A Randomized Placebo-Controlled Trial of Cysteamine Eye Drops in Nephropathic Cystinosis

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Eighteen patients with nephropathic cystinosis who were younger than 42 months and 11 patients 4 to 31 years of age were entered into a double-masked, randomized, placebo-controlled trial of topical cysteamine eye drops between November 1985 and September 1989. Eight of the younger patients and 2 of the older patients showed marked clearing of corneal crystals in one eye compared with the fellow eye. When the code was broken, all 10 patients were found to have received cysteamine eye drops in the improved eye. Of the remaining 19 patients 4 were unavailable for follow-up. In 15 patients no marked difference was noted between the two eyes. Eight have presumably been in the protocol for too short a time and several have been poor compliers with the therapy. These results not only demonstrate the potential for primary prevention of corneal cystinosis but also, for the first time, offer the possibility of reversing the corneal complications of cystinosis in older patients.


Nephropathic cystinosis is a rare autosomal recessively inherited disorder in which cystine accumulates within cellular lysosomes because of a defect in its transport across the lysosomal membrane. In cystinotic cells, free nonprotein cystine, which is poorly soluble in an aqueous solution, accumulates in concentrations 50 to 100 times normal, forming crystals in many tissues and resulting in functional damage. Although normal at birth, patients develop renal tubular Fanconi's syndrome between 6 and 18 months of age, with growth failure and rickets. Renal tubular deterioration continues, usually leading to end-stage renal disease by 10 years of age, requiring dialysis or renal transplantation. Patients who survive into their second and third decades by virtue of a renal allograft are susceptible to several nonrenal complications, including hypothyroidism, visual impairment, pancreatic endocrine insufficiency, myopathy, and neurologic deficits.

Although there is no cure for cystinosis, treatment includes replacement of renal losses and the oral administration of cysteamine hydrochloride (mercaptopurine), a free thiol with marked cystine-depleting ability. Young patients receiving long-term oral cysteamine therapy have shown improvement in growth and maintenance of renal function. However, there is no clinical evidence that oral cysteamine reverses the accumulation of crystals in the cornea.

The natural history of corneal crystal deposition in nephropathic cystinosis is now being elucidated. Corneal crystals are first seen on slit-lamp biomicroscopy at about 1 year of age. They initially appear patchily in the central cornea, but inexorably increase, invariably creating a homogenous pattern by 2 years of age. These findings are so characteristic that they often establish the diagnosis of cystinosis. As time progresses, the crystals eventually pack the full thickness of the peripheral cornea and the anterior two thirds of the central cornea. In the younger patients and many older patients, the corneal crystals may contribute to photophobia and varying degrees of discomfort, although they do not appear to cause a decrease in visual acuity. As a result of studies that showed that cysteamine effectively reduces the cystine content of cystinotic corneal cells in culture, a double-masked, randomized, placebo-controlled trial of topical cysteamine eye drops was initiated, with favorable results reported in 2 patients. We now present the findings of an expanded study involving 18 patients younger than 42 months (including the first 2 previously described) and 11 older patients, 4 to 31 years of age.

PATIENTS AND METHODS

Twenty-nine patients aged 2 months to 31 years, including two patients previously reported, were entered into the study. Four patients not included in the compilation of data are two infants who died of unrelated causes, 1 and 6 months after entry into this protocol, one 31-year-old man who discontinued the use of the eye drops after 1 month of therapy, and one 6-year-old boy who was too ill to continue in the trial.

All patients were diagnosed as having cystinosis based on a typical clinical presentation in addition to demonstration of a leukocyte cystine concentration greater than 3 mmol half-cystine per milligram of protein (normal concentration, <0.2 mmol half-cystine per milligram of protein). All patients in group 1 except patient 1 had
corneal crystals at the time of entry into the study and all were receiving oral cysteamine according to an approved research protocol (W.A.G.).

Permission to use topical cysteamine was obtained by amending the Food and Drug Administration's Investigational New Drug Exemption No. 11065 held by J. G. Thoene, MD, University of Michigan, Ann Arbor. After demonstrating safety in rabbit eyes* and obtaining approval by the National Eye Institute Institutional Review Board, a double-masked, randomized, placebo-controlled trial of 0.1% (10 mmol/L) cysteamine eye drops was initiated. One drop of cysteamine in normal saline was placed in one randomly selected eye hourly while the subject was awake. Normal saline was placed in the other eye according to the same schedule. An ophthalmic nurse taught the parents how to maintain sterility in administering the eye drops and how to maintain records of each application on a form supplied to them. The eye drops were prepared by the National Institutes of Health (NIH) Clinical Center's Pharmaceutical Development Service, which also administered the randomization code. Fresh bottles were used every 5 days to reduce the risk of contamination. The subjective assessment of compliance was assigned a score of 1 to 4 based on parents' estimations of parental adherence or patient adherence to both oral and topical cysteamine administration. Adherence was measured by assessing the overall medical status of the patient, the number of missed appointments, the parents' attitudes and behaviors, and the receipt of topical administration. A rating of 1 represented poor compliance and 4 reflected excellent compliance.

Patients were examined at the NIH Clinical Center every 3 to 4 months. The ocular evaluation included slit-lamp biomicroscopy and photography. A Zeiss photo-slit lamp (Oberkochen, Germany) with stereoscopic accessories, beam splitters, two camera bodies, and side-arm adapters was employed. Direct focal illumination with a moderately wide slit beam (5 mm), an aperture setting of f22, a flash intensity of 2, Ektachrome 200 film (Eastman Kodak, Rochester, NY), and optimal magnification (25×) were used.

Patients were examined by three ophthalmologists (M.K.-K., R.C.C., and M.B.D.) who were masked to the therapy. Each physician offered an independent clinical impression regarding whether there was a difference in the density of corneal crystals between the two eyes. Slides of the cornea were also assessed and evaluated independently by three “photographic” observers (E.M.K., M.A.G., and W.A.G.), who offered an independent decision as to whether there was a significant difference between eyes at each visit and between visits for each eye. This decision was based on a difference in the corneal score (CS) determined from a set of standard photographs described below. The end point was reached when there was unanimous agreement among the three clinical observers and the three photographic observers that there was a difference in the density of corneal crystals between the two eyes at the current visit and a decrease in the “better” eye from the previous visit based on a determination of the CS. At this point the code was broken.

To further evaluate the patients' slides more reproducibly, a library of standard transparencies was assembled from slides and ranked in order of increasing density of corneal crystals. Arbitrary units of crystal density, referred to as a CS, of 0 to 3.00 in increments of 0.155, were subjectively assigned to the transparencies to create a “standard curve” against which all the slides would be judged. In general, only slides with the light slit passing through the center of the cornea were evaluated, since crystal density varies with location of the cornea. Transparencies were chosen rather than prints because they were more comparable with the slides.

Because of variable success in clearing corneal crystals using 0.1% cysteamine eye drops, further toxicity studies were performed in animals to demonstrate the safety of higher concentrations of cysteamine, ie, 0.5%. After human use approval was obtained for 0.5% cysteamine eye drops most patients were changed to this higher concentration, and new patients received 0.5% cysteamine eye drops initially, still under the randomized protocol. As a result, some patients received 0.1% and others 0.5% cysteamine eye drops.

Group 1 (patients 1 through 16) consisted of children younger than 4 years and group 2 (patients 17 through 25) included patients 4 to 23 years of age (Table). Patients 1 through 5 initially received 0.1% cysteamine eye drops. Patients 6 through 11, initially treated with 0.1% cysteamine eye drops, did not show improvement and were switched to 0.5% eye drops in the randomized, treated eye. Patients 12 through 16 were recruited directly into the 0.5% cysteamine regimen. Patients 17 through 21 received 0.1% cysteamine eye drops; patients 19 through 21 were subsequently switched to 0.5% cysteamine in the randomized, treated eye. Patients 22 through 25 were randomized directly to receive 0.5% cysteamine.

**RESULTS**

Data are presented on 25 patients who were enrolled and followed up for their response to cysteamine eye drop therapy between November 1988 and September 1989. No adverse side effects were noted in any patients. The results are summarized in the Table. The masked portion of the protocol had a very stringent end point. All three clinical observers and three photographic observers were required to agree that there was both a difference in the density of corneal crystals between the two eyes and a decrease in the “better” eye from the previous

### Patients With Cystinosis Receiving Cysteamine Eye Drops

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<tr>
<th>Patient/Seq</th>
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<th>Time to End Point</th>
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*The end point denotes the time at which the randomization code was broken. In those patients not reaching the end point, the duration of follow-up is given. The compliance score is described in the "Patients and Methods" section.

‡Cysteamine crystals did not appear until 14 months of age.

§The number to the right is the number of months receiving 0.5% cysteamine.

NK§ indicates not known; insufficient information to gauge compliance.
visit. This occurred 10 times and, on each occasion, breaking the code revealed that the improved eye was the cysteamine-treated eye. This rate of success in correctly choosing the treated eye would be achieved by chance alone once in 1024 times (P < .002, two-tailed Student's t test). Moreover, the overall response rate of 40% (10/25) reflects a substantial beneficial effect, especially in view of an extremely variable compliance rate and the inclusion of patients with intensely crystal-laden corneas.

Group 1

Of these 16 children 2 to 42 months of age, 8 responded to 0.1% or 0.5% cysteamine therapy with a marked diminution in crystal density in the treated eye. The median time to end point was 8 months (range, 4 to 37 months).

Group 2

Of these 9 patients, aged 4 to 23 years, patients 23 and 25 reached the end point at 9 and 6 months, respectively.

Of those patients not reaching the end point, the duration of follow-up ranged from 0 months (not yet seen following randomization) to 39 months. An analysis of the compliance score of all patients indicated better compliance, on average, for those reaching the end point compared with those not reaching the end point.

REPORT OF CASES

Case 1.—A 1-month-old boy was first examined at NIH. The diagnosis of cystinosis was made at 2 weeks of age because an older sibling had the disease. In an effort to prevent the deposition of corneal crystals, one eye was randomized at 2 months of age to 0.1% cysteamine and the fellow eye received placebo drops. Treatment was begun before any crystals were noted. Oral cysteamine treatment was also begun. Corneal crystals were first seen in both eyes (CS 0.125) at 14 months of age, appearing in diffuse patches centrally. Because of a history of poor compliance, the mother was urged to be more diligent in instilling the medication. Ten months later the density of corneal crystals was significantly increased in the right eye (CS 0.75) but the left eye was virtually devoid of crystals (CS 0). The code was broken, revealing that the left eye had received the cysteamine drops (Fig 1), and both eyes were subsequently treated with cysteamine.

Case 2.—A 20-month-old boy was first seen at NIH when oral cysteamine was initiated. His eye examination at that time showed abundant corneal crystals bilaterally. At age 31 months, crystals were equal bilaterally (CS 2.00, Fig 2, left) and one eye was randomized to receive 0.1% cysteamine eye drops and the fellow eye to receive placebo drops. Following 7 months of therapy there was a marked reduction in corneal crystals noted in the right eye (CS 0.50, Fig 2, center) while in the left eye the crystals had increased (CS 2.25). The code was broken to reveal that the right eye had been treated with cysteamine drops. One month of 1% of cysteamine was then administered to both eyes with all corneal crystals disappearing centrally in both eyes during the ensuing 17 months (Fig 2, right). At this time treatment with 0.5% cysteamine was begun and after 10 months of therapy both eyes had remained clear.

Case 23.—A girl was first seen at NIH at age 13 years 9 months. Cystinosis had been diagnosed at 10 months of age. Following the development of renal failure she received a renal transplant at age 9 years, with a complicated course characterized by several episodes of graft rejection, gout, and hypothyroidism. There was a history of moderate photophobia, redness, lid swelling, tearing, and foreign-body sensation suggestive of corneal erosions. Her visual acuity was 20/25 -1 OD, and 20/32+1 OS. The patient was not seen again until age 16 years, when her history revealed a gradual loss of visual acuity and a marked increase in photophobia interfering with her normal activities. Topical medications, such as artificial tears and lubricants, had offered limited amelioration of symptoms. On examination, visual acuity was 20/100 OU. Marked photophobia precluded photography. The cornea showed marked crystal accumulation far exceeding a CS of 3.00 and with particularly heavy central deposition bilaterally. The patient was fitted with a plano soft lens in each eye and one eye was randomized to receive 0.5% cysteamine eye drops and the fellow eye to receive placebo drops. Oral cysteamine therapy was also initiated at this time. Nine months later she was using the drops 12 times daily and returned feeling more comfortable; her father described her as a "different person." The visual acuity was 20/40 OD and 20/125 OS. The right eye continued to show more crystals but the anterior one third showed fewer crystals and a central corneal haze was absent from the right eye but still present in the left eye (Fig 3). The code was broken, indicating the cysteamine drops were being administrated to the right eye. This patient was very happy, much easier to examine, and delighted to be able to qualify for a driver's license.

Case 25.—A 19-year-old woman was evaluated at NIH. The diagnosis of cystinosis had been made at 6 months of age and she received a short course of oral cysteamine therapy at age 8 years, which was discontinued when renal failure was diagnosed and dialysis instituted. An unsuccessful renal transplantation was performed within 3 months, followed by a second renal transplant soon thereafter. At age 19 years she complained of frequent foreign-body sensation, moderate-to-severe photophobia. Her visual acuity was 20/20 OD. The corneas had abundant crystals far exceeding a CS of 3.00 and there was prominent staining of the corneal epithelium with fluorescein. Marked photophobia precluded an ophthalmoscopic examination. When seen 2 years later at age 21 years the patient complained of an increase in photophobia and corneal erosions with pain, always more severe in the right eye. Topical artificial tears did not offer sufficient relief. In January 1989, one eye was randomized to receive cysteamine and the fellow eye to receive placebo drops. Oral cysteamine therapy was also initiated. The patient returned 6 months later reporting less eye discomfort and reduced pain and foreign-body sensation, especially in the right eye, which she predicted to be the treated eye. The ocular examination showed the visual acuity to be 20/16 OD and 20/20 OS. The external examination was much easier to perform due to reduced photophobia and it was obvious with the use of a hand light that the right cornea was markedly clearer than the left (Fig 4). Slit-lamp examination confirmed an overall decrease in crystal density in the right eye, especially in the anterior one third of the stroma. The code was broken to reveal that the right eye had been randomized to the cysteamine drops.

COMMENT

Since 1978 oral cysteamine has been successfully employed as cystine-depleting therapy in children with nephropathic cystinosis, with encouraging results in improving growth and preserving renal function. Recent recognition of nonrenal involvement in older, posttransplant patients has prompted the use of oral cysteamine in this group of patients as well. However, despite 11 years of use and abundant evidence of its cystine-depleting efficacy, oral cysteamine has given no indication that it can delay or prevent the accumulation of cystine crystals in patients' corneas. In contrast, direct application of cysteamine eye drops (0.1%) gave very encouraging results in young children with cystinosis who participated in a randomized, placebo-controlled study. Because of this, 27 additional patients have entered the study, which was expanded to include older patients and a higher concentration of cysteamine eye drops (0.5%). Again, the results have been gratifying.

In the 10 patients achieving our stringent end point, the cysteamine-treated eye always had significantly fewer crystals as measured by the CS (two-tailed Student's t test, P < .002). Note that all patients in group 1 were receiving oral cysteamine, which had no obvious effect on crystal accumulation in the placebo-treated eye.

Although our patient population was heterogeneous in age, duration of therapy, and compliance, several conclusions can be derived from this study. First, the best therapy of all may be prophylaxis (eg, patient 1). Since corneal crystals first appear in cystinosis at approximately 1 year of...
Fig 1.—Patient 1. Slit-lamp photograph. Placebo-treated right eye showing crystals in central cornea (corneal score, 0.75) at 26 months of age (left) compared with cysteamine-treated left eye showing no crystals (right).

Fig 2.—Patient 5. Left, Slit-lamp photograph showing corneal crystals in the right eye at age 31 months, at time of randomization to 0.1% cysteamine. The right eye and left eye each have a corneal score of 2.00. Center, 7 months later, at the time the code was broken. The treated right eye showed a decrease in crystals (corneal score, 0.50). Right, After an additional 5 months of 0.5% cysteamine eye drop therapy the right cornea became clear.

Fig 3.—External photograph of patient 23. The cysteamine-treated right eye (left) is more clear centrally than the placebo-treated left eye (right) after 9 months of 0.5% cysteamine therapy.

Fig 4.—External photograph of patient 25 six months after randomization to 0.5% cysteamine. The code was broken showing the cysteamine-treated right eye (left) to be clearer than the placebo-treated left eye (right).
age, these may be prevented by early institution of cysteamine eye drops. This, of course, depends on an early diagnosis. Although there is clinical evidence for heterogeneity in the severity of the clinical manifestations of nephropathic cystinosis, the natural history of crystal accumulation in the cornea is well documented. It is gratifying, however, that even in young patients with uniform abundant corneal crystal deposition (CS 2.00), topical cysteamine can result in a clear cornea. Perhaps the single most convincing example of this is provided by patient 5, a 5½-year-old boy whose corneas are now both clear. The natural history of the untreated disease would show abundant crystal accumulation in the corneas by this age and, indeed, the patient had these findings himself at 2½ years of age.

It is also clear that the concentration of cysteamine makes a difference. Patients 6 and 7 were treated with 0.1% cysteamine for well over 1 year without a clear-cut response, yet each responded within 8 months of receiving 0.5% therapy. Patient 14 took only 4 months to clear her cysteamine-treated cornea of crystals using 0.5% eye drops; this represents a very short duration of therapy. Many older patients (group 2, Table) were treated with 0.1% for 2 to 3 years without response, yet two other older patients treated with 0.5% responded after 6 to 9 months.

Equally apparent is that compliance makes a difference. The issue of compliance is difficult to deal with since it relates totally on the parents' or the patient's history. In some cases, eg, patient 11, there were several indicators of poor compliance, such as broken appointments, poor follow-up, and a lack of response to oral cysteamine treatment, all suggesting a lack of adherence to medical recommendations. Some parents (eg, the mother of patient 1) admitted to a lapse in administering the drops for several months while pregnant. However, following further counseling, compliance improved. Two older patients who were brothers (patients 20 and 21) also admitted to infrequent use of the drops. Therefore, in those patients who did not respond to medication, the issue of poor compliance remains. Of course, some nonresponder may have been treated for too short a period, and there may be other, unrecognized reasons for treatment failure as well.

Finally, older, posttransplant patients can benefit from cysteamine eye drops as surely as younger patients. The older patients' corneas may not lose all of their crystals, but in at least two patients (patients 23 and 25) the corneal haziness, which reflected very marked crystal accumulation, was cleared by cysteamine eye drops. These two patients reported a marked relief of the discomfort in their eyes on using cysteamine eye drops. The severe discomfort may be due to crystals in the most anterior stroma and at the level of the basal epithelial cells mechanically stimulating the sensory nerve endings located at this level. Following cysteamine eye drop therapy, the anterior stroma appeared to be more clear of crystals than the deeper portions of cornea, suggesting that the sensory nerve endings might no longer be irritated, resulting in relief of pain. Since the reports of pain relief were subjective, we did not emphasize them. However, reduction in corneal pain becomes more and more important as cystinosis patients grow older and the natural history of the disease dictates greater photophobia and more frequent corneal erosions. In fact, one 12-year-old patient had such debilitating corneal erosions that he required a penetrating keratoplasty for relief.19

Cysteamine eye drop therapy offers several potential benefits. One is the subjective improvement noted by some patients. A second is the prevention of the diathesis toward corneal erosions that accompanies a cornea packed with crystals. But perhaps the most surprising is the partial clearing that can occur in the very heavy crystal accumulation in older patients, such as patients 23 and 25.

In view of the promising results presented above, we will continue to pursue the optimal therapeutic regimen for administration of cysteamine eye drops. For example, once corneal crystals are removed, it may require less frequent administration of eye drops to prevent a recurrence. In addition, a greater frequency or concentration of cysteamine eye drops may be required for certain patients to exhibit objective evidence of improvement. Animal studies have influenced us to restrict ourselves to 0.5% for the time being. However, we shall continue to attempt to develop better provision systems for cysteamine with the goal of reducing the frequency of administration.

We are indebted to the National Institutes of Health Clinical Center Pharmaceutical Development Service, Bethesda, Md, for preparing the cysteamine eye drops; Patrick Clatto for assisting in documenting the clinical findings photographically; Lessie McCain and Georgina Kaufman for assisting in the clinical trials; and Stephanie Mance for preparing the manuscript. We would especially like to thank Daniel Seigel, ScD, for his critical review of the manuscript.

References