

THE EVALUATION AND TREATMENT OF GASTROINTESTINAL DISEASE IN CHILDREN WITH CYSTINOSIS RECEIVING CYSTEAMINE

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Objectives Cysteamine prevents organ damage in children with cystinosis, but may cause gastrointestinal (GI) symptoms. In this study we evaluated the nature of GI disease, and the value of omeprazole in controlling GI symptoms in these children.

Study design Upper GI disease was evaluated with endoscopy, gastrin levels, and acid secretion studies after oral administration of cysteamine, before and after 16 weeks of therapy with omeprazole. A symptom score was devised.

Results Eleven children (mean age, 5.7 years) were studied. After cysteamine ingestion, before and after omeprazole therapy, the mean maximum acid output was significantly higher than the mean basal acid output. The maximum acid output was measured within 60 minutes of cysteamine ingestion and was reduced by omeprazole therapy ($P < .01$). The mean peak gastrin level was 30 minutes postcysteamine and was higher than baseline ($P < .01$). The initial mean symptom score (maximum score, 14) was 6.9 and fell to 0.7 ($P < .0001$) after 16 weeks of omeprazole therapy. At endoscopy, two children had diffuse gastric nodularity, and nearly all had cystine crystal deposits.

Conclusions GI symptoms in children with cystinosis receiving cysteamine are often acid-mediated and improve with omeprazole. Cystine crystals were detected in the GI tract and may signify inadequate treatment with cysteamine. (*J Pediatr* 2003;143:224-30)

Cystinosis is an autosomal recessive disease caused by the abnormal accumulation of cystine within various tissues.¹ The nephropathic forms of cystinosis are associated with multi-organ damage, particularly progressive renal failure leading to dialysis and/or renal transplantation. To date, the only specific treatment for nephropathic cystinosis is the sulfhydryl agent, cysteamine; this drug lowers intracellular cystine levels, thereby reducing the rate of progression of renal failure^{2,3} and significantly diminishing damage to other organs.¹

Cysteamine is known to be ulcerogenic in laboratory animals and has been used specifically for this purpose.^{4,5,6} The mechanism of cysteamine-induced ulcerogenesis is most likely multifactorial and may involve increased gastrin and gastric acid production,⁵⁻⁷ delayed gastric emptying, and inhibition of bicarbonate and gastric mucus production.^{8,9} Oral cysteamine administered to four children with cystinosis caused a mean three-fold increase in gastric acid production above baseline.¹⁰ It is therefore not surprising that many children receiving cysteamine therapy have gastrointestinal (GI) symptoms. GI symptoms were found to occur in 93% of patients with cystinosis.¹¹ In a feasibility study where 66 families were interviewed by telephone, almost all children with cystinosis described GI symptoms which included swallowing dysfunction, anorexia, nausea, vomiting, retching, abdominal pain, and heartburn. These symptoms may have contributed to school absenteeism, suboptimal nutrition and growth, and reduced compliance for cysteamine therapy. If indeed cysteamine-associated GI symptoms are caused by increased gastric acid production, then acid-suppression should result in symptom relief, better compliance, and improved prognosis for the patient.

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BAO	Basal acid output	PAO	Peak acid output
GI	Gastrointestinal	UCSD	University of California at San Diego
MAO	Maximum acid output		

The purpose of this study was to evaluate the nature and cause of GI disease, and assess the value of the proton-pump inhibitor omeprazole (Prilosec, AstraZeneca, Wilmington, Del) in controlling upper GI symptoms and gastric acid output in children with cystinosis receiving cysteamine therapy.¹²

METHODS

Recruited patients were admitted to the University of California at San Diego (UCSD) General Clinical Research Center for baseline and then follow-up evaluation after 16 weeks of omeprazole therapy. The study was approved by the University of California at San Diego, Human Subjects Committee, and informed consent was obtained for each participant.

Patients

Cystinosis patients, ages 1 to 18 years, with GI symptoms were asked to participate in this study. All patients received regular cysteamine bitartrate (Cystagon, Mylan, Morgantown, WV) at a free-base dose of approximately 60 mg/kg/day. Acid suppressants, antibiotics, nonsteroidal anti-inflammatory drugs, prokinetic agents, and antihistamines were discontinued one month before admission. A mean leukocyte cystine level of <2.0 nmol half-cystine per mg protein over the past year was required for inclusion in the study.

Serum Gastrin

After subjects underwent an eight-hour overnight fast, except for water, 3-mL blood samples were taken at baseline and at 30, 60, 90, and 120 minutes after ingestion of the patient's regular dose of cysteamine. The cysteamine was administered in solution with water. Serum gastrin levels were measured in pg/mL using the Diagnostic Products Corporation (Los Angeles, Calif) gastrin¹²⁵ radioimmunoassay kit.¹³

Gastric Acid Secretion

On the second study day, and after an overnight fast for everything except water, a multiport 8 French nasogastric tube was inserted into children who did not have a pre-existing gastrostomy tube. To assure correct tube placement, 50 mL of water was instilled into the stomach, aspirated, and discarded with the overnight gastric contents. The hydrogen ion content within aspirated gastric contents was measured to provide basal acid output (BAO)/maximum acid output (MAO)/peak acid output (PAO) levels. The BAO was estimated from gastric contents collected over 60 minutes in four 15-minute aliquots. The patient's regular dose of cysteamine was then administered, the feeding tube was clamped for 30 minutes, and the gastric contents were again collected and discarded. Over the next two hours, gastric contents were collected in eight consecutive 15-minute aliquots. The MAO was the acid content in the first 60 minutes. The PAO was the highest two consecutive 15-minute collection periods multiplied by a factor of two to express acid secretion in the usual way, ie, $\mu\text{Eq/kg/hr}$. Gastric acid was measured by standard titration method¹⁴ by using a digital pH meter (PHM 82 Radiometer, Copenhagen, Denmark).

Upper GI Endoscopy and Biopsies

This was performed under general anesthesia using an Olympus GIF 100 or P140 endoscope (Olympus, Melville, NY) and through-the-scope biopsy forceps. Mucosal biopsies were fixed in formalin and Trump's solution and sent for hematoxylin and eosin staining and electron microscopy, respectively. Biopsy specimens were examined for inflammation and intracellular cystine deposition. Endoscopic findings were reported in a conventional manner.^{15,16}

Symptom Score

A symptom score was devised to assess GI symptoms at baseline, and at 4, 8, 12, and 16 weeks after commencing omeprazole. Data was obtained either in person or by telephone communication with the physician. Each of the seven symptom categories scored 0 to 2 points depending on the presence and severity of each symptom. Zero points were awarded if the symptom was absent; 1 point if the symptom was mild, did not interfere with daily activities and only required occasional treatment (eg, with oral antacids); and 2 points if the symptoms were severe enough to interrupt daily activities or require regular treatment (eg, with H₂-blockers). Previous GI bleeding was considered mild (1 point) if there was no associated hemodynamic compromise or anemia, and severe (2 points) if bleeds were multiple, caused anemia, or required blood transfusion. The symptom categories included: (1) heartburn or regurgitation; (2) abdominal pain or unexplained regular irritability in small children; (3) nausea or vomiting; (4) anorexia or early satiety; (5) dysphagia or odynophagia; (6) nocturnal waking with symptoms; and (7) gastrointestinal bleeding within the four months. The symptom score was the sum of each individual symptom category score. The maximum score was 14.

Omeprazole

Omeprazole was administered to children through an Investigation New Drug exemption. Open-labeled omeprazole was administered before meals either in whole capsule or suspension form, or mixed with apple puree. Children <10 years of age received 10 mg twice daily and children ≥ 10 years received 20 mg twice daily. Omeprazole dosage was increased by 50% only if upper GI symptoms were still present at the times of re-assessment, to a maximum of 20 mg twice daily for children <10 years age and 40 mg twice daily for children ≥ 10 years.

Statistical Analysis

Paired Student *t* tests were used to compare mean peak gastrin with baseline levels and to compare mean peak gastrin before omeprazole treatment versus postomeprazole treatment. Change in symptom scores during treatment were compared using paired Student *t* tests. Wilcoxon rank-sum tests were used for testing measures of increase in gastric acid production.

One-way repeated measures analysis of variance contrasts were used to identify differences between measures of acid production. Two-group repeated measures analysis of

Table I. Patient data in order of age

Patient	Age (y)	Time since diagnosis (y)	Mean leukocyte cystine since diagnosis*	GFR [†]	Cysteamine dose [‡]	Omeprazole dose [§]	Baseline symptom score	Final symptom score [¶]	Weight gain/Baseline [#] weight (kg)
10	2.2	1.6	1.6	139.3	58.8	4.3	8	0	2.0/8.55
1	2.7	1.5	1.8	139.7	48.9	4.0	3	1	0.8/9.2
3	2.8	1.0	0.9	148.6	48.0	3.1	10	0	0/12.5
5	3.1	2.1	1.6	72.1	43.0	4.2	9	2	0.3/9.3
11	3.5	1.9	1.3	103.4	92.1	1.3	4	0	1.4/15.2
2	6.0	5.0	1.4	109.4	59.2	2.6	7	1	0.4/15.2
8	7.8	2.7	1.8	52.8	58.1	2.1	7	0	2.0/17.2
4	8.0	6.7	0.9	81.3	57.6	1.6	7	2	1.1/24.2
6	9.6	7.3	1.2	93.8	64.2	1.8	5	1	0.8/21.8
9	10.7	8.1	0.7	68.3	77.7	1.2	5	0	2.2/30.9
7	12.3	8.9	0.8	68.5	52.3	2.6	9	1	0.7/30.6

*Leukocyte cystine levels are measured in nmol half-cystine per mg protein. Normal level is <0.2; cystinosis patients have values >2.0, and optimal levels with cysteamine therapy should be <1.0.

[†]Glomerular filtration rate (mL/min/1.73 m²) calculated from 0.55 length (cm)/plasma creatinine (mg/dL)¹⁷.

[‡]Cysteamine (mg/kg/day) given in four equal doses and calculated as free-base cysteamine.

[§]Omeprazole (mg/kg/day) dosage at end of study

^{||}Symptom score before omeprazole therapy.

[¶]Symptom score after 16 weeks of omeprazole therapy.

[#]Weight gain during the 16 week study period and baseline weight.

Table II. Pre- and post-omeprazole serum gastrin data from 11 children with cystinosis after cysteamine

	Pre-omeprazole therapy mean ± SEM (range)	Post-omeprazole therapy mean ± SEM (range)	P value
Mean baseline gastrin	48.8 ± 7.1 (0-84)	108 ± 27.1 (36-327)	.057
Mean gastrin 30 min Post-baseline	73.9 ± 10.5 (32-128)	187.8 ± 36.5 (51-366)	<.001
Mean peak gastrin over 2 h*	85.9 ± 12.1 (45-177)	217.6 ± 37.5 (55-366)	<.01
Mean peak gastrin over 2 h vs mean baseline	85.9 vs 48.8	217.6 vs 108	Pre-omeprazole <.01 Post-omeprazole <.01

Serum gastrin is reported as pg/mL. Observed significance is provided for different comparisons of serum gastrin.

*Mean of the highest gastrin levels measured within 2 hours post-cysteamine ingestion.

variance was used to test the effects of omeprazole treatment (pre- vs post-) and time and their interaction on gastrin levels. Slices tested treatment effects at individual times. The same analyses were used for gastric acid, with omeprazole treatment (pre- vs post-) and increase in acid production (BAO vs MAO vs PAO) as the main effects.

Pairwise tests were two-tailed. No formal adjustments were made to control the overall type I error rate. Instead, unadjusted *P* values are reported.

RESULTS

Eleven children, ages 1.7 to 12 years (mean age, 5.7 years, 8 girls and 3 boys), were enrolled into the study from July 2001 to January 2002 (Table I). The mean age at diagnosis was 22 months (1.8 years). None of the children had undergone renal transplantation. Their mean glomerular filtration rate was 97.9 mL/min/1.73 m².¹⁷ All children had negative *Helicobacter pylori* serology. Six of the 11 children

required nasogastric tube insertion, four had a gastrostomy tube, and one child had a gastrojejunostomy tube in place. The average dose of cysteamine was 59.9 mg/kg/day and the mean initial leukocyte cystine level was 1.2 nmol half-cystine per milligram. The mean omeprazole dose at the study's start and finish was 1.3 mg/kg/day and 2.6 mg/kg/day, respectively. The only adverse effect attributable to omeprazole was mild headaches in one child, but these were not severe enough to discontinue therapy.

Serum Gastrin

The mean baseline gastrin level increased from 48.8 to 108 pg/mL while patients received omeprazole (Table II). The highest mean gastrin level occurred 30 minutes after cysteamine ingestion in both cases. The mean peak gastrin levels measured over two hours, before and after omeprazole, were 85.9 pg/mL and 217.6 pg/mL, respectively, and were significantly higher than their baseline levels (*P* < .01 for both).

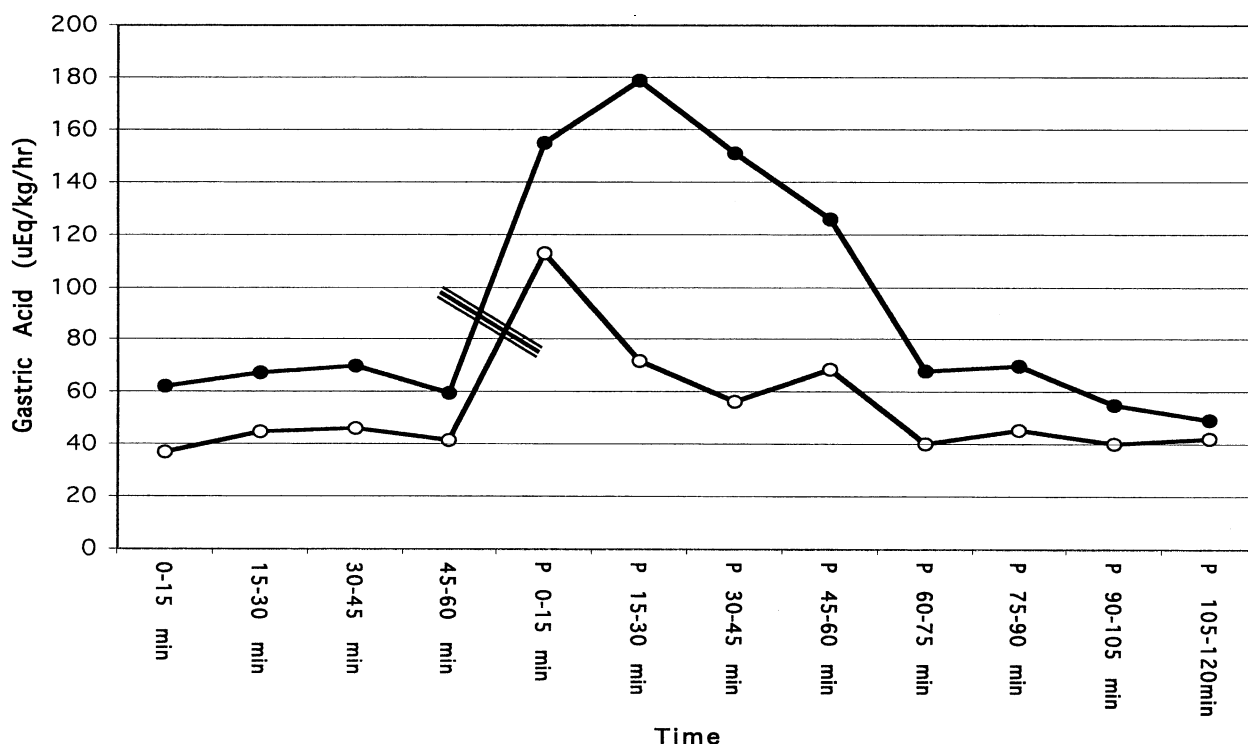


Fig 1. Gastric acid secretion in response to cysteamine is shown before (*closed circles*) and after (*open circles*) omeprazole therapy, and although collected in 15-minute periods is reported as $\mu\text{EqH}^+/\text{kg}/\text{hr}$. Time 0 to 60 minutes represents the baseline collection of acid. The cysteamine is then ingested and aspirated 30 minutes later (*triple diagonal line bar* represents the period when gastric aspirate was not collected). Times P 0 to P 120 minutes represent the acid collection after cysteamine is removed from the stomach. The BAO is from 0 to 60 minutes, the MAO is from P 0 to P 60 minutes, and the PAO in this case is from P 0 to P 30 minutes.

Table III. Pre- and post-omeprazole gastric acid output data for 11 children with cystinosis after cysteamine

	Pre-omeprazole therapy mean \pm SEM (range)	Post-omeprazole therapy mean \pm SEM (range)	P value
Mean BAO	256.5 \pm 41.1 (82.4 - 510)	168.8 \pm 47.8 (9.6 - 464.2)	.34
Mean MAO	611.2 \pm 90.8 (155.1 - 1216.1)	309.6 \pm 37.9 (101.5 - 480.5)	< .01
Mean PAO	728.2 \pm 90.8 (284.2 - 1298.3)	389.8 \pm 117.4 (154.2 - 732.8)	< .001
Mean MAO vs BAO	611.2 vs 256.5	309.6 vs 168.8	Pre-omeprazole < .01 Post-omeprazole .05
Mean PAO vs BAO	728.2 vs 256.5	389.8 vs 168.8	Pre-omeprazole < .001 Post-omeprazole < .01

Basal, maximal and peak acid output (BAO, MAO, PAO) are reported in $\mu\text{EqH}^+/\text{kg}/\text{hr}$. Observed significance is provided for different comparisons of gastric acid secretion.

One child had post-omeprazole serial gastrin levels measured on consecutive days, after intragastric and then intrajejunal cysteamine administration; although baseline levels were similar (150 vs 157 pg/mL), the peak gastrin level was almost three times higher after jejunal drug administration (680 vs 278 pg/mL).

Gastric Acid Secretion

Gastric acid production was markedly reduced after omeprazole therapy (Fig 1, Table III). Despite this, cysteamine ingestion resulted in mean MAO and PAO levels

significantly higher than the mean BAO, just as it did before omeprazole therapy. The pre-omeprazole PAO period in all patients occurred within the first 60 minutes of acid collection postcysteamine, and in seven patients within 30 minutes. The postomeprazole PAO period occurred within 30 minutes in eight patients.

Upper Gastrointestinal Endoscopy and Biopsy

Two children had diffuse, fine nodularity throughout the stomach (Fig 2). One child had submucosal hemorrhages in the gastric fundus from recurrent vomiting. Another child

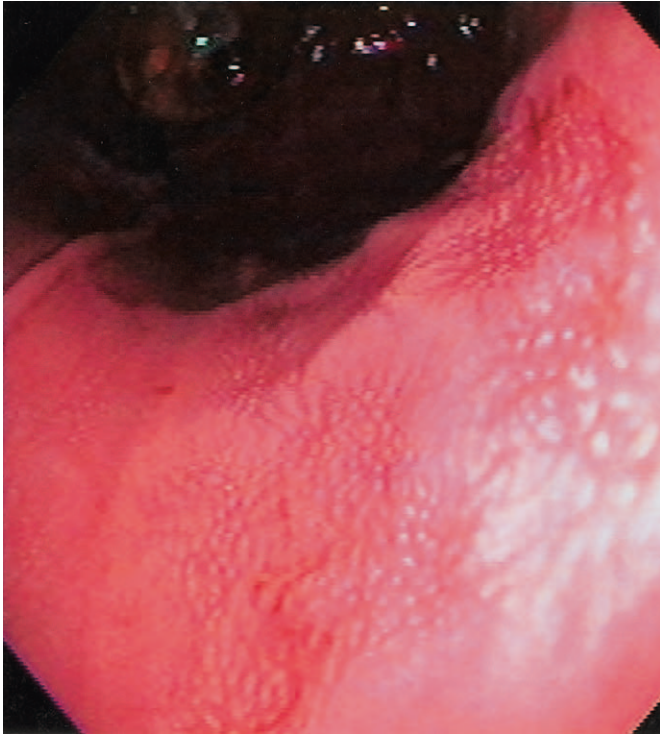


Fig 2. The gastric body as seen through the endoscope. Diffuse, fine nodularity is seen throughout the stomach. Mucosal biopsies did not show *Helicobacter pylori* infection or evidence of inflammation.

had inspissated bile-stained mucus adherent to the mucosa and a large pool of bile within the stomach. Light microscopy evaluation of biopsy specimens (two per region) from the distal esophagus, gastric body and antrum, duodenal bulb, and jejunum were normal in all except for two patients who had mild esophagitis with basal zone hyperplasia and intra-epithelial eosinophils. *Helicobacter pylori* organisms were not seen. Ten of 11 children, including the four patients with endoscopic abnormalities, had outlines of crystalline structures within the lysosomes of macrophage cells of the lamina propria (Fig 3) presumed to be cystine crystals. Of the 10 patients, one child also had crystals within the jejunal mucosa and one within esophageal mucosa. The two children with the diffusely nodular appearance had the highest levels of crystal deposition with between 18 and 20 crystals per cell.

Symptom Score

The mean symptom score at the start of the study was 6.9 and fell to 0.7 ($P < .001$) after 16 weeks of therapy with omeprazole (Table IV). The patient's symptoms continued to respond to omeprazole therapy at 8 to 12 months after starting treatment. Although they were not part of the symptom score, bloating (before 0.6, after 0.4) and excessive eructation or flatus (1.2, 0.5) were also scored before and after treatment with omeprazole.

DISCUSSION

Oral cysteamine causes duodenal ulcers in laboratory animals.⁴ The dose required, however, is 700 to 1000 mg/kg

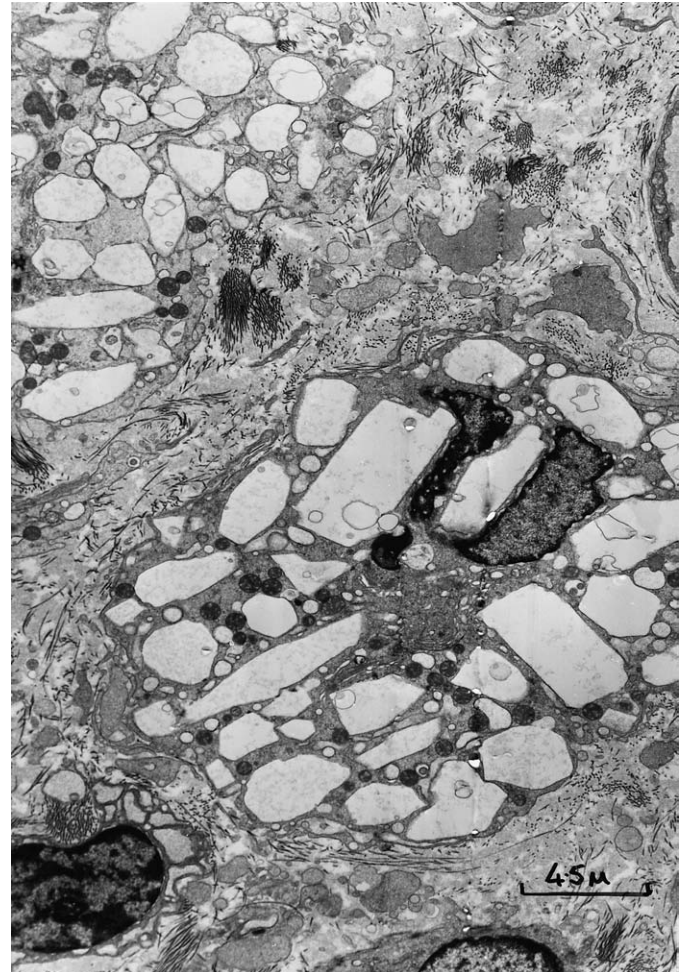


Fig 3. Electron microscopy (original magnification, $\times 9000$) of the gastric mucosal biopsy reveals several cytoplasmic lysosomal crystalline inclusions of varying shapes and sizes within histiocytes in the lamina propria. The biopsy specimen is fixed in 2.5% buffered glutaraldehyde, processed for routine electron microscopy and embedded in epoxy resin. Thick sections cut at one micron are stained with toluidine blue and selected areas are stained with uranyl acetate and lead citrate. Ultrathin sections are then examined in an electron microscope.

body weight or 40 to 60 times the per-kilogram body weight dose that is currently administered at any one time for the treatment of cystinosis.^{1,5-7} The exact mechanism by which cysteamine induces ulcerogenesis is unclear, but it likely involves gastric acid-hypersecretion^{6,18} secondary to hypergastrinemia.¹⁹ Low intraluminal pH will inhibit gastrin release through a negative feedback loop. High intraluminal pH, as seen in acid-suppression therapy, will cause hypergastrinemia.²⁰

In rat studies, a three- to four-fold increase in fasting gastric acid production above baseline was observed after the intraduodenal administration of 100 mg/kg of cysteamine.¹⁸ Lichtenberger et al demonstrated a three- to four-fold increase in fasting gastrin levels and a five- to six-fold increase in nonfasting gastrin levels above baseline in rats who received 280 mg/kg of intragastric cysteamine.¹⁹ In both sets, the peak gastrin level was at two hours post-ingestion, returned to

Table IV. Mean symptom score

	Heartburn	Pain	Nausea/Vomiting	Anorexia	Dysphagia	Nocturnal wakening	GI bleed	Total
Baseline	1.0	1.4	1.8	1.7	0.6	0.3	0	6.9
4 week	0.4	0.4	0.7	0.8	0.2	0	0	2.5
8 week	0.2	0.2	0.6	0.6	0.1	0	0	1.7
12 week	0	0.3	0.3	0.4	0.1	0	0	1.0
16 week	0.2	0.1	0.2	0.3	0	0	0	0.7
P value	.01	<.001	<.0001	<.0001	.025	.19	—	<.0001

The mean omeprazole dose at start and finish of the study was 1.3mg/kg and 2.6 mg/kg, respectively. Statistical analysis of the individual categories was by paired Student *t* test (baseline vs 16 weeks).

baseline at four hours in the fasting group, but remained elevated for longer in the group that were fed after receiving cysteamine. This postprandial hypergastrinemia in rats may, in part, be the result of the delayed gastric emptying caused by cysteamine, thereby increasing the contact time of food with the gastric mucosa, which may enhance and prolong the release of gastrin.⁸ Other effects of cysteamine that may contribute to ulcer formation include diminished duodenal mucosal blood flow, which is noted within minutes of drug ingestion and may result in the altered production of bicarbonate, mucus and epidermal growth factor from sub-mucosal Brunner's glands.^{9,21}

The mean fasting gastrin level was reported as 32.7 pg/mL in normal control children <3 years of age and 14.8 to 20.9 pg/mL in children >3 years of age.²⁴ Our patients had a fasting baseline hypergastrinemia (mean, 48.8 pg/mL) that increased and persisted for at least two hours after ingestion of cysteamine (Table II). In two studies of gastric acid secretion in normal children, the mean BAO was 40 to 67 μ Eq/kg/hr, and after pentagastrin (6 μ g/kg), there was a five- to eight-fold increase in acid output (MAO versus BAO).^{22,23} In the previous study of four cystinosis patients, the mean BAO was 30 μ Eq/kg/hr and after cysteamine (mean dose, 14.3 mg/kg), there was a three-fold increase in acid output (MAO vs BAO).¹⁰ In our study, the mean BAO was 256.5 μ Eq/kg/hr with similar large increases in MAO and PAO. We cannot explain the discrepancy but it is certainly compatible with our finding of a two- to three-fold increase in baseline gastrin levels compared with normal children.²⁴ Further studies to determine how the mode of drug delivery effects gastrin and acid production should be undertaken.

Cysteamine is clearly a potent gastric acid stimulant in humans, even at doses of 11 to 23 mg/kg. Patients in whom baseline acid production was suppressed with omeprazole still demonstrated a mean 1.8-fold increase in maximal acid production above baseline after cysteamine ingestion. The mean peak acid production was demonstrated within 60 minutes of cysteamine ingestion (Fig 1), and this correlated temporally with the onset of GI symptoms in the patients. The mean acid output returned to baseline levels within 90 minutes of cysteamine ingestion. Baseline hypergastrinemia and gastric acid hypersecretion reported here may be have been a residual effect of cysteamine that was ingested eight hours earlier. However, this would seem unlikely because plasma cysteamine

concentrations after oral cysteamine bitartrate peak at one to two hours, and gradually fall to immeasurable levels six hours later.²⁵

The mean symptom score fell during the study from 6.9 to 0.7, with the most dramatic improvement occurring within the first four weeks of omeprazole therapy. The most commonly reported symptoms of nausea, vomiting, anorexia, and pain responded best to acid suppression. Most patients required an increase in omeprazole dosage during the study, but had sustained control of symptoms at follow-up 8 to 12 months after the therapy began. This also argues against a nonpharmacological explanation for the decrease in symptom score. We had initially contemplated a placebo-controlled study, but the feasibility study indicated that patient recruitment would be hampered if prolonged or repeated use of the nasogastric tube was required.

The spectrum of GI symptoms in cystinosis patients is wide.¹¹ Some patients will have GI symptoms unrelated to cysteamine therapy and these patients may not respond completely to acid-suppression therapy with omeprazole. Although there is some crossover, we believe that the GI symptoms can be broadly categorized into those associated with intestinal dysmotility caused by intralysosomal cystine accumulation, including swallowing dysfunction, gagging, early satiety, and pseudo-obstruction, and those caused by cysteamine-induced gastric acid-hypersecretion such as nausea, vomiting, poor appetite, pain, and heartburn.

Long-term use of omeprazole has been studied in adults and is safe. Enterochromaffin-like cell hyperplasia was reported in more than 50% of patients who received long-term (mean, 7.9 years) proton-pump inhibitor therapy. This was thought to be a trophic effect of the associated hypergastrinemia. No evidence of dysplasia was reported even after 10 years of therapy.²⁶

Lysosomal cystine crystals were identified in gastric mucosa with electron microscopy in 10 patients; the two children with additional esophageal or jejunal involvement had the highest initial symptom scores. The easy identification of these crystals, despite depressed leukocyte cystine levels, suggests that the current recommended cysteamine dosage is either inadequate or not followed. We hope concurrent acid suppression will allow patients to tolerate more aggressive cysteamine therapy, thereby promoting better intra-cellular cystine depletion. We intend to use some of the cystine deposition data as a basis for further studies to establish the

value of electron microscopy of mucosal tissue as a means of assessing intestinal cystine content and therefore its use in monitoring the effectiveness of cysteamine therapy or drug compliance.

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