

Long-Term Treatment of Cystinosis in Children with Twice-Daily Cysteamine

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Objective Cystinosis causes renal and other organ failure. Treatment with 6-hourly cysteamine bitartrate (Cystagon, Mylan, Morgantown, West Virginia) reduces intracellular cystine and the rate of organ deterioration. A recent study showed that an enteric-release cysteamine required less frequent daily dosing. This report describes the long-term use of enteric-coated (EC) cysteamine bitartrate (Cystagon) in children with cystinosis.

Study design After a pharmacokinetic and pharmacodynamic study of EC-cysteamine in children with cystinosis, 5 patients remained on twice-daily treatment. White blood cell cystine levels were measured 12 hours after ingestion every 4 to 8 weeks. These levels were then compared with the patient's previous 6-h post-dose levels taken while on regular cysteamine bitartrate before entering the study. Blood chemistry was also measured.

Results Five children with cystinosis (mean age, 9 years; range, 8 to 17 years) who previously took cysteamine bitartrate (mean dose, 47 mg/kg body wt), received EC-cysteamine for 10 to 27 months (mean dose, 25 mg/kg body wt) and had mean white blood cell cystine levels of 0.77 and 0.71 nmol half-cystine/mg protein, respectively. During the study period, patients maintained adequate growth and there was no significant deterioration in renal or thyroid function. Two children were required to restart acid suppression after 6 months on EC-cysteamine therapy.

Conclusions Long-term, twice-daily EC-cysteamine, given at approximately 60% of the previous daily dose of cysteamine bitartrate, was effective at maintaining white blood cell cystine levels within a satisfactory range. There was no significant deterioration in renal or thyroid function. (*J Pediatr* 2010;156:823-7).

Nephropathic cystinosis, characterized by the abnormal lysosomal accumulation of cystine, is associated with progressive renal failure and, without specific therapy, renal transplantation before 10 years of age.¹ To date, the only specific treatment for nephropathic cystinosis is 6-hourly cysteamine bitartrate (Cystagon, Mylan, Morgantown, West Virginia), which lowers intracellular cystine. Life-long cysteamine therapy reduces the rate of progression of renal failure in children.^{2,3} In many patients, the need for renal transplantation is delayed until later in the second decade of life. However, in some patients, cysteamine induces gastric acid hypersecretion and gastrointestinal (GI) symptoms.⁴⁻⁶ It is therefore not surprising that poor compliance with therapy may ensue, leading to poor growth and deterioration of renal function and ultimately necessitating earlier kidney transplantation.⁷

A recent study of patients with cystinosis showed that when cysteamine was directly delivered into the small intestine through a tube, the white blood cell (WBC) cystine levels, used clinically to monitor response to cysteamine, remained depressed for up to 15 hours.⁸ From this study, we hypothesized that an enteric-release formulation of cysteamine bitartrate would be as effective as cysteamine bitartrate and would require fewer daily doses.

In our first study using enteric coated (EC)-cysteamine, 7 children with cystinosis received drug twice daily for 1 month and 12 hours after the dose. WBC cystine levels were measured weekly. The mean WBC cystine level for all patients was 0.4 nmol half-cystine/mg protein (optimum level <1, acceptable level <2 nmol half-cystine/mg protein).¹⁻³ One patient maintained a WBC cystine level <1 for 24 hours after a single dose of EC-cysteamine, a response that resembled that reported in 1976 after a single dose infusion of intravenous cysteamine hydrochloride in a patient with cystinosis.⁹ Of the 7 patients initially studied, 5 patients opted to receive long-term treatment with EC-cysteamine, and their outcomes are reported.

Methods

The University of California at San Diego (UCSD) Human Research Protection Program approved this study, and informed consent was obtained for each participant. Study subjects were recruited nationwide and admitted to the UCSD General Clinical Research Center.

EC	Enteric-coated
GI	Gastrointestinal
GFR	Glomerular filtration rate
PPI	Proton-pump inhibitor
WBC	White blood cell

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Children with cystinosis who had participated in a previous study¹⁰ continued to take EC-cysteamine twice daily. Patients were over 6 years age, able to swallow capsules, and had mean leukocyte cystine levels of <2.0 nmol half-cystine/mg protein over the past year. One child had undergone renal transplantation (patient 2) and 3 had taken acid suppression therapy (patients 1, 4, and 5) that was discontinued before starting EC-cysteamine. Chemistry, thyroid and liver function tests, blood count, and urinalysis were obtained.

Enteric-Release Cysteamine Bitartrate

Commercially available cysteamine bitartrate capsules (50 and 150 mg) normally dissolve in the stomach. The capsules were altered so they would disperse at pH 5.5 to 6. This was achieved by coating the capsules with Eudragit L30D 55 (Rohm GmbH & Co KG, Darmstadt, Germany) at The Coating Place Inc, Verona, Wisconsin, using the Model 600 Wurster unit. Before use, EC-cysteamine capsules were tested for stability in both acid and alkali solutions. The capsules remained intact after submersion in 0.1 N HCL at 37°C for 2 hours but dissolved within 30 minutes when placed into NaHCO₃ solution at pH 6.8 at 37°C.

White Blood Cell Cystine

WBC cystine levels were measured 12 hours after EC-cysteamine every month and then every 2 months after a steady dose had been established. Leukocytes were prepared locally and shipped to the UCSD Cystine Determination Laboratory. WBC cystine levels, reported as nmol half-cystine/mg protein, were measured using tandem mass spectroscopy (API 4000 LC/MS/MS; Applied Biosystems, Foster City, California) with previously described methods.¹¹⁻¹³

All available 6-hour post-dose WBC cystine levels from the same 5 patients, measured while taking 6-hourly cysteamine bitartrate for 4 years before entering this study, were obtained from the Cystine Determination Laboratory, UCSD. A comparison between the 6- and 12-hour post-dose WBC cystine levels obtained during cysteamine bitartrate and EC-cysteamine, respectively, was made in these patients.

Statistical Analysis

To compare the mean 6- and 12-hour post-dose WBC cystine level repeated measurements in the 5 study patients, mixed model¹⁴ restricted maximum likelihood (REML) repeated-measures analysis of variance (SAS Software 9.2, Cary, North Carolina)¹⁵ with subjects as a random effect was performed on the absolute leukocyte cystine levels. This method takes into account all observed data, even though some subjects may have missed some visits. Mixed-effects models are used to estimate the parameters (fixed effects) of the PK, PK-PD, or disease models, to quantify the between-subject variability, and to identify factors (covariates) that may influence these parameters.¹⁶ Main effects for sex and age at the beginning of the study were tested.

Results

Five patients with cystinosis, 3 female and 2 male (mean age, 11.8 years; range, 8 to 17 years), received EC-cysteamine for

10 to 27 months. The mean total daily dose of EC-cysteamine was 1140 mg/d (range, 700 to 1600 mg/d), which was 59% of the mean total daily dose of cysteamine bitartrate (1940 mg/d; range, 1200 to 2700 mg/d) taken by the same 5 patients before entering the study. All patients had normal liver and thyroid function tests; complete blood counts and urinalysis remained unchanged during the study. The mean increase in height and weight over the same time interval was 2.0 cm and 2.4 kg (Table I). During treatment with EC-cysteamine, subjects continued to grow along their prestudy height-for-age percentile curves. Patient 2 had undergone renal transplantation 2 years previously and was taking prednisone 5 mg/d, mycophenolate mofetil 1 g bid, and FK506 3 mg bid. Patient 5 received risperidone and sertraline.

The mean baseline serum creatinine before and after 10 to 27 months of EC-cysteamine therapy was 1.0 mg/dL (range, 0.6 to 1.5) and 1.1 mg/dL (range, 0.6 to 1.5), respectively, and the mean estimated GFR, calculated using the Schwartz formula,¹⁷ was 91.5 and 89 mL/min/1.73 m², respectively. Patient 2 had undergone kidney transplantation; therefore his serum creatinine was not used to calculate the mean values as cystine does not accumulate intracellularly in the transplanted kidney (Table II).

Post-Dose White Cell Cystine Levels

The mean 12-hour post-dose WBC cystine for patients taking twice-daily EC-cysteamine (for 10 to 27 months) was 0.71 (range, 0.1 to 4.57, <1 in 78% of measurements), whereas the mean 6-hour post-dose WBC cystine in the same patients while taking cysteamine bitartrate 4 times daily for 4 years immediately before entering the study was 0.77 (range, 0.1 to 3.62, <1 in 79% of measurements). There was no significant difference between 6-h and 12-hour post-dose WBC cystine levels with patients taking cysteamine bitartrate and EC-cysteamine, respectively ($P = .66$) (Figures 1 and 2).

Table I shows the mean and ranges of WBC cystine while taking twice-daily EC-cysteamine and 4-times-daily cysteamine bitartrate for 4 years before commencing the study.

Symptoms

Before starting the study, 3 of the patients took regular proton-pump inhibitor (PPI) therapy to control gastrointestinal symptoms. PPIs were stopped for the initial study,¹⁰ but after about 6 months of EC-cysteamine therapy, 2 patients were started back on PPI therapy for intermittent emesis. Although patient 2 had renal transplant rejection and patient 3 had Henoch-Schönlein purpura (see below), these events were not attributed to the EC-cysteamine. Both patients had WBC cystine levels <1 nmol half-cystine/mg protein before and during the events.

Patient 1. Before entering the study, this patient had severe nausea and vomiting that was controlled with PPI therapy. During the study, she had mild intermittent vomiting and abdominal pain. Gorging on high fat foods often exacerbated the patient's symptoms. She resumed PPI treatment 11 months into the study, and, along with some dietary advice, had improvement in her gastrointestinal symptoms.

Table I. Patient data

	Sex	Age at start (y)	Duration of therapy (mo)	Weight change (kg)*	Height change (cm)*	Total daily cysteamine dose (mg)	†Cysteamine dose mg/kg body wt (g/m ²)	‡Mean, standard deviation and range of WBC cystine on cysteamine	Total daily EC-cysteamine dose (mg)	§EC-cysteamine dose mg/kg body wt (g/m ²)	Mean, Standard deviation, and Range of WBC cystine on cysteamine
Patient 1	F	10	13	0.9	2	1200	50 (1.34)	1.24 (8) SD = 1.01 0.41-3.62	700	25 (0.67)	1.05 (12) SD = 0.54 0.27-1.97
Patient 2	M	13	12	3.1	5.4	2000	40 (1.36)	0.79 (8) SD = 0.48 0.23-1.53	1300	26 (0.89)	0.36 (11) SD = 0.19 0.1-0.6
Patient 3	F	15	27	2.5	0.4	2000	38 (1.31)	0.56 (5) SD = 0.24 0.21-0.89	1200	23 (0.79)	0.63 (20) SD = 0.49 0.1-2.35
Patient 4	F	8	11	2.3	2.4	1800	72 (1.93)	0.5 (13) SD = 0.28 0.16-1.0	900	36 (0.96)	0.67 (10) SD = 0.61 0.12-2.24
Patient 5	M	17	10	3.2	0	2700	33 (1.32)	0.85 (6) SD = 0.60 0.15-1.79	1600	17 (0.69)	0.89 (10) SD = 1.36 0.1-4.57
Mean		11.8	14.5	2.4	2.0	1940	47 (1.45)	0.77 (39) 0.1-3.62	1140	25 (0.8)	0.71 (63) 0.1-4.57

Patient 2 underwent renal transplantation 2 years before entering the study.

*Weight and height increase over the duration of treatment with EC-cysteamine.

†Total daily cysteamine bitartrate dose recorded as mg/kg body wt and as grams per body surface area. Cysteamine bitartrate was taken every 6 hours.

‡Mean 6-h post-dose WBC cystine level measured while taking cysteamine bitartrate over 4 years before entering the study. Parenthesis represents number of measurements taken during this time. SD indicates standard deviation. WBC cystine measured as nmol half-cystine/mg protein.

§Total daily EC-cysteamine dose recorded as mg/kg body wt and as grams per body surface area. EC-cysteamine was taken every 12 hours.

||Mean 12-hour post-dose WBC cystine level measured while taking EC-cysteamine over 10 to 27 months. Parenthesis represents number of measurements taken during this time.

Patient 2. This patient was 4 years post-renal transplantation. He did not report any GI symptoms during the study. However, 2 months after entering the study, he developed humoral rejection with positive donor-specific antibodies to the kidney. Although he responded to treatment with corticosteroids, intravenous immunoglobulin, and plasmapheresis (6 sessions over 2 weeks), his serum creatinine remained elevated above baseline. Before, during, and after the period of plasmapheresis therapy, the patient's WBC cystine levels remained <1 nmol half-cystine/mg protein, suggesting that cysteamine availability and absorption was not affected significantly by the plasmapheresis.

Patient 3. Nocturnal enuresis improved while taking EC-cysteamine therapy. She complained of occasional lethargy, body odor, and mild abdominal pain, but these symptoms were experienced with the same frequency and intensity as when she took cysteamine bitartrate. After 25 months, she had development of Henoch-Schonlein purpura with associated IgA-associated mesangial proliferative glomerulitis. She responded to steroid therapy and her renal function normalized. The patient remained on the study drug throughout this episode and at the time of writing remains on this treatment.

Patient 4. This patient required PPI therapy for nausea and vomiting before entering the study. She remained symptom-

Table II. Estimated glomerular filtration rate using Schwartz formula for children and adolescent girls and adolescent boys

	Age at start (y)	Tanner score	Duration of therapy (mo)	Mean 12-hour post WBC cystine*	Height (cm)		Serum creatinine pre/post* (mg/dL)		Estimated GFR (mL/min/1.73 m ²)	
					Pre-EC cysteamine	Post-EC cysteamine	Pre-EC cysteamine	Post-EC cysteamine	Pre-EC cysteamine	Post-EC cysteamine
Patient 1	10	1	13	1.0 (11)	124.5	126.5	0.83	1.0	82	70
Patient 2†	13	3-4	12	0.39 (10)	151.9	157.3	1.0	1.5	106	73
Patient 3	15	4	27	0.63 (20)	158.0	158.4	1.1	1.1	79	79
Patient 4	8	1	11	0.69 (9)	132.8	135.2	0.6	0.6	122	124
Patient 5	17	4	10	0.89 (10)	178.0	178.0	1.5	1.5	83	83
Mean	11.8		14.6	0.49	149	151.1	1.0	1.1	91.5	89

Schwartz formula: $GFR (mL/min/1.73 m^2) = K \times \text{height (cm)} / \text{serum creatinine (mg/dL)}$. K = proportionality constant, which is 0.55 for children and adolescent girls and 0.7 for adolescent boys.

*Mean WBC cystine levels in nmol half-cystine/mg protein measured every 1 to 2 months for the duration of treatment with EC-cysteamine. The number of samples taken for the duration of therapy is shown in parentheses.

†Patient 2, the only kidney-transplanted patient, developed humoral rejection 2 months after starting long-term EC-cysteamine therapy. Cystine does not accumulate intracellularly in the transplanted kidney; therefore this patient's data were not included in the calculations of the pre/post EC-cysteamine mean serum creatinine and GFR levels.

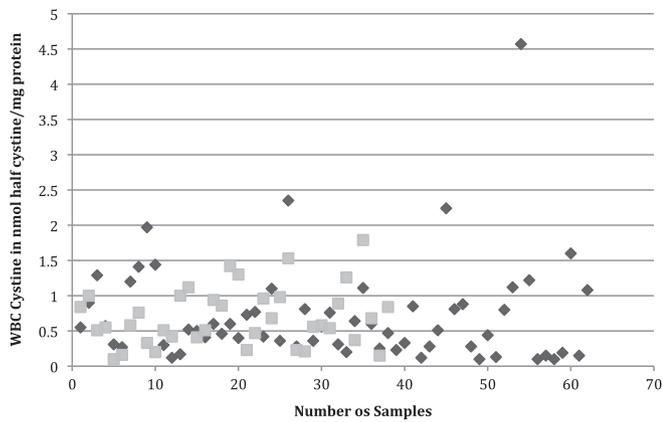


Figure 1. Six-hour post-dose WBC cystine levels in 5 patients receiving cysteamine bitartrate ($n = 39$) for 4 years are shown with filled squares. Twelve-hour post-dose EC-cysteamine ($n = 63$) for 10 to 27 months are shown with filled diamonds.

free for the first 6 months of the study without PPI therapy. This patient had WBC cystine levels ranging from 0.2 to 1.2 nmol half-cystine/mg protein, and, after an increase EC-cysteamine dose from 450 mg bid to 550 mg bid she had episodes of vomiting. Her PPI therapy was restarted and her symptoms partially improved. However, after a further 4 months of intermittent episodes of emesis, EC-cysteamine was discontinued. Accurately titrating the dose of EC-cysteamine to control WBC cystine levels and symptoms proved difficult. Cysteamine bitartrate therapy was restarted at her previous prestudy dose, and her subsequent WBC cystine levels were satisfactory.

Patient 5. He received regular PPI therapy to control abdominal pain, nausea, and vomiting before starting the study. He remained off PPI during the study and did not complain of any symptoms. Nocturnal enuresis improved while taking EC-cysteamine therapy.

Discussion

Two major milestones in the treatment of cystinosis are the development of renal transplantation and the approval of cysteamine bitartrate therapy. Regular 6-hourly daily treatment with cysteamine bitartrate diminishes the rate of renal dysfunction as well improving growth. However, taking lifelong cysteamine bitartrate every 6 hours is a difficult undertaking and may result in nonadherence.¹⁸ Over the past 5 years, we have undertaken studies in an attempt to show that cysteamine can still be effective when taken less often than every 6 hours during the day. Naso-enteric tube delivery of cysteamine solution directly into the small intestine resulted in a higher C_{max} for cysteamine and prolonged WBC cystine depletion than when drug was delivered by the same method directly into the stomach or colon.⁸ These “tube” study data suggested that an enteric-release formula-

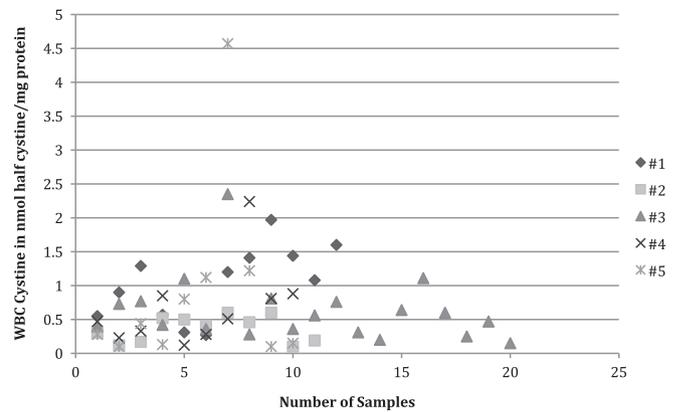


Figure 2. Twelve-hour trough WBC cystine levels in the 5 study patients with cystinosis treated with EC-cysteamine for up to 27 months.

tion of cysteamine might also prolong WBC cystine depletion and therefore require less frequent daily ingestion than cysteamine bitartrate capsules, which are known to disperse in the stomach. In a recent publication, we presented the results of an initial “proof of concept” study using EC-cysteamine in 7 children with cystinosis for 1 month.¹⁰ Five of these patients also received long-term twice-daily EC-cysteamine therapy.

In clinical practice, the efficacy of cysteamine therapy is monitored by measuring 6-hour post-dose WBC cystine levels. The target level of leukocyte cystine while on cysteamine treatment is <1 nmol half-cystine/mg protein,¹ whereas <2 is considered an adequate level³ to diminish the rate of decline of glomerular function. In our study using q12-hour EC-cysteamine 12-hour post-dose WBC cystine levels were measured and were <2 nmol half-cystine/mg protein in 95% and <1 in 78% of measurements (Figure 1). These levels compared favorably with 6-hour post-dose WBC cystine levels, measured for 4 years before entering this study in the same 5 children, where WBC cystine levels were <2 nmol half-cystine/mg protein in all patients and <1 in 79% of measurements. It should be noted, however, that the mean duration from time of cystinosis diagnosis to entering the study for subjects was 12 years, and these patients (as part of the study entry criteria) were on a well-established dosing regimen with cysteamine bitartrate. The mean effective dose of EC-cysteamine was 59% that of the mean dose of cysteamine bitartrate (1140 mg/d and 1940 mg/d, respectively) taken by the same children before entering the study.

Except for the transplanted patient (patient 2), there was no significant deterioration of renal function in the study patients as estimated by the Schwartz score (Table II). There was, however, morbidity during the study. One patient (patient 3) had development of Henoch-Schonlein purpura and had a transient increase in proteinuria. Her serum creatinine increased from 1.1 to 1.4 mg/dL before returning to baseline after treatment with systemic corticosteroids. Patient 2, who had previously undergone kidney transplantation, had humoral rejection but responded well to treatment. Neither of the events involving patients 2 and 3 were attributed to

cysteamine or the coating agent. A review of the literature did not reveal any associations between these 2 agents and any reported immune mediated events.

All patients reported improved sleeping patterns and 2 patients (patients 3 and 5) also had sustained improvement of their nocturnal enuresis. The exact reason for this remains unclear, but the duration of improvement (10 and 27 months) would make placebo effect less likely. Patients gained weight and height at a satisfactory rate during the course of the therapy (Table I).

Before entering the study, 3 patients (patients 1, 4, and 5) had required daily PPI therapy for GI symptoms including nausea, pain, and vomiting. Patient 5 remained GI symptom-free for the duration of EC-cysteamine therapy. The other 2 subjects (patients 1 and 4) remained symptom-free for over 6 months after starting EC-cysteamine but were eventually restarted on PPI therapy. This initial reduction in GI symptoms may have represented a placebo effect. The reason why patient 1 started to vomit again after 6 months of EC-cysteamine therapy was unclear and not related to a change in drug dosing. Recurrence of vomiting and pain in patient 4 correlated with the increase of EC-cysteamine dosing from 450 mg to 550 mg bid (>20% increase). In retrospect, this was a relatively large dose increment compared with the typical dose change of about 10% that would normally be made in patients taking regular cysteamine bitartrate. This may also be compounded by the fact that EC-cysteamine on a milligram-for-milligram dose basis is more effective than cysteamine bitartrate and that a 100 mg dose increase on EC-cysteamine would equate approximately to a 200 mg increase of regular cysteamine bitartrate per dose. It was difficult to titrate the dose increase because of the strength of the available EC-cysteamine capsule (50 and 150 mg), and future enteric-release formulations would most likely require lower dose capsules, for example, 25 and 100 mg capsules. It is also possible that there was some batch-to-batch variation in the enteric-coating process of the cysteamine and that the 2 patients (patients 1 and 4) who had symptoms at a similar time may have received some capsules that dispersed prematurely in the stomach. If this is so, then future enteric-release formulations, made for commercial rather than study use, would ideally have more "controlled" enteric release and therefore possibly fewer associated GI symptoms. It is unclear from our small study using a "proof of concept" formulation of cysteamine whether patients will need to take concurrent PPI therapy. It would appear, however, that patients who previously needed PPIs while on regular cysteamine bitartrate are likely to continue to do so when taking enteric-release cysteamine, whereas patients who did not take acid suppression before (patients 2 and 3) are unlikely to do so.

Effective cysteamine treatment administered twice rather than 4 times a day will improve quality of life for patients with cystinosis and will encourage long-term compliance with therapy. Twice-daily EC-cysteamine shows promise in maintaining satisfactory WBC cystine levels <2 and possibly reducing the rate of deterioration of renal function. EC-cys-

teamine as a formulation remains a "proof of concept" therapy designed specifically for this study and not intended for widespread or commercial use. We hope, however, that EC-cysteamine will pave the way for better-designed enteric-release preparations of cysteamine. ■

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