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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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 Epilepsia clinical trials, frequent and dose-dependent elevations in serum alanine aminotransferase (ALT) were observed. In Epilepsia-treated patients with LGS, DS, or TSC (10, 20, or 25 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 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 CBD added to VPA treatment (2/285 simulated ALT >3x ULN) and resolved before the CBD-induced elevation was due to VPA and CBD (or metabolites of each) inhibiting mitochondrial respiration.

METHODS

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.

REFERENCES

RESULTS
PBPK Model of CBD
- Model trained on 1500 mg BID clinical data
- Model validated on 750 mg BID clinical data
- 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.

VPA Simulations
- Simulation results with VPA alone with mitogenese "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.

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 concomitant VPA dosing.

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

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