EXPERT REVIEWS

Cysteamine ophthalmic solution 0.44% for the treatment of corneal cystine crystals in cystinosis

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Cystinosis is a rare autosomal recessive disease caused by abnormal accumulation of the amino acid cystine within lysosomes of various cells throughout the body, leading to multiple organ damage. Corneal cystine crystals are an ocular manifestation of cystinosis. Untreated, these corneal deposits worsen with time, often resulting in photophobia, ocular discomfort, blurred vision, and in severe cases, recurrent epithelial erosions, and band keratopathy. Oral cysteamine stabilizes renal and other systemic functions in these patients, but has no effect on cystine crystal accumulation in the cornea, due to the absence of a direct blood supply to the cornea. Cysteamine ophthalmic solution 0.44% reduces corneal cystine crystal deposition, helps clear existing crystals and is currently the only US FDA-approved therapy for the treatment of the corneal crystal involvement of cystinosis.

Keywords: cornea • crystals • cysteamine • cystinosis • ophthalmic

Cystinosis is a rare autosomal recessive disorder caused by mutations in the *CTNS* gene located on the short arm of chromosome 17 [1,2]. The *CTNS* gene encodes a lysosomal cystine transporter protein, cystinosin, which helps facilitate the efflux of cystine from lysosomes. The accumulation of the disulfide amino acid cystine within cellular lysosomes leads to the formation of cystine crystals in various tissues, including the kidney, thyroid, testis, pancreas, muscle, brain and eye [3]. This results in progressive dysfunction of multiple organs, leading to end-stage renal disease, diabetes, hypothyroidism, myopathy, and neurologic deterioration. Cystinosis is estimated to affect a total of approximately 600 children and adults in the USA [4].

Cystinosis appears in three phenotypic forms: infantile nephropathic, intermediate adolescent and benign adult, with the most severe type being the infantile form. While patients with cystinosis appear healthy at birth, progressive destruction of the proximal renal tubules soon results in renal Fanconi syndrome [5], which is characterized by increased urinary loss of water, essential electrolytes, minerals, glucose and proteins, as a result of failure of the renal tubules to reabsorb these substances. Rickets and growth retardation follow, and renal transplantation is generally required at an average age of 10 years [6].

Corneal cystine crystal accumulation is a common manifestation of all three types of cystinosis, which overlap to form a continuum of different degrees of severity. *In vivo* confocal microscopy and anterior segment optical coherence tomography studies reveal that the crystals are predominantly concentrated within the anterior corneal stroma [7]. The corneal cystine crystals present by 16 months of age and can result in severe photophobia, blepharospasm, recurrent current erosions and band keratopathy (Figure 1) [8–10]. Oral cysteamine bitartrate (Cystagon®, Mylan Pharmaceuticals), first used in the treatment of cystinosis in 1976 and approved by the US FDA in 1994, reduces intralysosomal cystine concentrations, stabilizes renal function and prevents the development of extrarenal complications in patients with cystinosis [11–13]. However, the oral formulation has no noticeable effect on corneal crystal accumulation [14], most likely because the cornea lacks a vascular supply, resulting in inadequate corneal cysteamine concentrations

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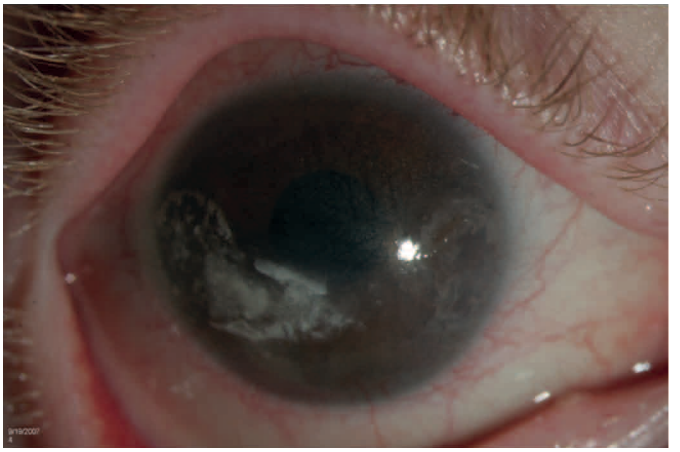


Figure 1. Band keratopathy and corneal neovascularization in patients with cystinosis.

[15]. Although corneal transplantation has been performed for disabling ocular symptoms [16], crystals may reaccumulate after keratoplasty [17]. The need for an additional route of delivery for the eyes motivated an aggressive research effort over several decades, culminating in the recent FDA approval of cysteamine ophthalmic solution for the treatment of corneal cystinosis.

Posterior segment findings can also occur with cystinosis. These findings include papilledema (Figure 2), retinal crystals, hypopigmentation of the retinal pigment epithelium (Figure 3) and retinal degenerative changes [18,19]. Early initiation of oral cysteamine therapy can reduce the frequency of posterior segment complications [19], but studies have not been done to assess the effects of cysteamine ophthalmic solution in preventing or treating posterior segment complications.

Cysteamine ophthalmic solution 0.44%

Cysteamine ophthalmic solution 0.44% (Cystaran™, Sigma-Tau Pharmaceuticals) was approved as an orphan drug by the FDA in October 2012 for the treatment of corneal cystine crystal accumulation in patients with cystinosis. It contains 6.5 mg/ml of cysteamine hydrochloride, which is equivalent to 4.4 mg/ml of cysteamine (0.44%) as the active ingredient. This formula is equivalent to the 0.55% cysteamine hydrochloride eye drops used in the clinical trials at the NIH. The difference in reported concentration represents different labeling practices, with the NIH version accounting for the moisture content of the hydrochloride, and the Cystaran version not. The eye drops are preserved with benzalkonium chloride, and require cold storage and attention to bottle expiration guidelines to ensure sterility and stability.

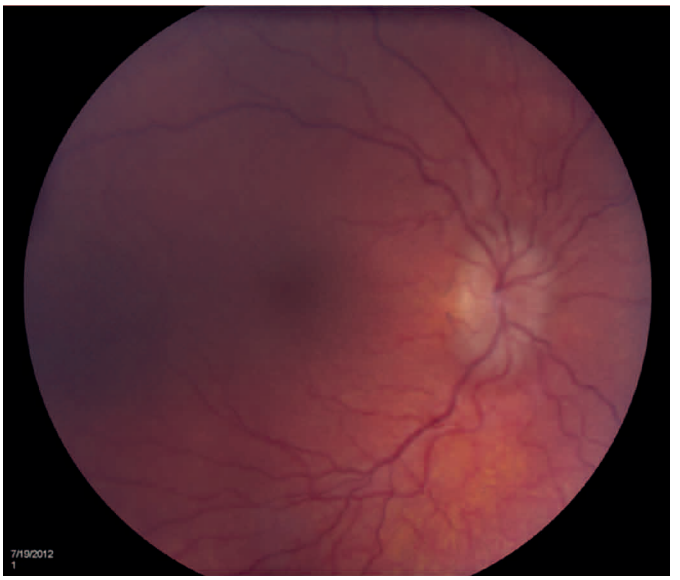
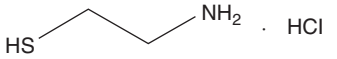


Figure 2. Papilledema in a patient with cystinosis.

Chemistry

Cysteamine is a sulfhydryl compound with two chemical names: 2-amino-ethanethiol hydrochloride and 2-mercaptoethylamine hydrochloride. Cysteamine hydrochloride is freely soluble in water and is soluble in 2-propanol and ethanol. The pH of a 1% solution of cysteamine hydrochloride in water is approximately 5.3. The compound's melting point is between 66 and 71°C. Cysteamine hydrochloride will deliquesce at standard room temperature and humidity. The Chemical Abstracts Services (CAS) registration number for cysteamine hydrochloride is CAS 156-57-0 and for cysteamine free base is CAS 60-23-1. The molecular formula is C_2H_7NS HCl with a molecular weight of 113.61 (77.15 for the free base). The molecular structure of cysteamine hydrochloride is:



The compound easily oxidizes to its disulfide form, cystamine, at room temperature. Clinical results show that cystamine is not as effective as cysteamine in the treatment of corneal crystals in cystinosis [20]. Cold storage of cysteamine solution is necessary to slow the degradation process.

Pharmacodynamics

Cysteamine lowers intracellular cystine concentrations by reacting with cystine to form cysteamine–cysteine mixed disulfide, which exits the lysosome via the lysine cationic transport system [21]. Cysteamine has been shown to deplete some cells of more than 90% of their excess cystine content [9]. However, oral cysteamine is not effective in the treatment of corneal crystals or the accompanying symptoms of photophobia, blepharospasm and eye pain, due to its lack of penetration to the avascular cornea [15]. By contrast, frequent administration of cysteamine solution directly onto the ocular surface is effective in dissolving corneal cystine crystals [9,15]. To date, no studies have been performed to specifically address the effects of cysteamine eye drops on the conjunctiva, iris, lens or retina.

Pharmacokinetics & metabolism

Systemic absorption of topical ocular cysteamine in preclinical studies has not been reported, and clinical data suggest that topical cysteamine does not penetrate to the aqueous humor of the eye [22]. The pharmacokinetics and metabolism of topical cysteamine are not known, as formal studies have not been conducted. However,

use of cysteamine eye drops is believed to have no impact on the systemic concentrations of orally administered cysteamine.

Kaiser-Kupfer *et al.* conducted a series of studies exploring topical cysteamine ophthalmic solution as a treatment for corneal crystals in patients with cystinosis [23]. One case study examined the effect of cysteamine in reducing the cystine concentration in cultured corneal stroma cells from a 13-year-old patient with debilitating cystinosis who had undergone a corneal transplant. The corneal epithelial cells were cultured and exposed to 1 mM cysteamine. Within 30 min, the cellular cystine content was reduced by 80%, suggesting that cystinotic corneal cells are susceptible to cysteamine's cystine-depleting effects. In a separate study, Kaiser-Kupfer *et al.* evaluated the potential ophthalmologic toxicity of cysteamine administered to the eyes of rabbits over a 21-day period. Daily clinical observations and a complete histopathological examination of the rabbits' ocular tissues following extended eye drop administration revealed no difference between cysteamine-treated and saline-treated eyes.

Clinical efficacy

Kaiser-Kupfer *et al.* performed the first placebo-controlled, double-masked, clinical trial of ophthalmic cysteamine. Two cystinosis patients, each under 2 years of age, received hourly topical cysteamine 0.1% in one eye and placebo in the fellow eye [23]. Over a 4- to 5-month period, the amount of corneal crystal accumulation was significantly reduced in the eyes that had received cysteamine drops.

Based on these results, a larger, randomized, placebo-controlled clinical trial was initiated to assess the tolerability and efficacy of 0.1% ophthalmic cysteamine. Of the 18 study patients with nephropathic cystinosis who received topical cysteamine, a significant fraction demonstrated reduction in the amount of corneal crystal deposition in the treated eye [24]. Due to the overwhelming success of the trial, patients were converted to a revised protocol in 1993, in which the therapy was extended to both eyes, and benzalkonium chloride was added to the formula as a preservative. While this trial was in progress, a preclinical study was conducted to evaluate the toxicity of higher doses (0.1–0.5%; 10–50 mM) of cysteamine ophthalmic solution administered to rabbits every hour, 8 h daily, over a 3-month period. Results from this toxicity study found that cysteamine doses at or below 0.5% did not produce clinical or histopathological signs of toxicity, such as an inflammatory response [25]. At room temperature, cysteamine in solution rapidly oxidizes to cystamine disulfide. There was interest in exploring whether cystamine solution would be as effective as cysteamine for treating corneal crystals, since cystamine would not require the cold storage that cysteamine does. In 1994, a double-masked study was conducted comparing the efficacy of 0.5% cystamine with 0.5% cysteamine; cystamine was determined to be less effective than cysteamine at reducing corneal crystal deposition [20].

In 1998, a new formulation consisting of 0.55% cysteamine hydrochloride solution combined with 1.85% monosodium phosphate, 0.10% disodium EDTA and 0.01% benzalkonium chloride, was developed by Sigma-Tau Pharmaceuticals, with the hope of creating a more convenient formula with longer shelf-life. This

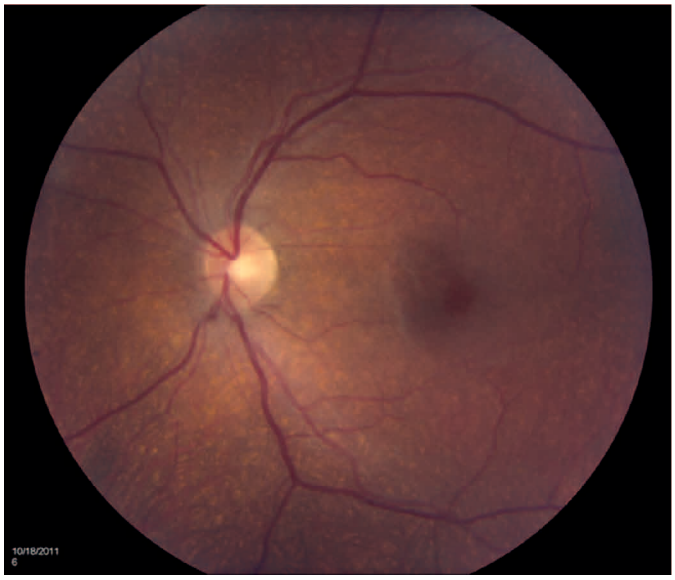


Figure 3. Retinal pigment epithelium mottling in patients with cystinosis.

combination retains cysteamine as a free thiol in stable form for 7 months at room temperature and up to 24 months with refrigeration [15]. A prospective, double-masked, randomized clinical trial was conducted to compare this new formulation with the standard formulation, which consisted of 0.55% cysteamine hydrochloride solution with 0.01% benzalkonium chloride. Treatment was masked to the study subjects, clinic staff and photograph graders.

The safety study was a single-center trial conducted at the National Eye Institute (MD, USA). Twenty subjects aged 1 year or older already receiving the standard preparation of cysteamine eye drops to both eyes, were randomized to receive the new formulation in one eye and continue the standard formulation in the fellow eye. The primary objective was to compare the frequency of predetermined serious adverse reactions between the two formulas over a 6-month period. No statistical difference in adverse events was found between the two preparations.

The efficacy study was conducted at three sites: the National Eye Institute, University of Michigan (MI, USA) and University of California (CA, USA). Sixteen subjects between the ages of 6 and 12 years, without prior topical treatment, were randomized to the new formulation in one eye and the standard formulation in the fellow eye. Ophthalmic examinations, including slit-lamp exam and standardized photography, were performed at 3 months' intervals. A phtotographic scale was developed to allow standard grading of the clinical photographs at a central reading center. The scores ranged from 0.00 (clarity at the corneal center) to 3.00 (greatest recognizable crystal density), divided into 0.25 increments [9,24]. The primary efficacy end point was a reduction of the corneal cystine crystal score (CCCS) by 1.00 or more units during a 1-year period when the baseline CCSS was greater than or equal to 1, or lack of increase of more than 1.00 unit in CCCS when the baseline CCCS score was less than 1. No patient experienced any of the primary ophthalmic safety events of severe redness, persistent pain or a decrease in visual acuity of greater

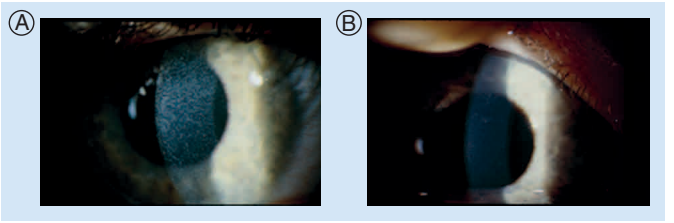


Figure 4. Cornea pre-treatment (A) and several years post-treatment (B) with cysteamine 0.44% ophthalmic solution in patients with cystinosis.

than one line on the ETDRS chart. Of those patients completing the 1-year follow-up, seven of 15 (47%) eyes receiving the standard formulation experienced a reduction in the CCCS of 1.00 after 1 year, while one of 15 (7%) eyes on the new formulation experienced such a decrease ($p = 0.04$). Based on these results, the new formulation was deemed less effective at reducing CCCS compared with the standard formulation.

The request for a New Drug Application to the FDA by Sigma-Tau Pharmaceuticals was submitted on behalf of the standard formulation, which consisted of 0.55% (50 mM) cysteamine hydrochloride solution with 0.01% benzalkonium chloride. Studies show that topical cysteamine, when administered six- to 12-times daily, reverses corneal crystal accumulation at any age (Figure 4), unless band keratopathy has already developed [9]. That formulation has now been used successfully by more than 250 patients, some for over 25 years.

Safety & tolerability

Topical cysteamine is well tolerated by patients. The most common adverse events reported are sensitivity to light, redness, eye pain and irritation, headache and visual field defects (FDA material-safety datasheet). These adverse effects are believed to result primarily from the primary condition, rather than the cysteamine drops.

Regulatory affairs

Sigma-Tau Pharmaceuticals received the FDA approval for cysteamine eye drops in October 2012, making it the first drug approved for the treatment of corneal changes in cystinosis. It has been designated as an orphan drug, allowing the manufacturer 7 years of exclusive marketing rights. The drug was made commercially available in May 2013. It is available in a 15-ml bottle and costs US$875 per bottle. Since the eye drop is stable for only 1 week, each bottle should be discarded weekly.

Expert commentary

Cysteamine ophthalmic solution is currently the only FDA-approved treatment for corneal cystine accumulation. No alternative therapies exist at this point. Through years of clinical studies, the drug has proven to be highly effective in reducing corneal cystine crystals and helping relieve debilitating ocular symptoms. While it is generally well tolerated, a fraction of patients experience an adverse reaction, presumably to benzalkonium chloride, the preservative used in the formulation. Benzalkonium chloride, a cationic detergent, has been known to be potentially damaging to the ocular surface [26]. Ocular symptoms such as burning, pain and hyperemia can be relieved by removing the preservative from the formulation, as was done for patients at the NIH who demonstrated a toxic reaction to benzalkonium chloride.

The current recommended dosing frequency for topical cysteamine is one drop every hour while awake. This dosing regimen is challenging for even the motivated patient, particularly in the early stages of treatment. It is reasonable to start patients at a lower frequency and gradually increase their dosing administrations. Patients who responded to cysteamine therapy often used the drops eight- to 12-times daily [9].

Five-year view

Due to ocular barriers and continuous tear turnover, frequent instillation of cysteamine eye drops is necessary to achieve clinical results. This demanding schedule is inconvenient for patients and families, and reduces compliance. If the drug could be modified to allow greater contact time with the cornea, less frequent dosing would be required. Efforts to develop a more viscous cysteamine formula are in progress, and results are promising [27,28]. Continued research efforts are needed to improve the treatment of ocular complications related to cystinosis.

Information resources

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Key issues

- Cysteamine ophthalmic solution 0.44% is currently the only US FDA-approved treatment for corneal crystal deposition in cystinosis.
- Cysteamine 0.44% is safe, but common adverse events include light sensitivity, eye redness and ocular irritation.
- The suggested dosing schedule is hourly while awake, though effective treatment is commonly achieved by dosing six- to 12-times daily.
- Development of a preparation that requires less frequent dosing may improve patient compliance and adherence.

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