Assessing the Potential for Hepatotoxicity for Combination Therapy of Valproate (VPA) and CBD using Quantitative Systems Toxicology (QST)

DILIsym Correctly Predicts CBD ALT Elevations and Evaluates Interaction Mechanism(s)

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Vinal Lakhani, PhD
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Project Scenario and Goal

- Epidiolex (highly purified CBD) is efficacious in treating seizures associated with Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and Tuberous Sclerosis Complex (TSC).
- In the clinical trials of these patients, ALT elevations were seen in 21% of trial participants taking CBD with concomitant valproate (VPA) compared with 3% in participants not taking VPA [Epidiolex prescription info].
- **GOAL**: To identify the mechanism(s) accounting for the higher incidence of ALT elevation observed during concomitant treatment with VPA and CBD by using a Quantitative Systems Toxicology (QST) model of hepatotoxicity (DILIsym®).
- **HYPOTHESIS**: Increased incidence of ALT elevations was due to VPA and CBD (or metabolites of each) inhibiting mitochondrial respiration.
DILIsym Input Data

Exposure

- Pharmacokinetics

Simulated Frequency & Severity of Liver Injury (ALT)
GastroPlus PBPK Models for VPA and CBD Optimized and Validated Against Clinically Measured Plasma Exposure

**VPA PBPK Model**

**CBD Metabolism & PBPK Model**

Nitsche and Mascher 1982

Taylor 2018

1000 mg BID

1500 mg BID
Parameterization of Hepatotoxicity Mechanisms for Both Compounds was Based on *in vitro* Assay Results

- Mechanistic *in vitro* data were collected for VPA, CBD, and its two main plasma metabolites (7-COOH-CBD, 7-OH-CBD) for three hepatotoxicity mechanisms: production of reactive oxygen stress (ROS), mitochondrial dysfunction, and inhibition of bile acid (BA) transporters.
  - The *in vitro* data were used to determine toxicity parameter values for each compound in DILIsym.

**Assay Evaluating Mitochondrial Toxicity (example: VPA)**

**Assay Evaluating Reactive Oxygen Stress Toxicity (example: CBD)**
VPA Simulations in DILIsym Accurately Predict Frequency and Dynamics of ALT Elevations Observed Clinically

- Simulations of VPA for 15 weeks with dose titration
  - 1st week: 5 mg/kg BID
  - 2nd week: 10 mg/kg BID
  - maintenance dose: 10 mg/kg BID

- Simulations with the mitochondrial biogenesis mechanism show resolution of ALT elevations with continued dosing, which matches clinical observations

- Simulated frequency of ALT elevations (12%) matches clinical observations (5 – 10%) [NIH LiverTox Website]
DILIsym CBD Simulation Results Predict an Exposure-Response Relationship with ALT Elevations

<table>
<thead>
<tr>
<th>CBD Dose</th>
<th>ALT &gt; 3x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 mg/kg BID Fasted</td>
<td>2/285 (0.7%)</td>
</tr>
<tr>
<td>12.5 mg/kg BID Fed</td>
<td>149/285 (52.3%)</td>
</tr>
<tr>
<td>10 mg/kg BID Fed</td>
<td>108/285 (37.9%)</td>
</tr>
<tr>
<td>5 mg/kg BID Fed</td>
<td>24/285 (8.4%)</td>
</tr>
</tbody>
</table>

In a trial of 16 healthy adults receiving 1500 mg/day CBD (fed state), 7 (44%) developed ALT elevations >3x ULN 

[Watkins et. al. 2020]

• Simulations of CBD for 15 weeks with dose titration
  – 1st week: 2.5 mg/kg BID
  – Increase by 2.5 mg/kg BID weekly until maintenance dose reached

• Doses are simulated under entirely “Fasted” or entirely “Fed” conditions

• Simulations predict exposure-dependent ALT elevations
  – Note: the exposure under “Fed” condition is about 5x higher than under “Fasted” condition for the same dose
VPA and CBD Combined Therapy Shows Two Separate Peaks in Simulated ALT

- VPA + CBD concomitant dosing simulated for 15 weeks in DILIsym
- VPA dosed alone for first two weeks; titrated (as outlined before) up to 10 mg/kg BID maintenance dose
  - Maintenance dose reached starting 7th week
  - All CBD doses were under “Fasted” condition
- Beginning on 3rd week, CBD was titrated up to 12.5 mg/kg BID
- Simulated ALT elevations had returned to near baseline levels before CBD dosing began
- After CBD dosing began, a second (less frequent) elevation in ALT levels was predicted
When CBD is Given After VPA Maintenance Achieved, Simulated Toxicity Effects Appear Additive

- **Combined therapy results** are shown above the dashed line
- **Individual therapy results** are reprinted below the dashed line for comparison
- By end of 2nd week, the ALT and bilirubin levels are nearly back to ULN levels
Mechanistic Investigations in SimCohorts Indicate
Strong Sensitivity to Oxidative Stress

- Mechanistic analyses performed using n=46
  lowest body weight SimCohort
  - CBD maintenance dose 12.5 mg/kg BID under
    “Fed” conditions

- Toxicity does not manifest if ROS is turned off

- Parent CBD has largest contribution to
  simulated ALT elevations
  - Metabolites also contribute to simulated toxicity

Simulation Results

<table>
<thead>
<tr>
<th>Mechanisms Off*</th>
<th>Chemical Species Off**</th>
<th>ALT &gt;3x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>24/46</td>
</tr>
<tr>
<td>ROS</td>
<td>None</td>
<td>0/46</td>
</tr>
<tr>
<td>ETCi</td>
<td>None</td>
<td>24/46</td>
</tr>
<tr>
<td>BAi</td>
<td>None</td>
<td>24/46</td>
</tr>
<tr>
<td>None</td>
<td>CBD</td>
<td>11/46</td>
</tr>
<tr>
<td>None</td>
<td>7-COOH-CBD</td>
<td>16/46</td>
</tr>
<tr>
<td>None</td>
<td>7-OH-CBD</td>
<td>23/46</td>
</tr>
</tbody>
</table>

*Mechanisms Off refers to mechanisms that were disabled during the simulation
**Chemical Species Off refers to drug/metabolite species whose toxicity was disabled during the simulation
DILIsym Simulation Results Summary

<table>
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<tr>
<th>Compound</th>
<th>Dose</th>
<th>ALT &gt; 3x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VPA Alone</strong></td>
<td>10 mg/kg BID</td>
<td>33/285 (11.6%)</td>
</tr>
<tr>
<td><strong>CBD Alone</strong></td>
<td>12.5 mg/kg BID Fasted</td>
<td>2/285 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>12.5 mg/kg BID Fed</td>
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<td>24/285 (8.4%)</td>
</tr>
<tr>
<td><strong>VPA + CBD</strong></td>
<td>10 mg/kg BID (VPA)</td>
<td>35/285 (12.3%)</td>
</tr>
<tr>
<td></td>
<td>12.5 mg/kg BID Fasted (CBD)</td>
<td></td>
</tr>
</tbody>
</table>

- Simulation results show an exposure-response relationship between CBD and frequency of ALT elevations
- The DILIsym simulations suggest that interference with mitochondrial respiration does not account for the large increase in frequency of ALT elevations observed in VPA-treated patients who start treatment with CBD