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Poster presentation

Using PK and PhysioPD modeling to clarify drug metabolism.

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ABSTRACT

Objectives: Ursodiol (Actigall®) (UDCA) is a bile acid, neither clinically tested nor approved by the FDA for use in pediatric patients, but it is being used to treat pediatric cholestasis. A microdosing study, using Accelerator Mass Spectrometry (AMS) was conducted to study the pharmacokinetics of UDCA in neonates. In addition to establishing the utility of AMS for PK analysis and creating a PK model for this population, the goal of this investigation was to gain insight into the mechanisms underlying PK variability, which is suspected to play a role in the wide variation in clinical efficacy. *Methods*: Concentration-time data were available for 8 infants that received radiolabeled microdoses of 8, 26, and 80 ng UDCA in ascending order, at 48-hour intervals (Cohort I, n=5) or a single, 80 ng radiolabeled dose in combination with 40 mg/kg unlabeled dose (Cohort II, n=3). Samples were analyzed with AMS. A total of 111 concentration-time data points were available for the analysis. We combined a mixed-effect, compartmental, PK modeling approach and a mechanistic, physiological (PhysioPD™) modeling approach, which incorporated data from a metabolomic analysis of bile acid metabolites. *Results*: The AMS data for UDCA concentrations were best described with a 2-compartment PK model. A PhysioPD model of bile acid metabolism was built based on public literature describing the mechanisms of bile acid metabolism. An important data source was metabolomic data, which were used to define bile acid state concentrations. The PhysioPD model could reproduce the UDCA concentration time-course data, based on its mechanistic representation of bile acid metabolism. Sensitivity analysis in the PhysioPD model identified the pathway most likely responsible for the significant PK variability. The pathway includes two transporters with known polymorphisms, which are strongly suspected to play a role in the variability in clinical efficacy.

Conclusions: The PK model was able to describe the data and observed variability, and the PhysioPD model offered insights into the cause of the interindividual variability. This will enable more focused future studies to investigate the pharmacokinetics and pharmacodynamics of UDCA.