Development of a Quantitative Systems Toxicology Model to Predict Drug-Induced Liver Injury in Pediatrics

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PURPOSE

Drug-induced liver injury (DILI) is an underrecognized cause of pediatric liver disease which accounts for almost 20% of pediatric acute liver failure cases and is a major reason for liver transplantation in the USA [1]. However, challenges such as inadequate numbers of available subjects, the need for special infrastructure and expertise, and ethical considerations often preclude extensive clinical studies in pediatric populations. In this study, our primary goal was to develop a pediatric representation in a quantitative systems toxicology (QST) modeling platform, DILIsym®, to explore children's relative susceptibility to DILI mediated by bile acid transport inhibition

OBJECTIVES

- To develop a pediatric representation within DILIsym
- To predict susceptibility to bile acid-mediated DILI in pediatric populations

METHODS

- DILIsym is a multi-scale, mathematical model of DILI, which includes key liver cell populations, intracellular biochemical systems, drug exposure, and drug-mediated toxicological mechanisms [2]
- Healthy and diseased adult populations were previously represented within DILIsym
- We represented individuals from four age groups: toddler, preschool, school age, and adolescent (1-, 4-, 10-, and 14-year-old, respectively)
- The PEAR-Physiology™ in GastroPlus® was used to accurately calculate the pediatrics physiology such as body weight, organ weights, organ volumes, and organ blood flow rates
- Parameters representing age-specific expression/activity of transporters and enzymes involved in bile acid homeostasis such as NTCP, MRP3/4, BSEP, and CYP7A1 were optimized based on available clinical ontogeny data [3]–[6] (Figure 1)
- Parameters without available ontogeny data were further optimized to recapitulate the clinically observed range of bile acid concentrations in respective age groups [7]
- A two-week simulation of a hypothetical inhibitor of bile acid transporters was performed in four pediatric individuals and a healthy adult subject to explore the potential impact of age on bile acid-mediated DILI (Figure 3)

RESULTS

- The serum bile acid levels simulated in our pediatric and adult subjects recapitulated the reported, decreasing trend from young to older ages [8]–[10] (Figure 2A)
- Simulated bile acid levels in our representative pediatric individuals aligned reasonably well with the observed data ranges [7]
- The total serum bile acid level in simulated pediatric individuals were within 90%-110% of the average reported values for respective age groups (Figure 2A)
- The serum unconjugated CDCA levels in simulated 1-, 4-, and 10-year-old subjects were higher than the average values, but still stayed in the reported ranges (Figure 2B)
- The serum unconjugated LCA levels in the simulated 10- and 14-year-old subjects were between 65%-82% compared with the average reported values for the respective age groups. In the 1- and 4-year-old subjects, simulated serum LCA levels were slightly overpredicted compared with the average reported values for the respective age groups (Figure 2C)
- The simulated total liver bile acid concentrations in pediatrics (1, 4, 10, and 14 year old subjects) were within 90%-135% compared with the representative healthy adult [11]
- In all age groups, the hypothetical inhibitor of bile acid transporters led to similar levels of hepatic bile acid accumulation, reduction of liver ATP, decline of fraction viable hepatocytes, and increase in plasma ALT; these toxicity responses occurred slightly quicker in pediatrics than in adults, but the magnitude of responses was comparable between pediatrics and the healthy adult (Figure 3)

CONCLUSIONS

- Four pediatric individuals (1- ,4- ,10-, and 14-year-old subjects) represented in DILIsym recapitulated observed serum bile acid profiles reasonably well [7]
- The QST modeling approach leveraging known physiology and available clinical data paves the path towards predictions of DILI in pediatrics

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The QST modeling approach leveraging known physiology and available clinical data paves the path towards predictions of DILI in pediatrics

NO AGE-DEPENDENT CHANGE AFTER BIRTH SEEN IN NTCP AND BSEP [3,4]. MRP3 PROTEIN ABUNDANCE LOWER IN INFANTS AND ADOLESCENTS THAN IN ADULTS [6]

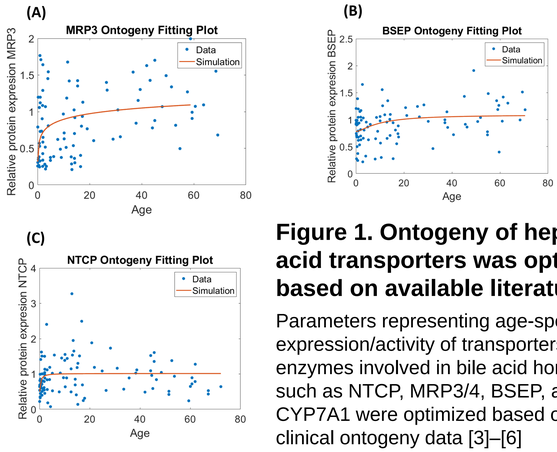

Figure 1. Ontogeny of hepatic bile acid transporters was optimized based on available literature data

Parameters representing age-specific expression/activity of transporters and enzymes involved in bile acid homeostasis such as NTCP, MRP3/4, BSEP, and CYP7A1 were optimized based on available clinical ontogeny data [3]–[6]

SIMULATED BILE ACID LEVELS IN REPRESENTATIVE PEDIATRIC INDIVIDUALS ALIGNED REASONABLY WELL WITH THE OBSERVED DATA RANGES

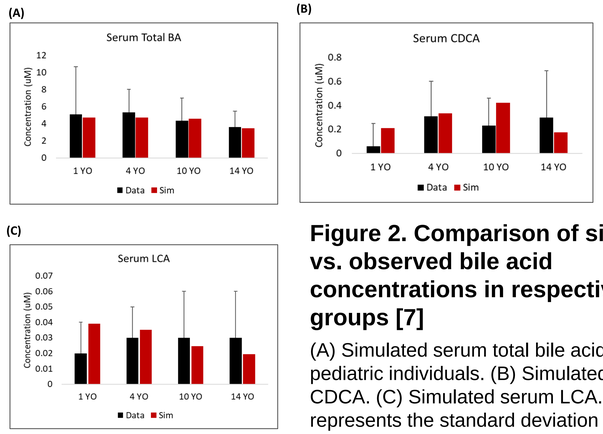

Figure 2. Comparison of simulated vs. observed bile acid concentrations in respective age groups [7]

(A) Simulated serum total bile acids in four pediatric individuals. (B) Simulated serum CDCA. (C) Simulated serum LCA. Error bar represents the standard deviation

THE HYPOTHETICAL INHIBITOR OF BILE ACID TRANSPORTERS LED TO SIMILAR LEVELS OF HEPATIC TOXICITY. THE RESPONSES OCCUR SLIGHTLY QUICKER IN PEDIATRICS THAN IN ADULTS

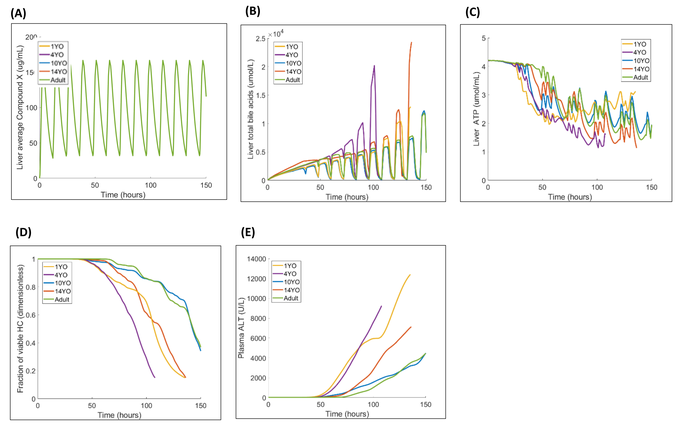

Figure 3. Comparison of simulated hepatotoxicity responses for adult and four pediatric individuals (1-, 4-, 10-, 14-year-old) using a hypothetical inhibitor of bile acid transporters

Simulations using a hypothetical inhibitor of bile acid transporters with competitive NTCP inhibition (Ki=126.5 umol/L), mixed BSEP inhibition (BSEP Ki = 2.4 umol/L, BSEP alpha Ki=2.4), and mixed basolateral efflux transporter inhibition (basolateral Ki = 12.9 umol/L, basolateral alpha Ki = 2.1) combined with a dynamic liver concentration-time profile (A) lead to the accumulation of bile acids in the liver (B), reduction of liver ATP (C), decrease in the viable fraction of all hepatocytes (D), and increase in plasma ALT (E) in four pediatric individuals and a representative healthy adult

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