Twice-Daily Cysteamine Bitartrate Therapy for Children with Cystinosis

Ranjan Dohil, MD, Meredith Fidler, PhD, Jon A. Gangoiti, MS, Frederick Kaskel, MD, PhD, Jerry A. Schneider, MD, and Bruce A. Barshop, MD, PhD

Objective Cystinosis causes renal and other organ failure. Regular 6-hourly cysteamine bitartrate (Cystagon; Mylan, Morgantown, West Virginia) reduces intracellular cystine and the rate of organ deterioration. A formulation of cysteamine requiring less frequent dosing may improve compliance and possibly patient outcome.

Methods Enteric-release cysteamine was prepared. For a period of 1 month, patients received their regular cysteamine dose every 6 hours (stage I). The patients then underwent pharmacokinetic and pharmacodynamic studies following washout periods using single-doses of cysteamine and enteric-release cysteamine (stage II). Finally, the patients commenced regular enteric-release cysteamine therapy (stage III). Weekly trough white blood cell (WBC) cystine levels were recorded.

Results Seven children with cystinosis (mean age, 11.8 years; range, 8-17 years) who received cysteamine and enteric-release cysteamine (mean dose, 45 and 28.8 mg/kg body weight/day, respectively) had mean WBC cystine levels of 0.7 ± 0.3 and 0.41 ± 0.22 nmol half-cystine/mg protein in study stages I and III, respectively. Study stage II showed that the mean time (T_{max}) to reach the maximum plasma cysteamine level (C_{max}) was longer for enteric-release cysteamine than for cysteamine (176 minutes vs 60 minutes; $P = .001$), but the mean C_{max} at the same dose was similar. Mean serum gastrin levels were similar after ingestion of cysteamine and enteric-release cysteamine.

Conclusions Twelve-hour enteric-release cysteamine, given at approximately 60% of the previous daily dose of cysteamine, was effective in maintaining trough WBC cystine levels within a satisfactory range. *(J Pediatr 2010;156:71-5)*.

The infantile and adolescent forms of cystinosis are associated with progressive renal failure, and many patients require renal transplantation.[1] To date, the only approved specific treatment for nephropathic cystinosis is the sulfhydryl agent cysteamine bitartrate (Cystagon; Mylan, Morgantown, West Virginia). This drug has been shown to lower intracellular cystine levels by reacting with intralysosomal cystine to form the mixed disulfide of cysteamine and cysteine, which then leaves the lysosome via the lysine transport system, thereby reducing the rate of progression of renal failure in children.[2,3] To maintain low intracellular cystine levels, patients are typically required to take cysteamine every 6 hours, which invariably means having to awaken from sleep. In addition, cysteamine may induce increased gastrin and gastric acid secretion, causing gastrointestinal (GI) symptoms in some patients.[4-6] These factors will contribute to poor compliance with therapy, which may result in poor growth and deteriorating renal function, ultimately necessitating earlier kidney transplantation.[7]

In patients with cystinosis, studies in which cysteamine was infused directly into various parts of the GI tract found higher maximum plasma cysteamine concentrations (C_{max}) when the drug was delivered into the small intestine compared with the stomach and colon.[8,9] As a result, white blood cell (WBC) cystine levels, which are used to monitor clinical response to cysteamine therapy, remained depressed longer in subjects with cystinosis. Based on the findings of that study, we hypothesized that targeted enteric delivery of oral cysteamine bitartrate might prolong the drug's effectiveness and hopefully allow less frequent daily administration.

The purpose of our study was to determine whether a targeted enteric-release preparation of cysteamine given twice daily can effectively maintain low WBC cystine levels (optimal level < 1 nmol half-cystine/mg protein) in patients with cystinosis.

Methods

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

Children over age 6 years with cystinosis and the ability to swallow whole cysteamine capsules were recruited to the study. Each patient's mean leukocyte

C_{max}	Maximum plasma cysteamine level
GI	Gastrointestinal
PPI	Proton pump inhibitor
T_{max}	Mean time to reach the maximum plasma cysteamine level
WBC	White blood cell

From the Department of Pediatrics, University of California San Diego, La Jolla, CA (R.D., M.F., J.G., J.S., B.B.) and Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY (F.K.)

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cystine level was < 2.0 nmol half-cystine/mg protein over the previous year. Regular cysteamine therapy was discontinued 2 days before entering the study, and acid-suppressant therapy was discontinued 7 days before entering the study (stage II; see below). Baseline chemistry tests, blood counts, and urinalysis were performed.

Enteric-Release Cysteamine Bitartrate

Cysteamine capsules dissolve rapidly in the stomach with or without concomitant acid-suppression therapy with a proton pump inhibitor (PPI).[10] Commercially available cysteamine (supplied by Cystagon) was altered so that the capsules would disperse rapidly at a pH of 5.5-6. This was achieved by coating the capsules with Eudragit L30D 55 (Rohm, Darmstadt, Germany) at an FDA-approved facility (The Coating Place, Verona, Wisconsin) using a Wurster Model 600 unit. Before use, the enteric-coated 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 $NaHCO_3$ solution (pH 6.8) at 37 °C.

Study Outline

The study was conducted in 3 stages:

Stage I. For 1 month, subjects received their regular daily "steady-state" dose of cysteamine every 6 hours.

Stage II. Subjects were admitted to UCSD's GCRC. After an overnight fast (except for water), serum gastrin, cysteamine, and WBC cystine were measured at baseline and at varying intervals after a single oral dose of either cysteamine or enteric-release cysteamine. On study day 1, patients received a single dose of cysteamine (eg, 500 mg, if the previous dose was 500 mg every 6 hours). On study day 3, after a 48-hour washout period, they received the same dose of enteric-release cysteamine (ie, 500 mg). On study day 5, after another 48-hour ashout period, patients received a double dose of enteric-release cysteamine (ie, 1000 mg in this example).

Stage III. For 1 month, subjects received a daily double dose of enteric-release cysteamine every 12 hours (ie, 1000 mg every 12 hours in this example). The maximum initial dose of enteric-release cysteamine in stage III was 1000 mg twice daily. Symptoms, including nausea, vomiting, pain, and lethargy, were recorded throughout this study period. In patients complaining of daily symptoms, the dose of enteric-release cysteamine was reduced by approximately 20% every 3-4 days until the symptoms improved.

Leukocyte Cystine, Plasma Cysteamine, and Gastrin Measurements

During stages I and III, WBC cystine was measured 6 hours after ingestion of cysteamine and 12 hours after ingestion of enteric-release cysteamine. In stage II, WBC cystine levels were measured at baseline and at 3, 6, 9, 12, 15, and 24 hours. Gastrin levels were measured at baseline and at 30, 60, 90, and 120 minutes, 3 hours, and 4 hours, and cysteamine levels were measured at baseline and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 minutes and 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours. Gastrin (pg/mL) was measured using a Diagnostic Products (Los Angeles, California) gastrin^{125} radioimmunoassay kit. Leukocytes were prepared locally and shipped to the UCSD Cystine Determination Laboratory in San Diego, California. Both leukocyte cystine levels, measured in nmol half-cystine/mg protein,[11] and plasma cysteamine levels were measured by tandem mass spectroscopy (API 4000 LC/MS/MS; Applied Biosystems, Foster City, California) as described previously.[10,12]

The mean differences between treatment groups were compared using the standard 2- sample paired *t*-test. A P value < .05 was considered statistically significant. All tests were 2-tailed. A mixed-effects linear model was used to estimate and compare steady-state mean trough WBC cystine levels between patients treated with cysteamine (stage I) and those treated with enteric-release cysteamine (stage III). The mixed-effects linear model was chosen because individuals are measured repeatedly through time (ie, 4 measurements per patient per stage). Longitudinal data such as in this study require special statistical methods, because observations on the same individual tend to be intercorrelated. This correlation must be taken into account to draw valid scientific inferences. Thus, the linear mixed-effects model provides an effective approach to longitudinal data analysis. In the model, treatment was included as a fixed effect, and patient was included as a random effect. The differences in least squares mean WBC cystine levels (ie, $\Delta = \mu C - \mu E$, where μC and μE reflect average intracellular cystine concentrations in experimental stage I and III, respectively) and associated 95% confidence intervals (CIs) were estimated using the model fit. Significant depletion in trough WBC cystine levels was inferred if the lower bound of the 95% CI for Δ was > 0.

Results

Seven patients were studied (**Table I**). Patient 2 had undergone renal transplantation 2 years earlier and was taking prednisone 5 mg/day, mycophenolate mofetil 1 g twice daily, and FK506 3 mg twice daily. Patient 7 was receiving risperdone and sertraline. All patients had normal liver function test values, and their serum creatinine levels ranged from 0.7 to 1.5 mg/dL (mean, 1.0 mg/dL). Patient 7 was receiving medication for attention deficit disorder. There were no reported adverse events or new symptoms (eg, nausea, vomiting, pain). Patients who previously took a PPI did not need to restart acid-suppression therapy.

Six-hour trough WBC cystine levels are given in **Table II**. WBC cystine levels ranged from 0.18 to 1.93 nmol half-cystine/mg protein (mean, 0.7 ± 0.3 nmol half-cystine/mg protein). Before entering the study, patients 1, 6, and 7 were also receiving long-term PPI therapy for symptoms including vomiting, nausea, abdominal pain, and heartburn.

Stage II

The mean T_{max} values, or time in minutes to reach the maximum plasma cysteamine concentration (C_{max}), are shown in

Table I. Patient data

Patient	Sex	Age, years	Weight, kg	Height, cm	Serum creatinine, mg/dL	Total daily cysteamine dose, mg, stage I*	Cysteamine dose, mg/kg, stage I*	WBC cystine, stage I†	Total daily enteric-release cysteamine dose, mg, stage III‡	Enteric-release cysteamine dose, mg/kg, stage III‡	WBC cystine, stage III†
1	F	10	24	120	0.8	1200	50 (1.34)	0.91	600	25 (0.67)	0.83
2§	M	13	50	153	0.8	2000	40 (1.36)	0.41	1300	26 (0.89)	0.18¶
3	F	15	53	158	1.2	2000	38 (1.31)	0.66	1200	23 (0.79)	0.58
4	M	9	28	129	1.2	800	29 (0.8)	0.33	800	29 (0.8)	0.42
5	M	11	49	151	0.7	2600	53 (1.8)	0.72	2000	41 (1.39)	0.30
6	F	8	25	126	0.8	1800	72 (1.93)	1.14	900	36 (0.96)	0.29¶
7	M	17	83	178	1.5	2700	33 (1.32)	0.65	1400	17 (0.69)	0.27
Mean		11.8			1.0	1871	45 (1.41)	0.70	1142	28 (0.88)	0.41

*During stage I, patients took their regular 6-hourly dose of cysteamine for 4 weeks.
†WBC cystine reported as nmol half-cystine/mg protein.
‡During stage III, patients took 12-hourly doses of enteric-coated cysteamine for 4 weeks.
§This patient underwent renal transplantation 2 years before entering the study.
¶Based on 2 measurements only.

Figure 1 (available at www.jpeds.com). The mean T_{max} was longer for enteric-release cysteamine than for regular cysteamine, suggesting likely enteric disintegration of enteric-release cysteamine. There was no difference in the mean C_{max} at the same dose of cysteamine and enteric-release cysteamine, but C_{max} was higher with the double-dose enteric-release cysteamine. Individual patient profiles for plasma cysteamine (pharmacokinetic) and WBC cystine (pharmacodynamic) levels are shown in Figure 2 (available at www.jpeds.com). Four of the 7 patients (1, 2, 3, and 4) had prolonged depletion of WBC cystine on day 5 (double-dose enteric-release cysteamine) compared with days 1 and 3. In fact, subject 2 had depletion of WBC cystine levels for more than 24 hours after receiving a double dose of enteric-release cysteamine. The serum gastrin levels for patients 2 and 5 were lost. The gastrin levels for patients 3, 4, 6, and 7 were normal (< 100 pg/mL) at all measurements on days 1, 3, and 5. Patient 1 had an elevated gastrin level > 100 pg/mL after both cysteamine and enteric-release cysteamine (Figure 3 and Table III; both available at www.jpeds.com).

Stage III

The initial dose of enteric-release cysteamine was 400-1000 mg every 12 hours (Table IV). However, because 4 of the initial 5 patients (1, 3, 6, and 7) exhibited symptoms, including abdominal pain, vomiting, and lethargy, their doses were reduced by 40%-50%, after which the symptoms improved (Table V; available at www.jpeds.com). After symptoms improved, dose escalation was not attempted. Patients 2 and 5 were studied last and were given enteric-release cysteamine at 60% of their previous total daily cysteamine dose. The mean final total daily dose of enteric-release cysteamine required to maintain adequate WBC cystine levels was 1142 mg/day (ie, 28 ± 8 mg/kg body weight per day, or 0.88 g/m^2 body surface area), or 62% of the previous mean total daily dose of cysteamine (Table I). The 12 hour-trough WBC cystine level (Table IV) ranged from 0.05 to 1.29 nmol half-cystine/mg protein (mean, 0.41 ± 0.22 nmol half-cystine/mg protein). Patients maintained low leukocyte cystine levels despite a 40% reduction in total daily cysteamine dose when given as enteric-release cysteamine rather than regular cysteamine. Two patients with nocturnal enuresis (3 and 7) exhibited improvement with twice-daily enteric-release cysteamine. We have no explanation for this result, except that it may reflect a less-disturbed sleep cycle. Three children receiving long-term daily PPI therapy did not require acid-suppression therapy during stage III. Patients 1 and 2 reported intermittent emesis and/or pain during stages I and III. Some patients had a reduction in reported symptoms during stage III after they were established on the lower dose of enteric-release cysteamine. The study design and size does not allow for the exclusion of the placebo effect, however (Table V).

Table II. Weekly WBC cystine levels in the 7 patients with cystinosis measured at 6-hour trough levels during stage I

	Patient							
Week	1	2	3	4	5	6	7	Mean/median*
1	1.1 (300 mg)	0.19 (500 mg)	-	-	1.76 (625 mg)	1.93 (450 mg)	-	1.25/1.43
2	0.51 (300 mg)	0.62 (500 mg)	0.48 (500 mg)	-	0.26 (625 mg)	1.1 (450 mg)	0.58 (650 mg)	0.59/0.55
3	0.57 (300 mg)	0.38 (500 mg)	0.47 (500 mg)	-	0.68 (625 mg)	1.0 (450 mg)	0.53 (650 mg)	0.61/0.55
4	-	0.45 (500 mg)	1.0 (500 mg)	0.33 (200 mg)	0.18 (625 mg)	0.54 (450 mg)	0.85 (650 mg)	0.56/0.50
Mean	0.73	0.41	0.65	0.33	0.93	1.14	0.65	0.71/0.56

Patients received regular cysteamine (dose in parentheses) every 6 hours daily. The mean total daily dose was 45 mg/kg body weight. Missing WBC cystine values were not available.
*Represents the mean of all study patients for that particular week.

Table IV. Symptoms occurring during stage I and stage III therapy in the 7 patients with cystinosis

Patient	Stage I: cysteamine every 6 hours; mean dose, 1871mg/day	Stage III: enteric-release cysteamine every 12 hours	
		Initial dose: mean, 1500mg/day*	Final dose: mean, 1142mg/day†
1	Intermittent emesis (PPI)	Emesis, lethargy	Intermittent emesis
2	None	None	None
3	Intermittent pain	Pain, lethargy, odor	Intermittent pain, odor
4	None	None	None
5	None	None	None
6	Intermittent emesis (PPI)	Pain, odor	None
7	Intermittent heartburn (PPI)	Heartburn, pain	None

Three patients (1, 6, and 7) were receiving long-term PPI therapy to control upper GI symptoms. These 3 patients remained off PPI therapy and had either no or minimal symptoms while receiving the final dosage of enteric-release cysteamine. The mean final total daily dose of enteric-release cysteamine required to maintain an adequate WBC cystine level was 1142 mg/day, or 62% of the previous mean total daily dose of cysteamine.

*Initial mean total daily dose of enteric-release cysteamine used at the start of stage III.

†Final dose in response to symptoms. Despite the reduced dosage, WBC cystine remained at a satisfactory level.

Results of the mixed-effects model comparing mean (steady-state) cystine levels between stages I and III are presented in Table VI (available at www.jpeds.com). The least squares mean cystine level was 0.70 ± 0.09 in stage I and 0.46 ± 0.09 in stage III. The lower bound of the 95% CI for the difference in mean cystine levels (cysteamine – enteric-release cysteamine) was > 0 (95% CI lower = 0.01), suggesting significantly depleted cystine levels with enteric-release cysteamine ($P = .05$). The intrasubject variance was estimated as $\delta^2_{\text{stageI}} = 0.205$ for stage I and $\delta^2_{\text{stageIII}} = 0.066$ for stage III ($P = .024$ based on the likelihood ratio test). This suggests that cystine level is more variable with steady-state cysteamine than with enteric-release cysteamine.

In addition, there was a significant difference in the intersubject variability of WBC cystine decrease after a single dose (following a washout period) between steady-state cysteamine and enteric-release cysteamine therapy (for cysteamine: postwashout vs steady state, $P = .005$; for enteric-release cysteamine: postwashout vs steady state, $P < .001$) (Figure 4; available at www.jpeds.com). This finding suggests that a washout period may result in depletion of hepatic, plasma protein, and/or white cell cysteamine tissue levels and cause an artifactual variability in plasma WBC cystine level that is less apparent at clinical steady state.

Discussion

Patients with the rare lysosomal storage disorder cystinosis previously lost their renal function by the end of the first decade of life; however, since the introduction of renal transplantation and, perhaps more importantly, the use of cysteamine, patients with cystinosis now have the potential to live longer, with diminished rate of organ dysfunction and better growth.[2,13,14] Cystinosis affects many body organs, making continued cysteamine therapy imperative, even after renal transplantation. This was highlighted in a retrospective case series from Gahl et al[15] comprising mostly patients who underwent transplantation, which suggested that the frequency of complications (eg, diabetes mellitis, myopathy, hypothyroidism, pulmonary dysfunction and death) increased the longer patients remained off regular cysteamine therapy and decreased with increasing time on cysteamine therapy. But life-long cysteamine therapy with doses every 6 hours is a difficult undertaking and dramatically affects quality of life not only for the patients, but also for their parents or partners.[7,14] Besides having to waken from sleep every night, many patients also experience GI symptoms shortly after drug ingestion.

Our efforts over the past few years have been targeted at gaining insight into the pharmacokinetics and pharmacodynamics of cysteamine specifically for treating cystinosis.[8,10] Our previous work suggested that rapid enteric release of cysteamine would result in a higher C_{max} for cysteamine and prolonged WBC depletion. A previous report revealed that a single dose of intravenous cysteamine given to a patient with cystinosis caused a rapid fall in WBC cystine level which was sustained for the next 24 hours.[16] This may have occurred because the intravenous cysteamine bypassed the hepatic first- pass metabolism, making more drug available for intracellular uptake within extrahepatic organs. Based on these results, we postulated that if a high plasma cysteamine level could be achieved through more effective enteric uptake, then perhaps more effective and sustained cystine depletion could be achieved.

In the present study, our findings indicate that when WBC cystine trough levels are used as a measurement of cellular cystine depletion, daily enteric-release cysteamine every 12 hours is as effective as cysteamine every 6 hours. The 6-hour trough WBC cystine levels for cysteamine and the 12-hour trough WBC cystine levels for enteric-release cysteamine were comparable. Moreover, when enteric-release cysteamine was used, only about 60% of the previous total daily dose of regular cysteamine was required (28 vs 45 mg/kg body weight/day). Some patients complained of pain, vomiting, or lethargy when they received equivalent daily doses of enteric-release cysteamine. This necessitated a dose reduction of enteric-release cysteamine, which resulted in symptom improvement. Despite this dose reduction, the 12-hour trough WBC cystine levels remained within the optimal desired range (< 1.0 nmol half-cystine/mg protein), thereby negating the need for gradual dose escalation on the basis of symptomatic tolerability. Maximizing the dose of enteric-release cysteamine or

similar formulations for each patient on the basis of symptom tolerability should be considered.During stage II, the 24-hour WBC cystine and cysteamine profiles were measured after a single dose of regular cysteamine and then after 2 different doses of enteric-release cysteamine. Cysteamine capsules are made to disintegrate within the stomach; thus, the use of enteric-release cysteamine was expected to result in a longer T_{max} and a higher C_{max}. In patients 1, 2, and 3, the WBC cystine level remained depleted for 12-24 hours after ingestion of double-dose enteric-release cysteamine. Other patients (6 and 7) had erratic WBC cystine and cysteamine profiles. The reasons for this are unclear, but might include intestinal dysmotility, such as delayed gastric emptying (patients 6 and 7 had chronic constipation, and one had proven delayed gastric emptying on a nuclear medicine scan), or batch-to-batch variation in the enteric coating of the cysteamine capsules. Another possible reason for the erratic cysteamine and/or WBC cystine profiles, particularly in patients 5, 6 and 7, is that stage II measurements were obtained after a single dose of cysteamine or enteric-release cysteamine ingested between 2 and 7 days after stopping regular cysteamine therapy. In other words, "steady-state" body cysteamine levels were disrupted, and cysteamine that was possibly bound to either circulating proteins or within the liver might have been depleted (**Figure 4**).

Although cysteamine hydrochloride has been shown to cause delayed gastric emptying in animals,[17] thereby suggesting an alternate neural mechanism for nausea and emesis, some patients with regular upper GI symptoms may respond to PPI therapy. In our study, 3 of the 7 patients who had previously received regular PPI therapy remained asymptomatic during the 4 weeks of enteric-release cysteamine therapy (stage III) and were not restarted on PPI therapy. This may well have been a placebo effect.

Our study shows that for the treatment of cystinosis, twice daily enteric-release cysteamine is effective in maintaining trough WBC cystine levels within the desired range when taken on a regular basis. The total daily dose of enteric-release cysteamine was less than the previous dose of cysteamine required to achieve desired WBC cystine levels. Despite these findings, however, it should be stressed that only a limited amount of enteric-release cysteamine was produced for this study as a "proof of concept." Further studies are needed to determine whether enteric-release cysteamine is an effective treatment for cystinosis. ■

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Reprint requests: Ranjan Dohil, MB, BCh, MRCP, UCSD Medical Center, Hillcrest, 200 West Arbor Drive, San Diego, CA 92103-8450. E-mail: rdohil@ucsd.edu.

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Table III. Weekly WBC cystine levels in the 7 patients with cystinosis measured at 12-hour trough levels during stage III

	Patient							
Week	1	2	3	4	5	6	7	Mean/median*
1	0.55 (600 mg)	-	0.4 (1000 mg)	0.72 (400 mg)	0.58 (700 mg)	- (900 mg)	-	0.56/0.57
2	0.9 (600 mg)	0.30 (650 mg)	0.73 (600 mg)	0.21 (400 mg)	0.05 (900 mg)	- (900 mg)	0.28 (1000 mg)	0.41/0.29
3	1.29 (300 mg)	0.12 (650 mg)	0.77 (600 mg)	0.52 (400 mg)	0.51 (1000 mg)	0.23 (450 mg)	0.1 (1000 mg)	0.51/0.51
4	0.57 (300 mg)	-	0.42 (600 mg)	0.23 (400 mg)	0.05 (1000 mg)	0.33 (450 mg)	0.44 (600 mg)	0.34/0.38
Mean	0.83	0.21	0.58	0.42	0.29	0.28	0.27	0.41/0.45

Patients received enteric-release cysteamine (dose in parentheses) every 12 hours daily. The mean total daily dose was 28 mg/kg body weight.
*Represents the mean of all study patients for that particular week.

Table V. Mixed-effects model comparing mean (steady-state) cystine levels in stage 1 and stage III

	Stage I, cysteamine	Stage III, enteric-release cysteamine
Least squares mean (standard error), nmol half-cystine/mg protein	0.70 (0.09)	0.46 (0.09)
Difference in least squares mean (cysteamine– enteric-release cysteamine)	0.24	
95% CI for difference	0.01-0.47	
Intersubject variance, σ^2	0.013	
Intrasubject variance, δ^2	0.137	

The least squares mean cystine level was 0.70 ± 0.09 in stage I and 0.46 ± 0.09 in stage III. The lower bound of the 95% CI for the difference in mean cystine levels (cysteamine – enteric-release cysteamine) > 0 (95% CI lower = 0.01), suggesting significantly depleted cystine levels with enteric-release cysteamine ($P = .05$).

Table VI. Gastrin levels after ingestion of cysteamine (day 1), enteric-release cysteamine (day 3), and double-dose enteric-release cysteamine (day 5) in patient 1

	Gastrin level, pg/mL		
Time, minutes	Day 1	Day 3	Day 5
0	78	80	61
30	92	87	44
60	99	59	54
90	154	127	63
120	104	147	156
180	99	88	75
240	75	55	72

All other study patients (3, 4, 6, and 7) had normal gastrin levels (< 100 pg/mL) on all 3 study days.

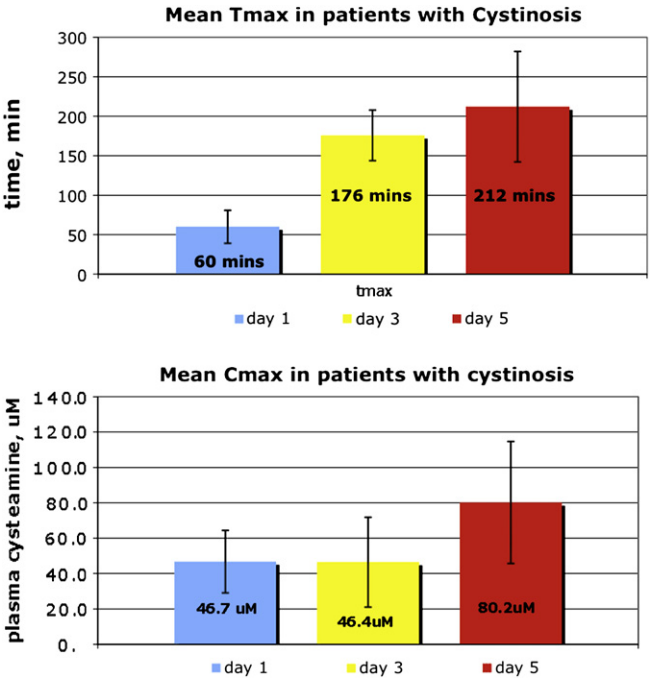

Figure 1. Mean T_{max} (in minutes) and C_{max} values for plasma cysteamine (μM) after drug ingestion in 7 patients during stage I. Drug dosage was as follows: a single dose of cysteamine on day 1, a single dose of enteric-release cysteamine on day 3, and a double dose of enteric-release cysteamine on day 5. The time to achieve T_{max} was longer on days 3 and 5 compared with day 1 ($P = .001$ and .002, respectively). For C_{max}, there was no difference between days 1 and 3, but C_{max} was higher on day 5 than on days 1 and 3 ($P = .01$ and .003, respectively). Mean area under the curve measurements for plasma cysteamine were 4871 for day 1, 5194 for day 3, and 11 814 for day 5. Error bars are standard error of the mean.

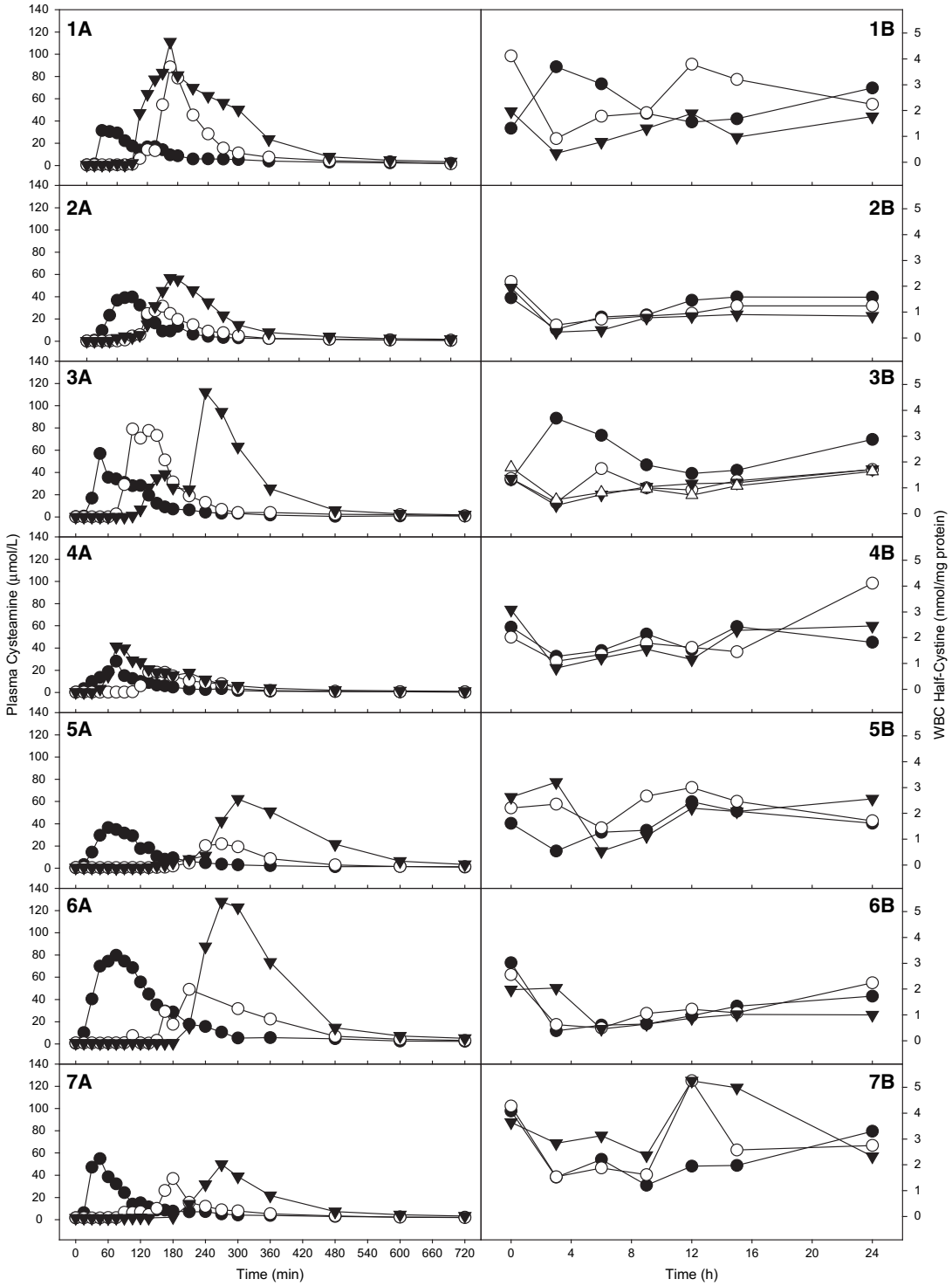

Figure 2. Plasma cysteamine levels (μM) and WBC cystine levels (nmol half-cystine/mg protein) measured at intervals following drug ingestion in 7 subjects with cystinosis. WBC cystine level was measured at baseline and 3, 6, 9, 12, 15 and 24 hours after drug ingestion. On day 1, a single dose of cysteamine (solid circles) was given; on day 3, a single dose of enteric-release cysteamine (open circles) was given; and on day 5, a double dose of enteric- release cysteamine (solid triangles) was given. No cysteamine was ingested for at least 48 hours before the single drug dose at time 0 on days 1, 3, and 5. The left panels, labeled with the patient number followed by "A," show the time course of plasma cysteamine; the right panels, labeled with the patient number followed by "B," show the WBC cystine levels. Subjects 1, 2, 3, and 6 exhibited prolonged WBC cystine depletion on day 5 compared with days 1 and 3.

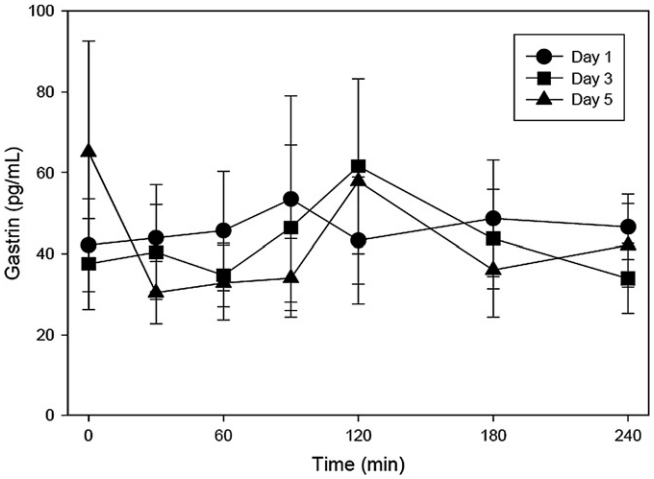

Figure 3. Mean gastrin levels following ingestion of cysteamine (day 1), enteric-release cysteamine (day 3), and double-dose enteric-release cysteamine (day 5) in 5 study patients (1, 3, 4, 6, and 7). No difference in gastrin levels was detected. Patients who had previously received PPI therapy for upper GI while on cysteamine therapy did not require acid-suppression therapy during the 4 weeks of treatment with enteric-release cysteamine. Error bars are standard error of the mean.

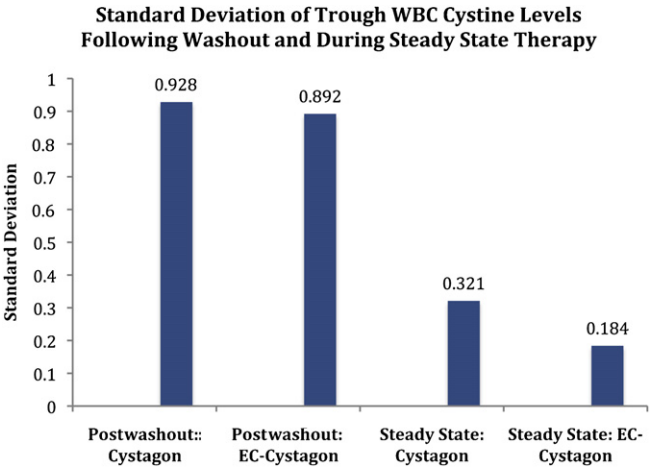

Figure 4. Standard deviation of trough WBC cystine levels in 7 children with cystinosis during "steady-state" cysteamine and enteric-release cysteamine therapy and also after a single dose of both (following a 48-hour washout period). There were significant differences between steady-state and postwashout cysteamine ($P = .005$) as well as for enteric-release cysteamine ($P < .001$).