Physiology-based Versus Allometric Scaling Of Clearance In Children: A Comparison

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INTRODUCTION

- Scaling of clearance to children is a prerequisite for the prediction of pharmacokinetics in children
- Allometric scaling is the most common method but has limited use in very young children
- Physiology-based scaling is more difficult but has been shown to predict clearance in children of all ages
- **Objective:** Compare the two clearance scaling methods and determine if the age below which the allometric equation is no longer appropriate, is dependent on the major clearance pathway of the drug

METHODS

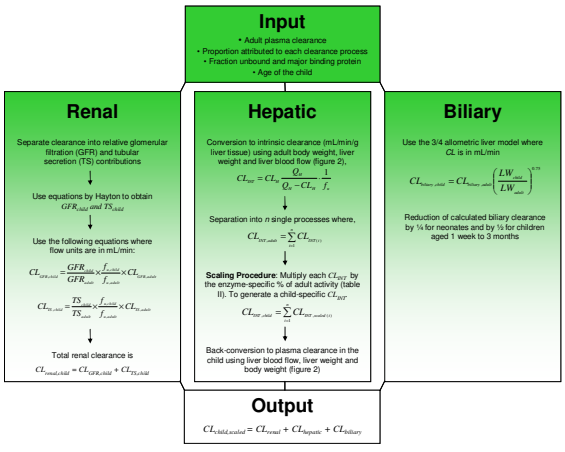
- Age-dependent clearance values were predicted using both the allometric equation and the physiology based method for a set of 15 drugs, eliminated via different routes (renal, hepatic via CYP3A4, CYP1A2, and UGT2B7)

Allometric Approach

Uses the ratio of the child's body weight (BW_{child}) to that of adults (BW_{adult}) to convert total clearance in an adult (CL_{adult}) to total clearance in a child (CL_{child} in L/h) as in the following equation:

$$CL_{child} = CL_{adult} \times \left(\frac{BW_{child}}{BW_{adult}} \right)^{0.75}$$

Physiology-Based Approach [1]



- For each method, the predicted/observed clearance ratio was calculated and plotted against age.
- A visual assessment was made to determine the appropriateness of each method and if they were process specific

RESULTS

Comparison of Methods

- Allometric equation consistently overpredicted clearance in children under the age of about one year. Above, at least, an age of 4, the allometric approach is appropriate (**Figure 2**).
- The physiology-based method accurately predicted clearance in children of all ages except premature neonates.

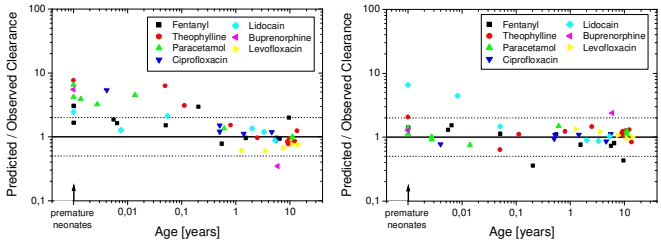


Figure 3. Predicted/observed clearance ratios vs. age using the allometric (A) and physiology-based (B) approach. The solid line indicates a perfect match of predicted and observed values.

Process-Specific Differences

- The extent of the overprediction appears to be process specific (e.g. about 10x for CYP3A4 and only 2-3x for glomerular filtration) (**Figure 3**).
- The age at which the allometric approach accurately predicted clearance was process specific and followed the *in vitro* trends associated with the enzyme specific ontogeny.
  - CYP3A: fully developed by the age of 6 months
  - CYP1A2: the last enzyme to fully develop; between the ages of 1 to 15 years.
  - UGT2B7: fully developed by the age of 6 months
- The passive process of renal filtration was over predicted in children under 2 years of age and over predicted in children older than 2 years using the allometric approach.

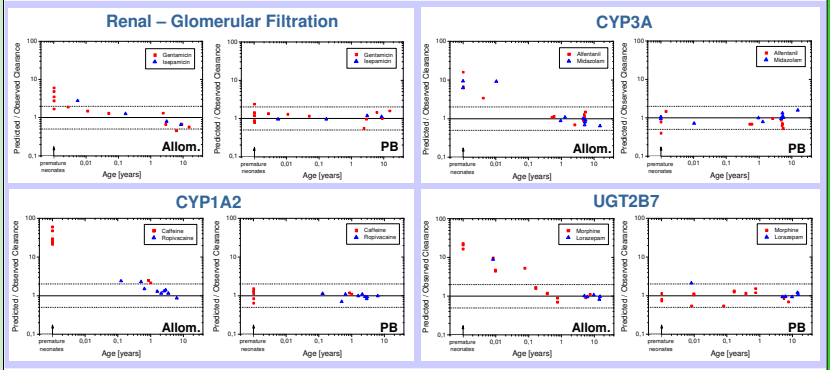


Figure 3. Predicted/observed clearance ratios vs. age using the allometric (Allom.) and physiology-based (PB) approach. The solid line indicates a perfect match of predicted and observed values.

CONCLUSIONS

- **The allometric method is biased (overprediction) when the maturity of the process driving clearance is not fully developed. The extent of bias is process-specific.**
- **For older children, the allometric equation provided an accurate means of scaling clearance for active clearance processes.**
- **Because the physiology-based approach takes into account the maturity of the clearance process, it was appropriate for children from term to 18 years of age.**

[1] Edginton et al. A mechanistic approach to scaling clearance in children. Clinical Pharmacokinetics. *In Press.* (2006)

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