Reuse of a published model to support compassionate use of novel drug formulation for a rare disorder

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Objectives: Drug development for rare disorders has complexities beyond those seen with common diseases. With fewer subjects available for clinical trials, designing trials and recruiting enough subjects to reach a meaningful outcome can be difficult. Modeling is advantageous in this context to explore new scenarios without additional clinical testing.

Urea cycle disorders (UCD) are rare genetic disorders that typically manifest shortly after birth and are associated with hyperammonemia [1]. Currently, sodium phenylbutyrate (BUPHENYL, PBA) is used to treat urea cycle disorders by increasing ammonia excretion into the urine. The drug is given with food since BUPHENYL has a bitter taste which has been cited as a impediment to patient compliance [2]. Lowering the sodium phenylbutyrate dose would provide a health benefit to patients by reducing sodium intake. Recent data have shown that sodium phenylbutyrate achieves higher and more rapid exposure when administered in the fasting state. Acer is developing an immediate release, taste-masked formulation of sodium phenylbutyrate (ACER-001), allowing dosing in the fasting state. A comparison of the effects of ACER-001 (administered in the fasting state) to BUPHENYL (administrated in the fed state) was needed to support an application for compassionate use of ACER-001. Because of the limited number of available clinical trial subjects, modeling was used to compare efficacy and toxicity.

Methods: We implemented a published mechanistic PK/PD model of BUPHENYL in UCD [3] in MATLAB SimBiology and confirmed that the simulated results matched the published outcomes. The model was then extended to incorporate ACER-001 administered in the fasting state. The updated UCD model was used to compare the effects of different doses of BUPHENYL administered in the fed state to corresponding doses of ACER-001 administered in the fasting state. Comparisons were made using two Virtual Patients (VPs) representing an Adult (>18 y) and a Child (3-5 y). The drugs, dosed at a mole equivalent of 0 - 21 g phenylbutyrate (PBA), covered the full dose range approved for PBA use. Simulation outcomes included urinary phenylacetylglutamine (U-PAGN) for efficacy and phenylacetic acid (PAA) Cmax for toxicity.

Results: The ACER-001 PK modeling suggested that increased drug absorption and bioavailability account for its increased exposure when administered in the fasting state. Research with the UCD model showed that fasting administration of ACER-001 increased drug exposure and efficacy measures by 43% in both VPs compared to BUPHENYL. In the Adult VP, none of the evaluated doses of ACER-001 resulted in a PAA concentration above the tolerable range. Due to the Child VP's smaller body size, doses of ACER-001 above 8.5 g PBA daily resulted in a PAA concentration above the tolerable range. In comparison, Buphenyl dosed at 8.5 g did not result in a PAA concentration exceeding the tolerable range.

Conclusions: Consistent with clinical observations, fasting administration of ACER-001 in the UCD model results in increased absorption and bioavailability with increased drug exposure. Fasting administration of ACER-001 is predicted to increase efficacy in proportion to the increased drug exposure, allowing for a 30% decrease in the administered dose while still achieving the same level of efficacy as BUPHENYL. Fasting administration of ACER-001 would allow for a decreased PBA dose, lower sodium intake, and the possibility to administer the drug at more convenient times.

References:

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