

Objectives

- Characterize the PK of ursodiol in newborn.
- Demonstrate the usefulness of AMS as a tool for studying PK in neonates
- Create a physiological model of bile acid trafficking in infants.

Background

Pediatric Drug Development

Children are physiologically different from adults; therefore, drug studies conducted in adult populations cannot be simply extrapolated to pediatric populations. The Pediatric Research Equity Act (PREA) authorized the US FDA to require pediatric studies of new drugs that are likely to be used in a substantial number of children. However, many new drug applications still do not adequately address pediatric assessment, and little or no pediatric data exists for drugs approved before PREA. As a result, most medicines are prescribed to children in an off-label manner, with dosages extrapolated from adult data through body weight and surface-area calculations. This lack of pharmacokinetic information can result in adverse effects due to high doses, or suboptimal benefit due to inadequate doses.

One of the many reasons for the dearth of clinical drug testing in newborns is a lack of sensitive and non-invasive tools to support clinical trials. The volume of blood necessary for pharmacokinetic studies, typically 100 to 500 ml per study in adults, presents a major obstacle to the study of pharmacokinetics in neonates.

AMS

Accelerator Mass Spectrometry (AMS), commonly used for fossil dating, is an extremely sensitive way to measure carbon-14 (¹⁴C). It offers sensitivity several orders of magnitude greater than conventional drug assay methods, enabling detection of ¹⁴C-labeled drugs in blood volumes of microliters rather than milliliters.

Cholestasis

Neonatal cholestasis (reduction of the normal flow of bile from the liver to the small intestine) is a common affliction of premature neonates admitted to the neonatal intensive care unit. Ursodiol (Actigal®), an endogenously produced bile acid, is approved to treat cholestasis in adults. Ursodiol (UDCA), while not approved by the FDA for use in pediatric patients, is frequently used to treat neonatal cholestasis.

The mechanism of action of ursodiol for treatment of cholestasis in neonates is unknown. Its efficacy varies widely from patient to patient. The pharmacokinetics of ursodiol in neonates, which may explain its wide variation in efficacy, have never been characterized. Measurement of UDCA pharmacokinetics (PK) requires differentiating between endogenous and exogenous compound by using a labeled tracer. This is the first clinical study of UDCA PK in neonates.

Ursodiol (ursodeoxycholic acid) is a normal part of human bile

Ursodiol is used to treat

- Gallstones
- Primary biliary cirrhosis
- Biliary atresia
- Parenteral nutrition-associated cholestasis

In adults, Ursodiol functions by

- Inhibiting cholesterol absorption
- Suppressing cholesterol synthesis, secretion
- Solubilizing cholesterol
- Reducing bile viscosity
- Increasing bile flow

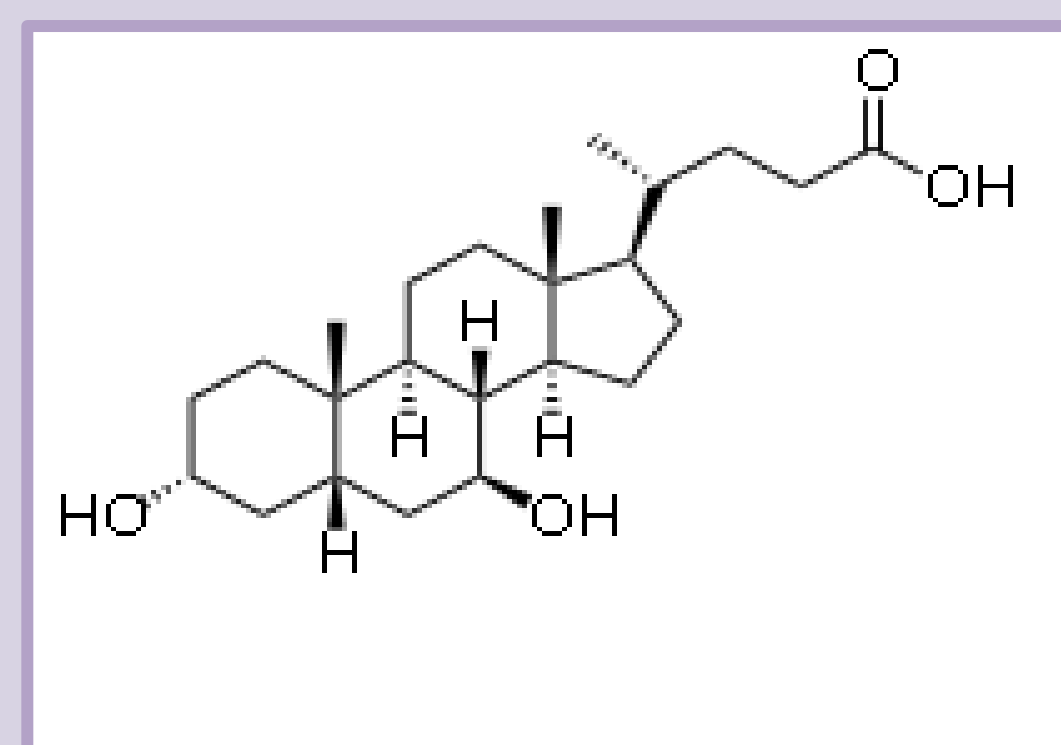


Figure 2. Structure of Ursodiol

References

1. Hepner, G.W. and L.M. Demers, Dynamics of the enterohepatic circulation of the glycine conjugates of cholic, chenodeoxycholic, deoxycholic, and sulfolithocholic acid in man. *Gastroenterology*, 1977. 72(3): p. 499-501.
2. LaRusso, N.F., et al., Dynamics of the enterohepatic circulation of bile acids. Postprandial serum concentrations of conjugates of cholic acid in health, cholecystectomized patients, and patients with bile acid malabsorption. *N Engl J Med*, 1974. 291(14): p. 689-92.
3. Hofmann, A.F., et al., Description and simulation of a physiological pharmacokinetic model for the metabolism and enterohepatic circulation of bile acids in man. *Cholic acid in healthy man. J Clin Invest*, 1983. 71(4): p. 1003-22.

Clinical Trial

This Study was approved by the Loma Linda University Institutional Review Board and FDA-registered Radioactive Drug Research Committee. The study drug was synthesized in a radiochemistry laboratory (Moravek Biochemicals).

Eligibility Criteria:

- Neonates admitted to the LLUCH Neonatal Intensive Care Unit
- No cholestasis
- Weight ≥ 1,900 g
- Vascular indwelling catheter for multiple blood draws
- Nasogastric tube in place
- Hemoglobin > 11 g/dl

Table 1. Subject demographics

Patient Demographics	(n=5)
Gestational Age (weeks)	36 (35-40)
Weight at Study Entry (grams)	2,755 (1,910-3,180)
Height (cm)	45 (42-47)
Body Surface Area (m ²) Haycock et al.	0.189 (0.151-0.208)
Gender (n - M/F)	5 (3/2)
Age at Study Entry (days)	2 (1-6)

Exclusion Criteria:

- Major gastrointestinal congenital anomalies
- Neonatal hepatitis
- Anatomic evidence of bile duct obstruction (biliary atresia)
- Choledocal cyst
- Symptoms suggestive of cystic fibrosis

Study Protocol:

- ¹⁴C-ursodiol was administered to neonates via NG tube in three different doses (1, 3.3, or 10 nanoCuries of radioactivity; 8, 26, or 80 nanograms of ursodiol) separated by intervals of 48 hrs.
- Blood samples (0.25 ml each) were drawn ≤ 0.5 hrs before each dose
- administration, then again at 0.5, 1.5, 3, 6, 12, and 24 hrs after each dose
- Blood samples were centrifuged to separate serum from RBCs and then stored separately at -80° C until AMS analysis.
- Patient 4 was withdrawn from the study after the 2nd dose due to discharge, and Patient 5 was withdrawn after the 2nd dose due to withdrawn parental consent.

Pharmacokinetic Analysis

- Non-compartmental analysis was conducted in PK solver.
- Compartmental analysis was conducted in Nonmem.
- PhysioPD models were built using JDesigner in the Systems Biology Workbench. Data for the model were compiled from literature¹⁻³.

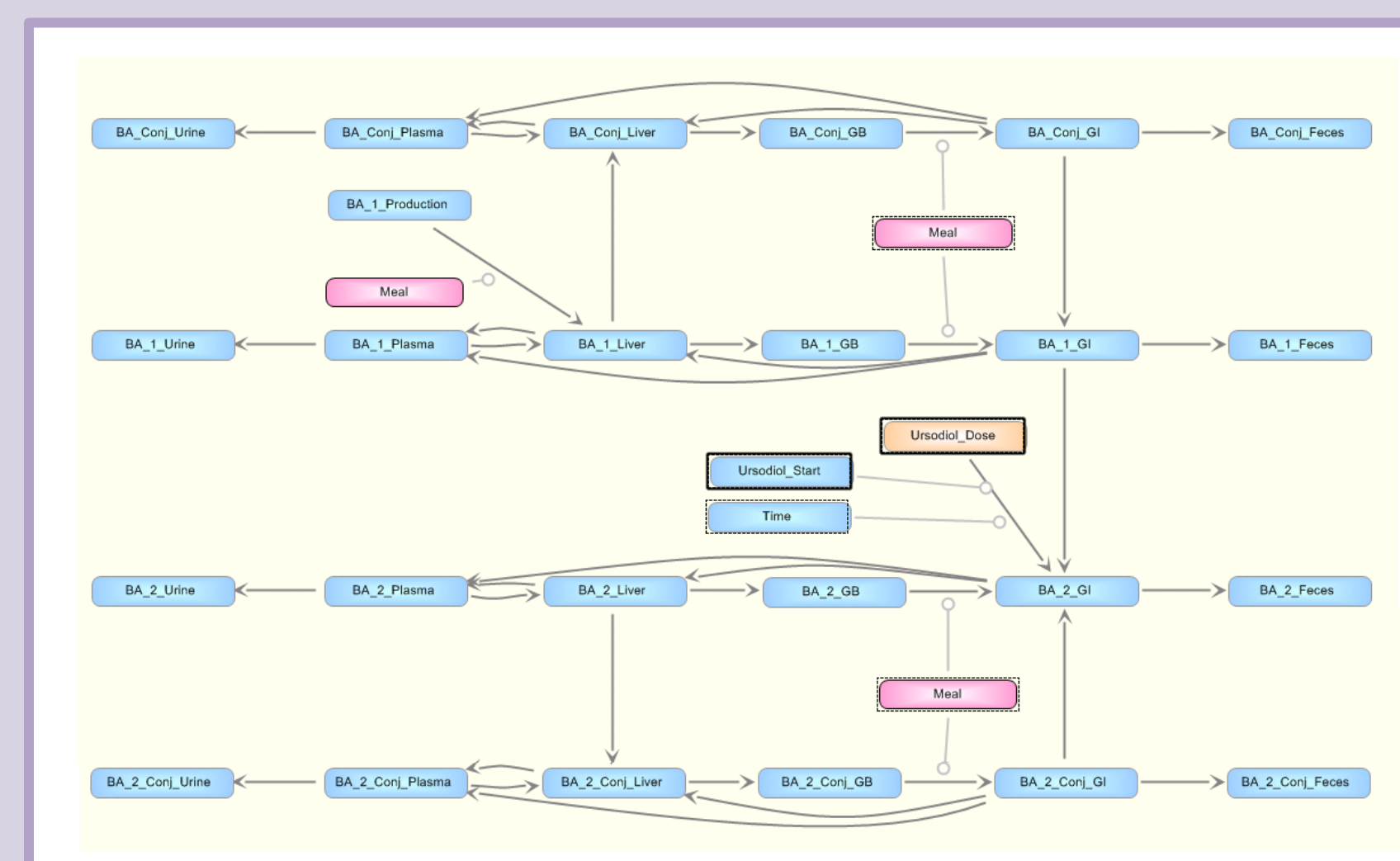


Figure 3. Graphical PhysioMap® of the mathematical model of adult bile acid metabolism and ursodiol pharmacokinetics.

To evaluate the effects of ursodiol on bile acid kinetics, a PhysioPD® model of adult bile acid metabolism has been developed. This model should permit us to evaluate the PK/PD of ursodiol in adults and estimate a PK parameters for the compartmental model of drug. The parameters within the model will then be modified to infant bile metabolism and compared with the PK model outlined in this poster.

Results

Initial evaluation of the data showed that while the doses administered were extremely small, the lowest measured drug concentration was significantly higher than the lower limits of quantification (LLOQ). This indicates that the total amount of labeled drug administered in future studies can be reduced, thus lowering the label exposure in newborns. Furthermore, smaller sample volumes may be needed in future clinical studies.

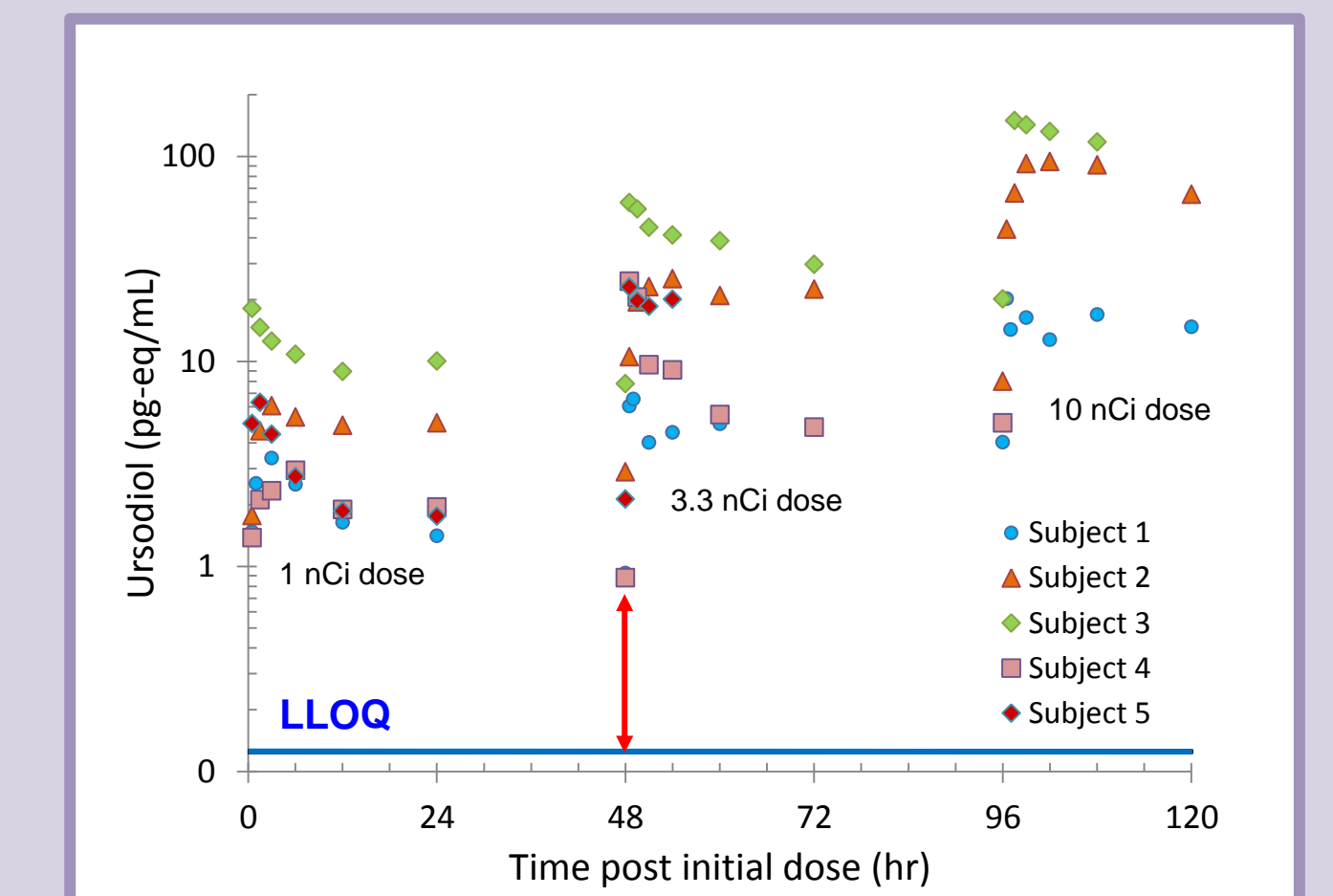


Figure 4. Ursodiol concentration compared to lower limit of quantification. Difference is shown as a red arrow.

Non-compartmental Analysis

Non-compartmental analysis (NCA) was conducted on the drug concentration data for the 8 ng dose. Each subject was evaluated separately and the results for all five subjects included in the analysis. A large variability was observed in the estimated parameters.

Table 2. NCA results

Parameter	Unit	Median	Mean	SD
t _{1/2}	h	42.95	44.13	14.15
t _{max}	h	3.00	2.70	2.17
C _{max}	ng/L	6.08	7.37	6.21
t _{lag}	h	0	0	0
AUC 0-inf	pg/ml*h	226.45	417.72	452.79
V _z /F	L	1.96	2.05	1.19
CL/F	L/hr	0.035	0.038	0.026

Compartmental Analysis

Table 3. Population PK parameters

Parameter	Unit	Value	RSE
K _a	h ⁻¹	1.65	0.76
CL	L/hr	0.0216	0.39
V ₂	L	0.935	0.94
Q	L/hr	1.24	0.76
V ₃	L	1.21	0.19
IV CL		0.76	0.68
IV V ₂		1.2	0.9
IV V ₃		0.86	0.5

Mixed effect modeling identified a 2-compartment model as the best fit of the data, as can be seen in various diagnostic graphs below. Furthermore, there was a generally good agreement with the NCA results of apparent CL and V values. Similar to the NCA results, large interindividual variability in the PK parameters was identified.

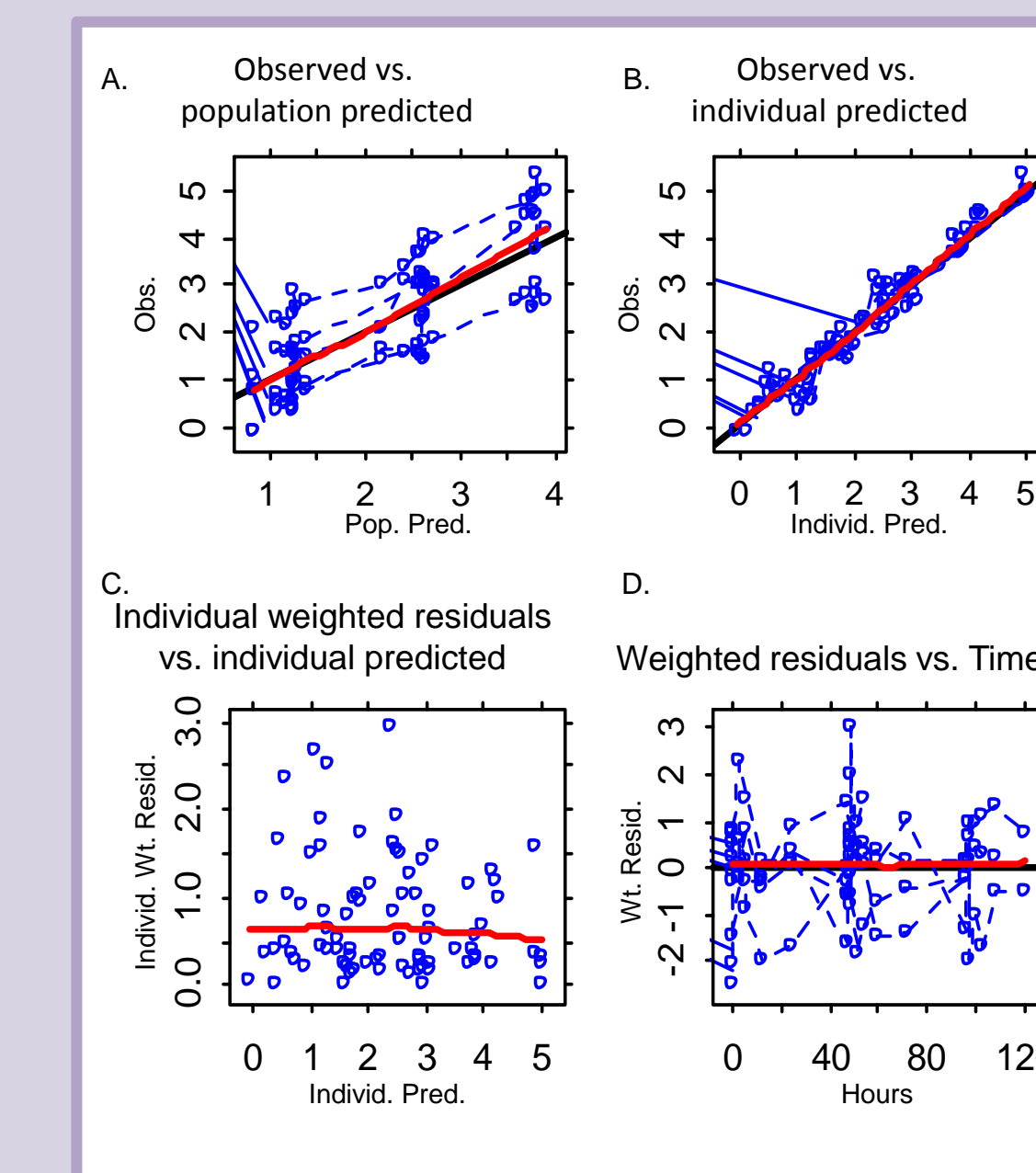


Figure 5. Comparison of observed versus predicted values for the population model is variable as expected but clearly shows a trend (A). Comparison of the individual fit models with data shows a reasonable fit and trend (B). Comparison of the weighted residuals and either predicted values or time show no trends (C and D).

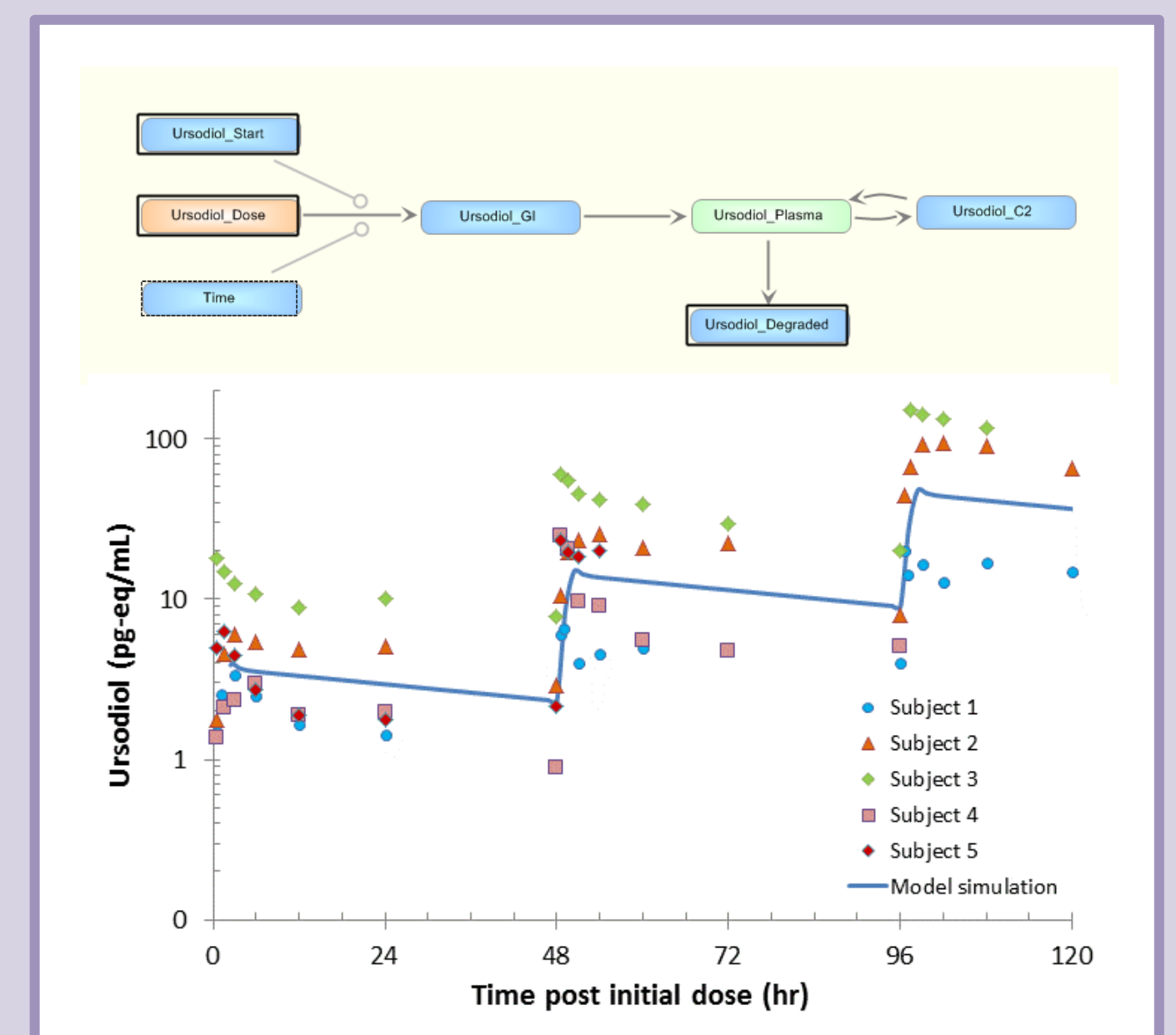


Figure 6. The 2 compartment population model was converted to a JDesigner ODE-based model and compared to the trial data. The blue line is the simulation results from the PK portion of the PhysioPD model plotted with the original data. As expected, the PK model provides a reasonable match with the data. This model is being expanded and incorporated into the PhysioPD model of bile acid kinetics.

Conclusions

- A 2-compartment model fitted the data best.
- AMS can be used to study complicated PK in neonates.
- The sample volume and dose of labeled ursodiol can be lowered for any future studies and still provide measurable data.
- A physiological model of bile acid trafficking in adults had been developed and is being modified for infants.