Update on the Development of Intravenous Topiramate for Neonatal Seizures

2011 Epilepsy Pipeline Update
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James Cloyd, PharmD
Weaver Endowed Chair-Orphan Drug Development
Director, Center for Orphan Drug Research
College of Pharmacy, University of Minnesota
IV Topiramate Formulation

- **Topiramate**
  - Molecular weight = 339
  - Water solubility = 9.8 mg/ml (practical solubility ≈ 7 mg/ml)
  - Degrades in aqueous solutions

- **Sulfobutyl cyclodextrin (Captisol®, CyDex Pharmaceuticals)**
  - A pharmacological inert substance that can increase the solubility and stability of selected drugs
  - FDA approved (Geodon, Vfend, Abilify)
  - Issue-will require pre-clinical toxicology studies in age-appropriate animals
Cyclodextrins Enhance a Drug’s Water Solubility, Stability in Aqueous Solutions

Topiramate formulation: 10 mg/ml solution dissolved in a 10% w/v Captisol®
Pharmacokinetic & Safety Study in Adult Patients taking Topiramate

- **Aim:** determine bioavailability and safety of IV TPM
  - Bioavailability must be characterized to determine appropriate dosing as patients switch from IV to oral therapy
  - Safety in adults must be shown before children/neonates

- **Methods:**
  - Nonradioactive, stable-labeled technology
  - 25 mg dose of SL IV TPM given in addition to morning dose (n=20)
Pharmacokinetic & Safety Study in Adult Patients

- Results
  - Enrollment
    - 20/20 subjects completed
  - Safety
    - No serious adverse events
    - Adverse events: nausea/vomiting and tingling/numbness in arms and legs
Half life: 28.3 hours
F: 106%
CL: 1.07 L/hr
Vd: 0.68 L/kg
## Mean Topiramate PK Parameters in Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>Inducers</th>
<th>Non-Inducers</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (L/hr)</td>
<td>2.03 +/- 1.07</td>
<td>3.31 +/- 0.64</td>
<td>1.35 +/- 0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.79 +/- 0.22</td>
<td>1.01 +/- 0.20</td>
<td>0.67 +/- 0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>27.6 +/- 9.7</td>
<td>21.2 +/- 7.1</td>
<td>31.1 +/- 9.2</td>
<td>0.023</td>
</tr>
<tr>
<td>CmaxIV (ug/mL)</td>
<td>0.56 +/- 0.15</td>
<td>0.47 +/- 0.08</td>
<td>0.61 +/- 0.16</td>
<td>0.052</td>
</tr>
<tr>
<td>F %</td>
<td>97 +/- 24</td>
<td>97 +/- 25.9</td>
<td>97 +/- 21.2</td>
<td>1</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (hr*ug/mL)</td>
<td>16.0 +/- 7.0</td>
<td>7.8 +/- 1.6</td>
<td>19.8 +/- 5.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Comparisons between inducers and non-inducers
Two-way Crossover Study of Oral and Intravenous Topiramate in Healthy Volunteers

• **Aims:** Determine, in adult healthy volunteers, the IV dose needed to produce equivalent exposure as an oral dose and the safety of the IV TPM formulation

• **Methods**
  – N=12
  – Subjects given single dose of IV and oral TPM. Doses separated by a minimum of 2 weeks
  – 2 subjects received 50 mg
  – 10 subjects received 100 mg
Mean TPM Concentration-Time Profiles in 12 Adult Volunteers

10/10 subjects exhibited CNS effects at end of infusion
No changes in cardio-respiratory function
# Topiramate Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV (mean +/- SD)</th>
<th>Oral (mean +/- SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>1.33 +/- 0.26</td>
<td>1.22 +/- 0.260</td>
<td>0.334</td>
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<tr>
<td>V&lt;sub&gt;d&lt;/sub&gt; (L/kg)</td>
<td>1.06 +/- 0.29</td>
<td>0.94 +/- 0.24</td>
<td>0.279</td>
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<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>42.3 +/- 6.2</td>
<td>41.2 +/- 7.5</td>
<td>0.693</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>n/a</td>
<td>1.35 +/- 0.96</td>
<td>n/a</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ug/mL)</td>
<td>1.99 +/- 0.89</td>
<td>1.80 +/- 0.64</td>
<td>0.542</td>
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<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (hr*ug/mL)</td>
<td>72.6 +/- 21.1</td>
<td>79.1 +/- 26.4</td>
<td>0.536</td>
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<tr>
<td>Bioavailability</td>
<td></td>
<td>1.08</td>
<td></td>
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</tbody>
</table>

*No significant effect of age, height, weight, or sex on t<sub>1/2</sub>, V<sub>d</sub>, CL, or F%*
What Do We Now Know?

- IV TPM is safe at the doses and infusion rates used in our studies.
- IV TPM is stable in 10% Captisol up to 1 yr.
- Onset of pharmacologic effects following IV TPM occurs in minutes.
- PO TPM is consistently and extensively absorbed.

∴ IV doses = PO doses in adults.
Project Timeline

- Fall 2007: Epilepsy Research Foundation grant to fund formulation of IV TPM for patient and healthy volunteer studies
- Summer 2008: TPM-cyclodextrin formulation available, submitted IND (patients) to FDA, FDA Orphan Grant awarded for patient study
- Fall 2008-Winter 2010: Patient study (N=20) started and completed
- Fall 2009-Spring 2010: Healthy volunteer study started and completed
- Fall 2010: Conference call with FDA
- Fall 2010: TRND application submitted to NIH
- Summer 2011: Meet with FDA to determine additional studies needed prior to neonate studies
- Fall 2011: Submit IND (children and neonates)
- 2012-2013: Complete pre-clinical toxicology and older children studies
- 2012: Begin pilot dose ranging and safety study in neonates
- 2014: FDA approval of IV topiramate (CyDex) for use as replacement therapy in older children and adults
- 2014: Begin controlled efficacy and safety neonatal seizure trial