Gastrointestinal Issues in Cystinosis

Ranjan Dohil MD
University of California, San Diego
Outline

- Gastrointestinal symptoms
- Cysteamine absorption study
- Enteric-coated cysteamine study
Common GI Symptoms

Current symptoms

- Nausea/ vomiting 83%
- Poor appetite 71%
- Diarrhea/Constipation 57%
- Abdominal Pain 50%
- Swallowing difficulties 41%

Common Gastrointestinal Symptoms

**Cysteamine**

- Gastric Acid Hypersecretion
  - Vomiting, nausea
  - Anorexia, poor swallowing
  - Pain / heartburn

**Cystine deposition?**
- Hypothyroidism
- Poor diet, Medications

**Intestinal Dysmotility**
- Bloating
- Burping / gagging
- Swallowing dysfunction

Cysteamine
Mechanism of Ulcerogenesis with Cysteamine (Rats)

↑ Gastric Acid
↓ Bicarbonate
↓ Mucus
↓ Gastric Emptying
↑ Gastrin

Cysteamine
Mean Serum Gastrin Levels After Cysteamine in Children with Cystinosis

- 32.7 pg/ml = mean serum gastrin for < 3 yrs
- 14 -20 pg/ml = mean serum gastrin for >3 yrs

Pediatr Nephrol 2005;20:1786-93
Gastric Acid Output Following Cysteamine Ingestion, Before and After Omeprazole (Prilosec) therapy.

Graph showing gastric acid output levels over time.

Axes:
- Y-axis: Baseline, Cyst, Post-Cysteamine
- X-axis: Time (0-15 min, 15-30 min, 30-45 min, 45-60 min, 60-75 min, 75-90 min, 90-105 min, 105-120 min)

Legend:
- Pre-omep
- Post-omep

Graph indicates a significant increase in gastric acid output following Cysteamine ingestion before omeprazole treatment, followed by a decline post-omeprazole.
GI Symptoms Before and After Omeprazole (Prilose)

- Heartburn: P = 0.001
- N/V: P = <0.0001
- Anorexia: P = <0.0001
- Dysphagia: P = 0.025
- Noct Wake: P = 0.19
- GI Bleed: P = 0.49

P-values indicate statistical significance of symptom reduction after Omeprazole treatment.
Stomach

- Symptom score 9
- Diffuse nodularity.
- LM - Normal
- EM - Large number of cystine crystals detected.

*Journal of Pediatrics 2003;143:224-230*
Intracellular Cystine Crystal Deposition
x 12,000
Omeprazole (Prilosec) / Esomeprazole (Nexium)

- Proton-pump inhibitors (PPI’s)
- Capsule, solutab or liquid.
- 30-60 minutes before meals / cysteamine
- Single dose causes gastric pH > 4 for 10-12 hrs
- Well tolerated in renal failure
- Children metabolize PPI’s rapidly
# PPI Initial Dose Recommendations

<table>
<thead>
<tr>
<th>PPI</th>
<th>Infant</th>
<th>Child &lt; 30 kg</th>
<th>Child &gt; 30kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>0.5-1mg per kg/day</td>
<td>10mg qd</td>
<td>20mg qd</td>
</tr>
<tr>
<td>Lanzoprazole</td>
<td>0.7-1.5mg per kg/day</td>
<td>15mg qd</td>
<td>30mg qd</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>0.5-1mg per kg/day</td>
<td>10mg qd</td>
<td>20mg qd</td>
</tr>
</tbody>
</table>
Does everyone with cystinosis need acid-suppression therapy?

- Cysteamine does not induce gastric-acid hypersecretion in all.

- Only patients with regular GI symptoms such as N/V, pain, heartburn, have increased gastrin levels.
Summary- GI Symptoms

- GI symptoms are common, but do not occur in everyone.
- May be related to cysteamine or disease.
- When symptoms caused by cysteamine, patients often have increased acid and gastrin production.
- Proton pump inhibitor drugs (PPI’s) adequately reduce cysteamine-induced acid production.
Cysteamine Absorption Study

Aims

- Determine how well cysteamine was absorbed from the intestinal tract.
- How effective cysteamine is when infused into varying sites
- Decide whether a slow-release or a targeted cysteamine delivery system would be feasible.

Intestinal Cysteamine Absorption

Naso-enteric catheter

Administer cysteamine into stomach, small intestine and colon

Gastrin (Acid production)

Cysteamine (Absorption)

White Cell Cystine (Efficacy of cysteamine)
Cysteamine Absorption

- Cystinosis patients (12-18yrs) /Controls
- Patients ≥ 12 years with cystinosis
- Off cysteamine for 48 hrs
- Off acid suppression therapy for 1 week
- Insertion of a naso-enteric tube
- Infuse cysteamine into the stomach, SI and colon on days 1, 3 and 5 of the study
- Drug washout-period 24 hrs
- Position of tube confirmed fluoroscopically
Catheter in cecum
Plasma Cysteamine Concentration in Control Subjects

Cmax = maximum plasma level.  SI > Stomach > Colon
Mean Plasma Cysteamine levels in Children with Cystinosis

$C_{\text{max}} = \text{maximum plasma level.}$  
$\text{SI > Stomach > Colon}$
The AOC change from baseline was effected by Cmax for cysteamine (p <0.001).
Summary - Cysteamine Absorption

- Cysteamine absorption occurs most rapidly and effectively from the small intestine ($\uparrow C_{max}$, $\downarrow T_{max}$).
- Cysteamine absorption from the colon is poor.
- High plasma cysteamine levels ($\uparrow C_{max}$) probably result in prolonged leukocyte cystine depletion.
Enteric-coated Cystagon

Targeted rapid release of cysteamine within SI

- Overcome hepatic *first pass* metabolism
  - High plasma cysteamine levels
  - Prolonged WC cystine depletion
  - Fewer doses

- Less direct gastric irritation/gastrin release
  - ↓ Gastric acid release
  - Fewer GI symptoms
Enteric-coated Cystagon

- Targeted rapid release of cysteamine within SI
- Coated with Eudragit L55D30
- Intended capsule dispersion at pH 5.5
- Healthy adult controls
- Children with cystinosis
Enteric-coated Cystagon Study

**Phase 1** - Weekly leukocyte cystine levels for one month on regular Cystagon four times daily.

**Phase 2** - Inpatient 24 hr leukocyte cystine and plasma cysteamine profiles
- off acid-suppression
- off regular cysteamine

**Phase 3** - Weekly leukocyte cystine levels for one month on EC-Cystagon twice daily
Enteric-coated Cystagon Study
Phase 2-Inpatient Schedule

• Day 1 - Single regular dose of Cystagon
• Day 3 - Single dose Enteric-coated Cystagon
• Day 5 - Double dose Enteric-coated Cystagon

No regular Cystagon for 48hrs before and during the study
Enteric-coated Cystagon Study (Phase 2)

Cystagon, EC-Cystagon (regular and double dose)

Administer drug orally (days 1, 3, 5)

Gastrin (Acid production)

Cysteamine (Absorption)

White Cell Cystine (Efficacy of cysteamine)
Mean Gastrin Levels in Cystinosis (n=5)
Mean Cysteamine Profiles in Cystinosis Patients

Mean plasma cysteamine cc

Day 1 cystagon
Day 3 EC-Cystag
Day 5 EC-Cystag

Time, n
Plasma Cysteamine Profile After Single Dose
Single Patient

PATIENT N

- series 1
- series 2
- series 3

随着时间 (h)
White Cell Cystine Profile After Single Dose
Single Patient

**WBC cystine level**

- 500 mg
- 500 mg EQ
- 1000 mg

**Time (hours):** 0, 3, 6, 9, 12, 15, 18, 21, 24

- Level ranges from 0 to 2.5
- Graph shows the decline and rise in WBC cystine levels over time for different doses.
White Cell Cystine Profiles After Single Dose

“The Good”
White Cell Cystine Profiles After Single Dose

“The Odd”

Graph showing White Cell Cystine Profiles over time (hours) for Patient P.
## Phase 1

### White Cell Cystine Levels on q6h Cystagon for One Month - Before Inpatient Study

<table>
<thead>
<tr>
<th>Week 1</th>
<th>N</th>
<th>L (300mg)</th>
<th>E (450mg)</th>
<th>J</th>
<th>P</th>
<th>C (500mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.48 (500mg)</td>
<td>0.51 (300mg)</td>
<td>1.1 (450mg)</td>
<td>-</td>
<td>0.58 (650mg)</td>
<td>0.62 (500mg)</td>
</tr>
<tr>
<td>3</td>
<td>0.47 (500mg)</td>
<td>0.57 (300mg)</td>
<td>1.0 (450mg)</td>
<td>-</td>
<td>0.53 (650mg)</td>
<td>0.38 (500mg)</td>
</tr>
<tr>
<td>4</td>
<td>1.0 (500mg)</td>
<td>-</td>
<td>0.54 (450mg)</td>
<td>0.33 (200mg)</td>
<td>0.85 (650mg)</td>
<td>0.45 (500mg)</td>
</tr>
<tr>
<td>Mean (q.6h)</td>
<td>0.65</td>
<td>0.73</td>
<td>1.14</td>
<td>0.33</td>
<td>0.65</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Mean leukocyte cystine for all patients = 0.65
# Phase 3

## White Cell Cystine Levels on q12h EC-Cystagon

One month after Discharge

<table>
<thead>
<tr>
<th>Week</th>
<th>N</th>
<th>L</th>
<th>E</th>
<th>J</th>
<th>P</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.4 (1000mg)</td>
<td>0.55 (600mg)</td>
<td>- (900mg)</td>
<td>0.72 (400mg)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>0.73 (600mg)</td>
<td>0.9 (600mg)</td>
<td>- (900mg)</td>
<td>0.21 (400mg)</td>
<td>0.28 (1000mg)</td>
<td>0.30 (650mg)</td>
</tr>
<tr>
<td>8</td>
<td>0.77 (600mg)</td>
<td>1.29 (300mg)</td>
<td>0.23 (450mg)</td>
<td>0.52 (400mg)</td>
<td>0.1 (1000mg)</td>
<td>0.12 (650mg)</td>
</tr>
<tr>
<td>9</td>
<td>0.42 (600mg)</td>
<td>0.57 (300mg)</td>
<td>0.33 (450mg)</td>
<td>0.23 (400mg)</td>
<td>0.44 (600mg)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.58</td>
<td>0.83</td>
<td>0.28</td>
<td>0.42</td>
<td>0.27</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Mean leukocyte cystine for all patients = 0.43
Symptoms on Double Dose EC-Cystagon

- Abdominal pain
- Nausea / Vomiting
- Lethargy
- Odor

- Nocturnal wetting improved in two.

Improved with dose reduction (60-70%)
# White Cell Cystine Levels on q12h EC-Cystagon

## Continued Therapy in Two Children

**“Good”**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>L</th>
<th>E</th>
<th>J</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>1.08 (500mg)</td>
<td></td>
<td></td>
<td>0.13 (700mg)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.36 (600mg)</td>
<td></td>
<td></td>
<td>0.8 (700mg)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>2.35 (550mg)</td>
<td></td>
<td></td>
<td>1.1 (700mg)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>0.28 (650mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>0.36 (600mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean q12h</td>
<td>0.88 (600mg)</td>
<td></td>
<td></td>
<td></td>
<td>0.67 (700mg)</td>
</tr>
</tbody>
</table>

**“Odd”**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>L</th>
<th>E</th>
<th>J</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12</td>
<td>1.08 (500mg)</td>
<td></td>
<td></td>
<td>0.13 (700mg)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.36 (600mg)</td>
<td></td>
<td></td>
<td>0.8 (700mg)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>2.35 (550mg)</td>
<td></td>
<td></td>
<td>1.1 (700mg)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>0.28 (650mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>0.36 (600mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean q12h</td>
<td>0.88 (600mg)</td>
<td></td>
<td></td>
<td></td>
<td>0.67 (700mg)</td>
</tr>
</tbody>
</table>
Summary

- Enteric-release Cystagon appears to work when given twice daily
- Lower dose of EC-Cystagon (60-70% previous total dose)
- Titrate dose according to white cell cystine levels and symptoms
- Subjects able to tolerate the EC-Cystagon well
Future Plans

- Complete present study
- Follow patients on EC-Cystagon for 1 year
- Measure white cell cystine and cysteamine 24 hr profiles on regular twice daily therapy.
- Develop better formulation
Acknowledge:

- Children and parents
- Jerry Schneider MD
- Meredith Fidler PhD
- Bruce Barshop MD
- John Gangoiti MS
- Jean Aufderheide
- Sara Albani
- Nursing staff of the GCRC

- Cystinosis Research Foundation
“Short cuts usually reflect on the final result”
Possible Factors That Might Influence Plasma Cysteamine Levels

- Rate of gastric emptying
- Empty stomach / pH within the stomach
- Capsules did not open correctly
  - early release in stomach
  - erratic release in SI
- Small intestinal (SI) transit time too fast
  - release into colon
- Drug coating problems with batch-to-batch variation.
- Off regular cysteamine therapy for 2 - 6 days.
White Cell Cystine Profiles After Single Dose

PATIENT F

- PMS day 1
- PMS day 3
- PMS day 5
Mean Cysteamine Profiles in Controls (n=8)

Mean plasma cysteamine concentration

- 450 mg Cystagon
- 450 mg coated Cystagon
- 900 mg coated Cystagon

Time, min: 0, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660, 720

Concentration: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50
White Cell Cystine Profiles After Single Dose

“The Odd”

White Cell Cystine Level

EM_10/16/06
EM_10/18/06
EM_10/20/06

0 3 6 9 12 15 24

time (hours)
White Cell Cystine Profiles After Single Dose

<table>
<thead>
<tr>
<th>PATIENT E</th>
</tr>
</thead>
<tbody>
<tr>
<td>day 1</td>
</tr>
<tr>
<td>day 3</td>
</tr>
<tr>
<td>day 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>time, h</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>value</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
</tbody>
</table>
Gastrin Profile in Single Patient with GI Symptoms

![Gastrin Profile Graph](image)

- **Gastrin levels L**
  - Blue line: day 1
  - Yellow line: day 3
  - Red line: day 5

- **Axes:**
  - Y-axis: Gastrin levels (L)
  - X-axis: Time (min)

- **Legend:**
  - Blue: day 1
  - Yellow: day 3
  - Red: day 5
Summary- Gastric Acid

- Proton pump inhibitor drugs (PPI’s) adequately reduce cysteamine induced acid production.
- PPI’s improve GI symptoms.
- PPI’s are well tolerated.
- PPI’s do not alter cysteamine absorption.
- Not all patients need PPI therapy.