent lithotomies and episodes of renal colic per 100 patient-years of observation were used as indices to measure the efficacy of D-penicillamine treatment. By both measurements, D-penicillamine significantly improved the clinical course of patients. The incidence of acute drug sensitivity reactions (rash, fever, and/or arthropathy) was in excess of 40 percent. Delayed drug-induced proteinuria occurred in 34 percent of treated patients. We conclude that D-penicillamine is useful in the treatment of cystinuria. Because of the significant number of untoward drug reactions, however, we believe the drug should be instituted only in selected, high-risk patients.

INTRODUCTION

Cystinuria, a disorder of cystine and dibasic amino acid transport, is inherited as an autosomal recessive trait. The transport defect affects the epithelial cells of the renal tubules and the mucosa of the small intestine. Because of the renal defect, an excessive quantity of cystine, the least soluble of the naturally occurring amino acids, is present in the urine. This predisposes to the formation of renal, ureteral, and bladder calculi composed of cystine. The major causes of morbidity and mortality in this disorder are the sequellae of stone formation: renal and ureteral colic, urinary tract infection, obstruction, and compromise of renal function. There are several recent comprehensive reviews of cystinuria [1–3].

Patients with cystinuria are treated primarily with large quantities of oral fluids to reduce the concentration of cystine in the urine. Therapy may also include urinary alkalinizing agents since the solubility of cystine increases significantly above urine pH 7.5 [4]. Several years ago experiments showed that cystine, which is readily crystallized from the urine of cystinuric subjects, could not be crystallized from the
same urines after the addition of D-penicillamine *in vitro* [5]. This phenomenon depends on a thiol-disulfide exchange reaction that forms a penicillamine-cysteine disulfide 50 times more soluble than cystine [6]. Oral consumption of one to two grams of D-penicillamine per day, in divided doses, has been shown to reduce urinary cystine concentration, stabilize stone disease, and even dissolve existing stones [5,7,8]. In the treatment of cystinuria, therefore, fluid ingestion is frequently combined with urinary alkalinizing agents and/or D-penicillamine. We have undertaken a study to define more clearly the efficacy of and untoward reactions to D-penicillamine in the management of cystinuria.

**MATERIALS AND METHODS**

**Patient Selection**

Medical records were retrieved from six medical centers in the northeastern United States for all patients with the diagnosis of cystinuria during the years 1940 to 1978. From this group, we identified 56 patients who met one or more of the generally accepted diagnostic criteria for cystinuria: (a) cystine stone removed at surgery or passed spontaneously; (b) chemical analysis of urine demonstrating excessive excretion of cystine and dibasic amino acids; (c) positive urine nitroprusside test [8]; and (d) cystine crystalluria.

**Clinical Evaluation**

Data on age at presentation, sex, race, and presenting symptoms were recorded. Clinical progress was evaluated from hospital history and clinic notes, reports of intravenous pyelograms and abdominal X-rays, and reports of urologic surgical procedures. Events scored included: (a) urinary tract lithotomy (nephrolithotomy, ureterolithotomy, nephrectomy for stone disease, and cystolithotomy); and (b) episodes of presumed renal colic associated with X-ray findings demonstrating a stone, passage of a stone, or finding a stone at surgery.

It was necessary to select comparable groups of D-penicillamine-treated and D-penicillamine-untreated patients to test the efficacy of the drug. In our review of medical records, we found that the most commonly cited indication for D-penicillamine use was the failure of more conservative measures (such as fluid administration) to control the disease. A simple comparison of D-penicillamine-treated versus D-penicillamine-untreated groups would, therefore, introduce a systematic bias because D-penicillamine is usually prescribed in more advanced cases. To select a more comparable population of clinically advanced cases, we used an initial urinary tract lithotomy as the signal event to enter a patient into the study. We make the assumption that the surgical event denotes relatively severe disease. Since therapy preceding the lithotomy did not affect entrance into the study, we accept some variation in severity of disease within the study group. Operative procedures, as a signal event, have the advantage of easy identification in medical histories. Thirty-five of the 56 patients had such a surgical procedure.

Patient-years of observation following the operation were used as the denominator for the events scored in these 35 patients. This provided an index to evaluate the efficacy of D-penicillamine in relatively advanced cystinuria. Statistical significance was evaluated by chi-square analysis [9,10].

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Treatment Modalities

Three forms of medical treatment were distinguished. First, treatment with oral fluids consisted of instructing the patient to consume large volumes of water or other fluids routinely. Patients were instructed to drink so as to never feel thirst, and in amounts adequate to require voiding at least once each night. Second, treatment to promote urinary alkalinization consisted of instructing the patient to ingest, at intervals throughout the day, sodium bicarbonate or sodium citrate solution and, in some cases, acetazolamide at bedtime. Third, D-penicillamine treatment consisted of oral administration of one to two grams of the drug per day in divided doses. Documented evidence or narrative report of non-compliance with a treatment program prompted exclusion of the patient-years of observation in question. An attempt was made to employ D-penicillamine as a component of therapy in 32 of the total population of 56 patients (57 percent) and in 24 of the subgroup of 35 patients (69 percent) who had undergone a lithotomy. In the tabulation of episodes of lithotomy or renal colic, an individual patient could contribute to the D-penicillamine treatment and D-penicillamine non-treatment groups if, for example, the drug was instituted and then withdrawn.

Evaluation of Side Effects

In the 32 patients who received D-penicillamine at some time during treatment, note was made of untoward reaction(s) attributed to the drug. Note was also made of whether or not the side effect necessitated withdrawal of the drug.

RESULTS

Characteristics of the Population

Data from the medical records of 56 individuals who met one or more of the generally accepted diagnostic criteria of cystinuria are presented in Table 1. Each criterion would, on its own, be sufficient to make the diagnosis. In this group the diagnosis of cystinuria was generally made by stone or gravel analysis and/or urine

| TABLE 1 |
| --- |
| Diagnostic Criteria for Phenotypic Cystinuria in 56 Patients |
| Criteria | Number | Percent | Patients for whom this was the only criterion |
| --- | --- | --- | --- |
| Cystine stone (removed at surgery or passed spontaneously) | 51 | 91 | 4 | 7 |
| Urinary cystine excretion greater than 400 mg/day or 250 mg/g of creatinine | 33 | 59 | 2 | 4 |
| Positive nitroprusside test | 29 | 52 | 1 | 2 |
| Paper chromatographic electrophoresis showing excessive excretion of cystine and dibasic amino acids | 23 | 41 | 0 | 0 |
| Cystine crystalluria | 17 | 30 | 1 | 2 |
chemical assays. For 48/56 patients (86 percent), the diagnosis was supported by several other criteria. Conversely, few (14 percent) of our patients had the diagnosis made by a single criterion. A near equal sex distribution was found (Table 2). In the 47 patients where race was known, Caucasians were predominant.

The reasons for clinical presentation are shown in Table 3. Most patients sought medical attention with the well-known signs of nephrolithiasis: renal colic, hematuria, stone passage, recurrent urinary tract infections, and back pain. A surprisingly large number of patients (20 percent) were discovered while asymptomatic. Chemical or microscopic urinalysis, usually undertaken as a screening measure in relatives of a patient with cystinuria, was used to make the diagnosis in these patients. Mean age at onset of first symptom (excluding asymptomatic patients identified by routine screening) was 17.4 ± 9.9 years for males and 19.5 ± 8.4 years for females. The mean age of diagnosis of the asymptomatic patients was 19.8 ± 10.9 years.

**Efficacy of D-Penicillamine**

The data in Table 4 show that patients with clinically advanced cystinuria on treatment programs that included D-penicillamine required significantly less urinary tract surgery for stone removal than did patients on treatment programs that did not include the drug. The findings demonstrate, moreover, that D-penicillamine treat-

| TABLE 2 |
| --- |
| **Population Characteristics of 56 Cystinuric Patients** |
| | Patients | Percent |
| **Sex** | | |
| Male | 29 | 52 |
| Female | 27 | 48 |
| **Race** | | |
| Caucasian | 44 | 79 |
| Black | 3 | 5 |
| Unknown | 9 | 16 |

| TABLE 3 |
| --- |
| **Presenting Medical Problems in 56 Patients with Cystinuria** |
| | Number | Percent* |
| Renal colic | 28 | 50 |
| Hematuria | 11 | 20 |
| Asymptomatic** | 11 | 20 |
| Stone passage | 7 | 13 |
| Recurrent urinary tract infections | 5 | 9 |
| Back pain | 3 | 5 |
| Anuria | 2 | 4 |

*Total is greater than 100 percent because some patients had more than one presenting complaint.

**No urinary tract symptoms. The diagnosis was made by: screening relatives of a cystinuric patient, 9; routine urinalysis, 1; urine biochemical tests done during evaluation of a mentally retarded child, 1.*
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TABLE 4
Frequency of Subsequent Urinary Tract Lithotomy and Renal Colic in 35 Patients with Cystinuria*

| Treatment Modality          | Number of Lithotomy Operations | Operations per 100 Patient-Years | Number of Episodes of Renal Colic | Episodes per 100 Patient-Years |
|-----------------------------|--------------------------------|----------------------------------|----------------------------------|-------------------------------|
| Fluids or Fluids/Alkali    | 210.5                          | 28                               | 13.3                             | 53                            | 25.1                          |
| Fluids/D-penicillamine or  |                                |                                  |                                  |                               |                               |
| Fluids/Alkali/D-penicillamine | 114.7                     | 2                                | 1.7                              | 16                            | 13.19                         |

*All patients had undergone at least one surgical procedure for stone removal prior to inclusion in this study.

ment programs significantly reduced episodes of renal colic. The decrease—from 25.1 episodes/100 patient-years in the D-penicillamine untreated group to 13.9 in the D-penicillamine treated group—is significant at the \( p = 0.05 \) level. Although one might speculate that the institution of penicillamine in a patient with stones would temporarily increase the attacks of colic as dissolving stones are passed, we observed no such tendency.

Side Effects of D-Penicillamine

Thirty-two of our 56 patients were treated with D-penicillamine sometime during the course of their illness. Side effects attributed to the drug are detailed in Table 5. Rash, fever, pruritus, and arthropathy were common early side effects. The usual interval from initiation of the drug to manifestation of each of these four side effects was nine to ten days. Late onset untoward reactions included proteinuria and abnormalities of taste and smell. Proteinuria (greater than 500 mg/24 hr) occurred in 34 percent of the patients with a median time to onset, after initiation of the drug, of five months. Proteinuria occurred as early as one month following initiation of D-penicillamine and as late as 45 months after instituting the drug. The three episodes of abnormalities of taste and smell occurred one to two months after the drug was begun.

Eighteen of the initial 32 attempts to treat patients with D-penicillamine were halted because of side effects (56 percent). Institution of and maintenance on the

TABLE 5
Side Effects of D-Penicillamine in 32 Patients with Cystinuria

| Side Effect               | Number | Percent |
|---------------------------|--------|---------|
| Rash                      | 14     | 44      |
| Fever*                    | 12     | 38      |
| Proteinuria**             | 11     | 34      |
| Pruritus                  | 7      | 22      |
| Arthropathy               | 5      | 16      |
| Abnormalities of taste/smell | 3   | 9       |

*Greater than 99.6° po or 100.3° pr; not associated with infection
**Greater than 500 mg/24 hr
drug for a period of one year or more was eventually achieved in eight of these 18 patients. Overall, D-penicillamine therapy was known to have been instituted and maintained for a period of one year or more in 17 of the 32 patients (53 percent).

DISCUSSION

In the initial 1810 case report describing the condition now known as cystinuria, the diagnosis was based on stone analysis [11]. Currently, the diagnosis of the disease continues to rest most often on stone or crystal analysis. In addition, the diagnosis can be made by urine chemical studies. Our population of cystinuric patients is similar to that reported from the Mayo Clinic [12] in that quantitative urine cystine measurements and/or stone analysis were the principal means of establishing the diagnosis. The two groups differ in that more patients in our series had the diagnosis supported by several diagnostic tests.

Except for three Blacks, all patients in whom race was known were Caucasian (Table 2). Cystinuria has been reported rarely in Blacks and Orientals [13,14]. Our finding of an equal sex distribution is expected for this autosomal recessive trait. Males have been alleged to be more severely affected—perhaps due to the greater likelihood of urethral obstruction [2]. The recent Mayo Clinic study, however, found that the morbidity and severity of cystinuria were not significantly different in men and women [12]. Our finding that the median age at presentation for males and females was 17.3 and 19.6 years, respectively, agrees with other published experience [1,12].

The presenting signs and symptoms of cystinuria are those common to most forms of urolithiasis: gross hematuria, renal colic with or without stone passage, urinary tract infection, and back pain (Table 3). A substantial percentage of our patients with cystinuria (20 percent) were discovered as a result of screening—usually conducted among relatives of affected individuals. Screening has not generally been reported as an important method of identifying affected individuals. It may become more important in coming years as population screening becomes more widely employed. It will be interesting to study these asymptomatic individuals to learn if early institution of therapy changes the natural history of the disease.

Following initial reports of the usefulness of D-penicillamine in human cystinuria, there have been descriptions of the ability of the drug to "dissolve" clinically important stones, and to stabilize or improve the course of the disease [5-8,12]. Unfortunately, there has never been a controlled trial of the therapeutic efficacy of D-penicillamine in cystinuria. The low incidence of cystinuria (~1:10,000) makes it unlikely that such a study will ever be done. To date, the most careful clinical evaluation of the role of D-penicillamine in cystinuria has been reported by Dahlberg and his colleagues at the Mayo Clinic [12]. Utilizing measurements of "metabolic activity" of stone disease—that is an assessment of "active," "inactive," or "indeterminate activity" of disease based on X-ray changes or gravel passage [15]—the authors analyzed data from 54 patients. Thirty patients were treated with fluids and alkali alone and became "metabolically inactive." On the other hand, 15 of the 24 patients in the D-penicillamine-treated group experienced dissolution of calculi or significant reduction in stone size.

In our patient population, the use of measurements of "metabolic activity" was impractical because of variability in the detail, availability, and frequency of X-ray reports of stone size and changes. In addition, there was insufficient documentation to allow the use of frequency of urinary tract infections or episodes of stone passage as indices. Fortunately, lithotomy procedures and hospital or office visits for renal
colic associated with a stone are generally well documented and useful indices of clinical progress. Because we found that the institution of D-penicillamine was most often undertaken because of the failure of more conservative measures in an individual patient, we believe that a systematic bias is introduced if one simply compares D-penicillamine treatment programs to those that did not include the drug. We attempted to avoid this bias by limiting our analysis to patient-years of observation following an initial lithotomy—a sub-population of more “severely” affected individuals.

In the selected population of “severely” affected cystinuric patients, treatment programs which included D-penicillamine significantly reduced the frequency of renal colic and lithotomy surgery (Table 4). It thus appears that penicillamine can modify in a favorable way the natural history of cystinuria. Although we can give no assurance of equal compliance to all treatment programs, we have no reason to believe that addition of D-penicillamine to treatment programs altered compliance with hydration as the principal therapeutic modality.

A substantial literature is accumulating on the side effects of D-penicillamine [3,16-18]. The reported toxic effects include: sensitivity reactions of the serum-sickness sort, hematologic dysfunction including leukopenia, agranulocytosis, and thrombocytopenia; taste and smell abnormalities; nephrotoxicity manifested as proteinuria, nephrotic syndrome, or a rapidly progressive glomerulonephritis; and nausea and epigastric distress. About 40 percent of our patients (Table 5) developed serum sickness evidenced by rash, fever, pruritus, and/or arthropathy. Even more distressing is our observation that about one-third of the D-penicillamine-treated patients developed significant proteinuria. In none, however, did this progress to the nephrotic syndrome.

Proteinuria caused by D-penicillamine resolved, in all cases, when the drug was stopped. Reinstitution of the drug, at conventional doses, was generally followed by recurrence of proteinuria. In our experience, reinstitution of the drug by a “desensitization” regimen is best for avoiding recurrence of proteinuria and other side effects. The “desensitization” technique utilizes initial doses of D-penicillamine of 10 to 25 mg/day. The dose is raised slowly, at three-day intervals, until a dose of 1 to 1.5 gm/day is reached after approximately 30 days.

The Mayo Clinic series of 43 cystinuric patients who received D-penicillamine differed from our group in the reported frequency of side effects [12]. The Mayo Clinic group was subject to fewer episodes of rash with fever or lymphadenopathy (28 percent), abnormalities of taste or smell (14 percent), or “high grade” proteinuria (9 percent). One patient had drug-related granulocytopenia. We have no explanation for the lower incidence of side effects in the Mayo Clinic Study.

The side effects of D-penicillamine in 33 patients with Wilson's Disease have also been reported [19]. Rash, fever, and/or adenopathy occurred in 48 percent of the patients. Ecchymosis, particularly at pressure points, was reported in 18 percent of the group. Leukopenia or thrombocytopenia was an untoward effect in 24 percent. None developed significant proteinuria. The variation in the frequency and distribution of side effects related to D-penicillamine in patients with cystinuria and Wilson's Disease may be ascribed to dose variation, duration of use, the patient's general medical condition, and, possibly, to differences in the antigenicity of the drug in various disease states.

D-penicillamine has been shown to be a useful adjunct in the treatment of cystinuria. Because of the dangers of D-penicillamine therapy, however, we recommend that it be used only if fluids and urinary alkalization have been unsuccessful,
or if the patient has already lost one kidney from stone disease. Drugs that may provide an alternative to D-penicillamine in the management of cystinuria are currently under investigation [20-22].

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