Prediction of Clearance in Children Using a Combined Physiology-based and Enzyme Ontogeny Approach

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INTRODUCTION
Clearance is a critical pharmacokinetic concept for scaling dosage, understanding the risks of drug-drug interactions and environmental risk assessment. Clearance is age-specific and dependent on the physiological maturity and enzymatic ontogeny of the responsible elimination processes [1]. These change dramatically during childhood making clearance assessments difficult. This study aimed to predict clearance through the scaling of various individual elimination pathways in the age range from premature neonates to sub-adults.

METHODS

1. Conversion into Intrinsic Clearances

\[
\frac{CL_{\text{hepatic}}}{Q_u} = \frac{CL_{\text{renal}}}{f_u} = \frac{Q_u}{CL_{\text{cl}200}}
\]

2. Separation into Single Processes

- Hepatic Clearance
  - Cytochrome P450s (CYP1A2, 2E1, 3A4)
  - Glucuronidation (UGT2B7, 1A6)
  - Sulfonation
  - Biliary
- Renal Clearance
  - Glomerular Filtration (GF)
  - Tubular Secretion (TS)

3. Scaling to Children

- Hepatic processes by age, based on in vitro and in vivo studies
- Renal processes by age and weight [2]
- \( f_u \) by age [3]

CONCLUSIONS

- Relative importance of each elimination process altered in children. May be important for drug-drug interactions.
- Method provides a reasonable prediction of clearance in children from premature to subadults and, would be an important aspect of pediatric clinical trial preparation for the guidance of dosing regimens.
- Currently being integrated into the physiology-based pharmacokinetic modeling package, PK-Sim® (Bayer Technology Services GmbH, Leverkusen, Germany)

REFERENCES