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

Compound Sets

Model Development compounds: clearance dominated (>90%) by one process

Test compounds: 2 to 4 clearance processes

Required Information: Adult plasma clearance value, proportion attributed to each clearance process, fraction unbound (f_u)

Procedure

1. Conversion into Intrinsic Clearances

$CL_{hepatic}$: $$CL_H^{INT} = CL_H \frac{Q_H}{Q_H - CL_H} \cdot \frac{1}{f_u}$$

Cl_{renal}: $$CL_R^{INT} = CL_R \cdot \frac{1}{f_u}$$

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]

Sum of all intrinsic clearances = Predicted Intr. Clearance in Child

4. Back-Conversion to Plasma Clearance

based on child's BW, LW, Q_H and predicted f_u [3]

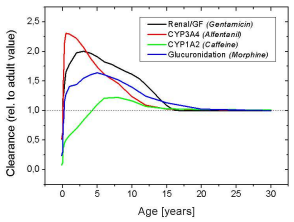

Figure 1. Age dependence of clearance for four compounds used in model development. Relative differences between clearance in adults and children is due to the ontogeny of the clearance process, the protein to which it is bound (albumin or alpha-1-acid glycoprotein) and f_u.

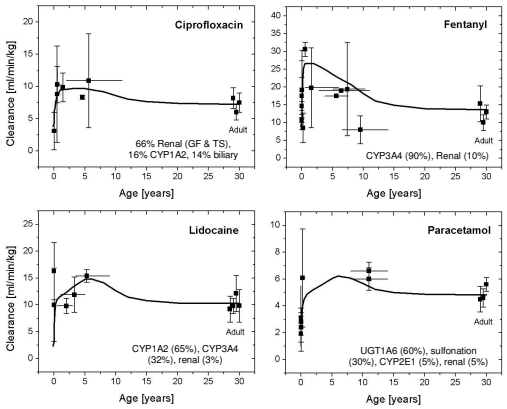

Figure 2. Age dependence of clearance for four test compounds as compared to observed values (■). Vertical lines are standard deviation and horizontal lines are the age range studied.

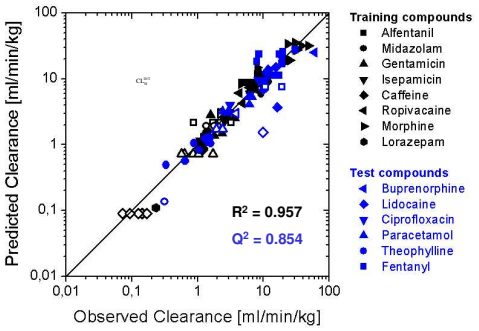

Figure 3. Observed clearance vs. predicted clearance for model development and test compounds. Closed symbols represent term neonates and children. Open symbols represent preterm neonates.

RESULTS

- Similar age-dependent pattern for all compounds (Figures 1 & 2)
- Clearance low for neonates, rise above adult clearance around 6 months and decline to adult levels in the 20's
- High correlation for both model development and test compounds (Figure 3)
- Clearance in premature neonates well-predicted (model development compounds R^2 = 0.921; test compounds Q^2 = 0.810)

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 sub-adults and, would be an important aspect of pediatric clinical trial preparation for the guidance of dosing regimes.
- Currently being integrated into the physiology-based pharmacokinetic modeling package, PK-Sim®
  (Bayer Technology Services GmbH, Leverkusen, Germany)

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