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

Poster #:
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Vinal V Lakhani[1], Grant Generaux[1], Brett A Howell[1], Paul B Watkins[1,2,3], Diane M Longo[1]

[1]DILIsym Services Inc., a Simulations Plus Company, Research Triangle Park, NC, USA

[2]UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, 201 Pharmacy Lane, CB #7569 Kerr Hall, Chapel Hill, NC

[3]UNC Institute for Drug Safety Sciences, University of North Carolina at Chapel Hill, 6 Davis Drive, Research Triangle Park, NC

CONTACT INFORMATION: VLakhani@dilisym.com .

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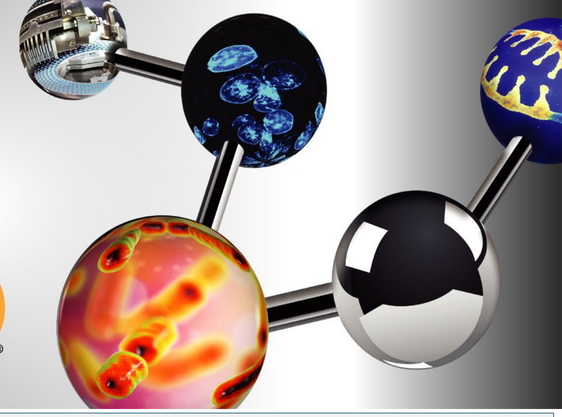
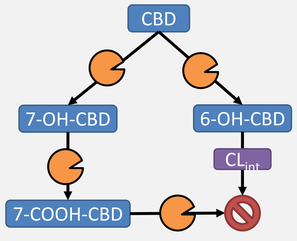


PURPOSE

Highly purified cannabidiol (CBD) (approved as Epidiolex in the US) is efficacious in treating seizures associated with Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and Tuberous Sclerosis Complex (TSC). In Epidiolex clinical trials, frequent and dose-dependent elevations in serum alanine aminotransferase (ALT) were observed. In Epidiolex-treated patients with LGS, DS, or TSC (10 or 20 mg/kg/day dosages), the incidence of ALT elevations >3x the upper limit of normal (ULN) was 21% in participants taking CBD with concomitant valproate (VPA) compared with 3% in participants not taking VPA; this interaction was not pharmacokinetic. **Here, we aimed to identify the mechanism(s) accounting for the higher incidence of ALT elevation observed in individuals treated with VPA and CBD.**

METHODS

We used a Quantitative Systems Toxicology (QST) model of hepatotoxicity (DILIsym®) to test the hypothesis that increased incidence of ALT elevation was due to VPA and CBD (or metabolites of each) inhibiting mitochondrial respiration. Thus, we assessed any effect of CBD, and its two main plasma metabolites (7-COOH-CBD, 7-OH-CBD) using *in vitro* assays that can provide output variables associated with three hepatotoxic mechanisms: production of reactive oxygen stress (ROS), mitochondrial dysfunction, and inhibition of bile acid (BA) transporters. We also verified the ability of VPA to inhibit mitochondrial respiration. These *in vitro* data were used to quantify drug and metabolite effects which, combined with predicted liver exposure values, parameterized the DILIsym mathematical model to predict likelihood of liver toxicity for the following scenarios: administration of VPA only, CBD only, and VPA plus CBD.



This cartoon depicts how the PBPK model of the parent compound (CBD) and its metabolites was organized. Both hydroxy metabolites were produced in parallel using enzyme kinetics (orange "Pac-Man"). The carboxy metabolites was produced from the 7-hydroxy metabolite. The 6-hydroxy was cleared via intrinsic liver clearance, and the 7-carboxy metabolite was cleared using enzyme kinetics (orange "Pac-Man").

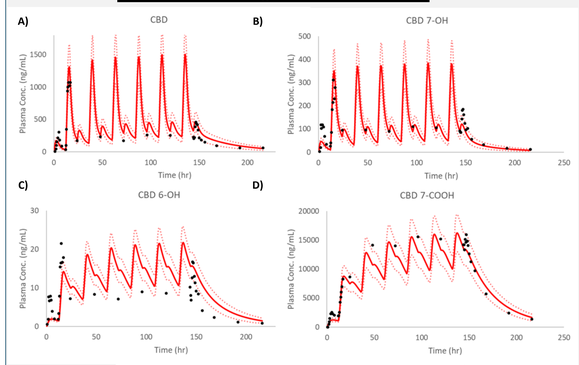
REFERENCES

[1] Valproate **LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].**

[2] Watkins PB, Church RJ, Li J, Knappertz V. Cannabidiol and Abnormal Liver Chemistries in Healthy Adults: Results of a Phase I Clinical Trial. **Clin Pharmacol Ther**. 2020.

RESULTS

CBD 1500 mg BID Alternating Fasted/Dfed

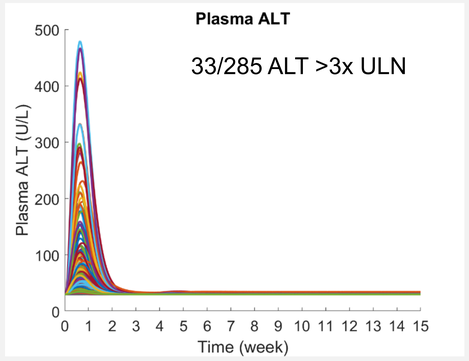


PBPK Model of CBD

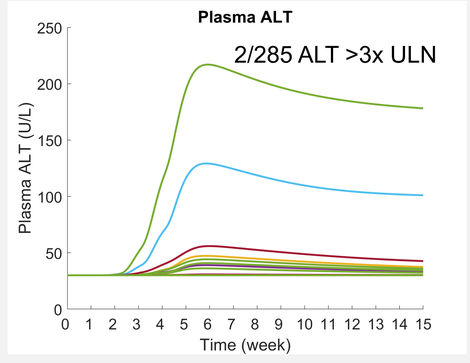
- Model trained on 1500 mg BID clinical data
- Model validated on 750 mg BID clinical data
- Alternated between "Fasted" and "Fed" conditions
- Population-level simulations indicate the PBPK model encompasses the clinical data
- The 6-OH-CBD metabolite has the lowest exposure and was omitted from toxicity analysis. The metabolite is included here to show the breadth of the PBPK model

VPA Simulations

- Simulation results with VPA alone with mitogenesis "on" in the model were consistent with clinical observations (5-10% with ALT >3x ULN [1]): ALT levels were transiently elevated (12% simulated ALT >3x ULN) and resolved upon continued dosing
- Dosing started at 5 mg/kg BID for the 1st week, then increased to the maintenance dose of 10 mg/kg BID during the 2nd week
- Mitochondrial biogenesis was necessary to accurately capture the resolution of ALT elevations



VPA Titrated to 10 mg/kg BID



CBD Titrated to 12.5 mg/kg BID

CBD Simulations

- Simulations of CBD alone predicted delayed dose-dependent ALT elevations consistent with clinical experience [2]
- Dosing started at 2.5 mg/kg BID and increased by 2.5 mg/kg BID every week until the maintenance dose of 12.5 mg/kg BID was reached
- Simulation results shown here under the entirely "Fasted" condition
- Other maintenance doses were simulated under an entirely "Fed" condition, which showed the dose-dependent ALT elevations

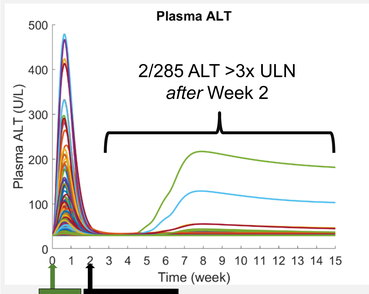
RESULTS

Mechanisms Off*	Chemical Species Off**	ALT >3x ULN
None	None	24/46
ROS	None	0/46
ETCi	None	24/46
BAi	None	24/46
None	CBD	11/46
None	7-COOH-CBD	16/46
None	7-OH-CBD	23/46

*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

Mechanistic Analysis

- ROS production is the dominant hepatotoxicity mechanism underlying simulated ALT elevations
- Parent compound (CBD) plays the largest role in simulated ALT elevations



Concomitant Dosing

VPA was dosed alone for two weeks prior to the addition of CBD. The predicted frequency of ALT elevations (>3x ULN) for CBD added to VPA treatment (2/285 simulated patients) did not differ from the frequency predicted in simulations when only CBD was dosed, largely because the VPA-induced ALT elevations had resolved before the CBD-induced elevations.

CONCLUSIONS

- PBPK modeling of CBD highlighted the importance of paying special attention to the "Fasted" vs "Fed" state
- Mechanistic analysis suggest that ROS production is the dominant hepatotoxicity mechanism, and the parent compound provided the largest contribution to simulated toxicity
- **The DILIsym simulations suggest that interference with mitochondrial respiration does not account for the increased frequency of ALT elevations observed in VPA-treated patients who start treatment with CBD**

DISCLOSURES

Vinal Lakhani, Grant Generaux, Brett Howell, and Diane Longo are employees of DILIsym Services Inc. Paul Watkins chairs the Scientific Advisory Board for the DILI-sim Initiative and serves as a paid consultant for GW Research Ltd.

ACKNOWLEDGEMENTS

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