

COMPARTMENTAL ANALYSIS OF URSODIOL PK IN NEONATES USING AMS

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BACKGROUND: One of the reasons for the dearth of clinical drug testing in newborns is a lack of sensitive and non-invasive tools to support clinical trials. Most medicines prescribed to children are done off-label, with dosages extrapolated from adult data through body weight and surface-area calculations. Ursodiol (UDCA), while not approved by the FDA for use in newborns, is used to treat pediatric cholestasis. Measurement of UDCA PK requires differentiating between endogenous and exogenous compound by using a labeled tracer. This is the first clinical study of UDCA PK in neonates.

METHODS: In an ongoing UDCA clinical trial on pre-term infants, Accelerator Mass Spectroscopy (AMS), which allows much lower sample volumes and radiological exposure, is used to collect accurate PK measurements. Five subjects in the NICU were given 3 escalating doses of radiolabeled UDCA (8, 26, 80 ng) at 48 hr intervals. Subjects did not have cholestasis and caloric intake was parenteral. Three subjects completed 2 doses, 1 subject completed 2 doses, and 1 subject completed 1 dose.

RESULTS: Non-compartmental analysis, with stripping to remove the effect of earlier doses, showed that the UDCA concentrations were dose-proportional. Compartmental analysis yielded a 3-compartment model with a gall bladder compartment.. The apparent V_{dist} was 145 ± 31 ml; T-half was 20.3 ± 5.5 hr. The model was extended to represent cholestasis and predict changes in bile release.

CONCLUSION: AMS and PK/PD modeling provide validated, essential tools for neonatal PK and trial design. AMS sensitivity allows a significantly lower tracer dose. Low intra-subject variability indicates that AMS provided useful data supporting modeling and insight into UDCA PK. High inter-subject variability implies significant physiological variability between newborns. Modeling suggested several experiments to reduce the variability. The PK model constructed from AMS data can be used to study bile flux in cholestatic patients.