Establishing maturation functions for kidney transporters using a combined population pharmacokinetic and physiology-based pharmacokinetic approach

**Introduction**

Active secretion by kidney transporters largely contributes to the elimination of drugs that are substrates for these transporters, however, there is limited information regarding the maturity of their expression and activity throughout the paediatric age-range [1]. This information could lead to more accurate clearance (CL) predictions for drugs that are renally actively secreted and, ultimately, to improved paediatric drug development.

**Methods**

**Population PK model**

\[
CL_{\text{amoxicillin}} = GFR \times f_u \times \theta_i
\]

**PBPK Kidney sub-model**

\[
CL_{\text{amoxicillin}} = GFR \times f_u \times \theta_i + \frac{(Q_h - GFR) \times f_u \times CL_{\text{INT}} \times OATs}{Q_h + f_u \times CL_{\text{INT}} \times OATs}
\]

**Results**

- The maturation profile for OAT transporters (i.e., \(CL_{\text{INT,OAT}}\)) is best described by a sigmoidal \(E_{\text{max}}\) relationship on the basis of PMA as a covariate (Figure 1).
  - The mature \(CL_{\text{INT,OAT}}\) value is 31 ml/h/g kidney (RSE% of 17%).
  - Half of the mature \(CL_{\text{INT,OAT}}\) value (\(\theta_i\)) is reached at PMA of 74.9 weeks (~8 months) (RSE% of 9%).
- Figure 2 shows the total renal CL of amoxicillin (\(CL_{\text{amoxicillin}}\)) where:
  - The contribution of GFR changes with cBW, PMA and the estimated individual correction factor \(\theta_i\) (Figure 2).
  - The median contribution of active tubular secretion is 29% (range: 11% - 47%) (Figure 2).
  - The individual correction factor for GFR (\(\theta_i\)) of intensive care children is 2.04 (RSE% of 8%).

**Conclusion**

- We used a combined popPK and PBPK approach on clinical data to quantify the in vivo maturation for active tubular secretion for a broad paediatric age-range. This method could be extended to drugs that are substrates for other kidney transporters.
- As direct measurements to quantifying transporters proteins levels throughout the pediatric age-range remains demanding, the presented method is a potential alternative to derive kidney transporters maturation.
- The estimated maturation function for kidney OATs could be used for CL extrapolations of other OAT substrates from adults to children.

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**References:**


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