Cysteamine Eyedrops for Cystinosis

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CYSTINOSIS

- AR; 1 in 200,000 births
- Storage of cystine in cells because of genetic defect in transport of cystine out of lysosomes.
- Crystals form in cells and destroy tissues.
<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>None</td>
</tr>
<tr>
<td>Infancy</td>
<td>Renal tubular Fanconi syndrome</td>
</tr>
<tr>
<td></td>
<td>Growth retardation</td>
</tr>
<tr>
<td>Early childhood</td>
<td>Photophobia</td>
</tr>
<tr>
<td>Late childhood</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Adolescence and</td>
<td>Cerebral calcifications, diabetes, diabetes mellitus,</td>
</tr>
<tr>
<td>adulthood</td>
<td>retinal blindness, myopathy, swallowing difficulty</td>
</tr>
</tbody>
</table>
Treatment of Cystinosis

Chemically reacts with cystine to form products that can exit the lysosome and the cell.

HS-CH$_2$-CH$_2$-NH$_2$

CYSTEAMINE
Effects of Oral Cysteamine

- Lowers cystine content of cells and tissues by 90%.
- Retards renal deterioration.
- Enhances growth.
- Prevents late complications of cystinosis.
Oral cysteamine does not dissolve corneal cystine crystals.
Cysteamine eyedrops do dissolve corneal crystals.

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year old</td>
<td><img src="image1" alt="Untreated 3-year old" /> <img src="image2" alt="Treated 3-year old" /></td>
<td></td>
</tr>
<tr>
<td>20-year old</td>
<td><img src="image3" alt="Untreated 20-year old" /> <img src="image4" alt="Treated 20-year old" /></td>
<td></td>
</tr>
</tbody>
</table>
Library of Corneal Crystal Densities
Corneal Crystal Accumulation
Cysteamine Eyedrop Therapy

12 mo  20 mo  32 mo  57 mo
0.25  0.00  2.00  0.00

15 mo  40 mo  43 mo  56 mo
1.00  0.00  0.50  0.00
Cysteamine Eyedrop Therapy

69 mo

85 mo

133 mo

157 mo

3.00

0.00

3.00

0.00

86 mo

109 mo

237 mo

249 mo

3.00

0.00

3.00

0.25
Cysteamine Eyedrop Therapy

262 mo: 3.00
303 mo: 0.25
342 mo: 2.50
354 mo: 0.25
304 mo: 3.00
316 mo: 0.25
394 mo: 3.00
406 mo: 0.25
Cysteamine Eyedrop Therapy
Cysteamine Eyedrops: Timeline

1986: NEI/NICHD show safety and efficacy of cysteamine eyedrops in two children (NEJM).
1986-present: NIH physicians provide eyedrops to cystinosis patients under protocol and IND.
1995-present: Sigma-Tau Pharmaceuticals sponsors drug development.
   - Provides human-use drug to NIH for patients.
   - Prepares NIH clinical data for FDA.
   - Large investment in personnel and money.
2000: NIH publishes natural history of eye crystals.
2010: Sigma-Tau submits IND; FDA fast-tracks it. NIH records now being inspected.
Lessons

- Clinical research is a partnership of investigators, patients, and pharmaceutical companies.
- The FDA cannot approve a drug unless a New Drug Application is filed.
- Knowing the natural history of a disease is an integral part of obtaining approval for a drug.
- There do exist pharmaceutical companies that address the niche market of rare or orphan diseases.
Cysteamine Eyedrops

- Dissolve corneal crystals if begun at any age.
- Cannot treat the band keratopathy once it occurs.
- Relieves the photophobia of cystinosis.
- Moving to New Drug Approval.
Band keratopathy in a 14-year old girl
Transmission EM of conjunctival cell
(Dr. T. Kuwabara)

Scanning EM of liver Kupfer cell
(Dr. Kamal Ishak)
Approved August 15, 1994