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

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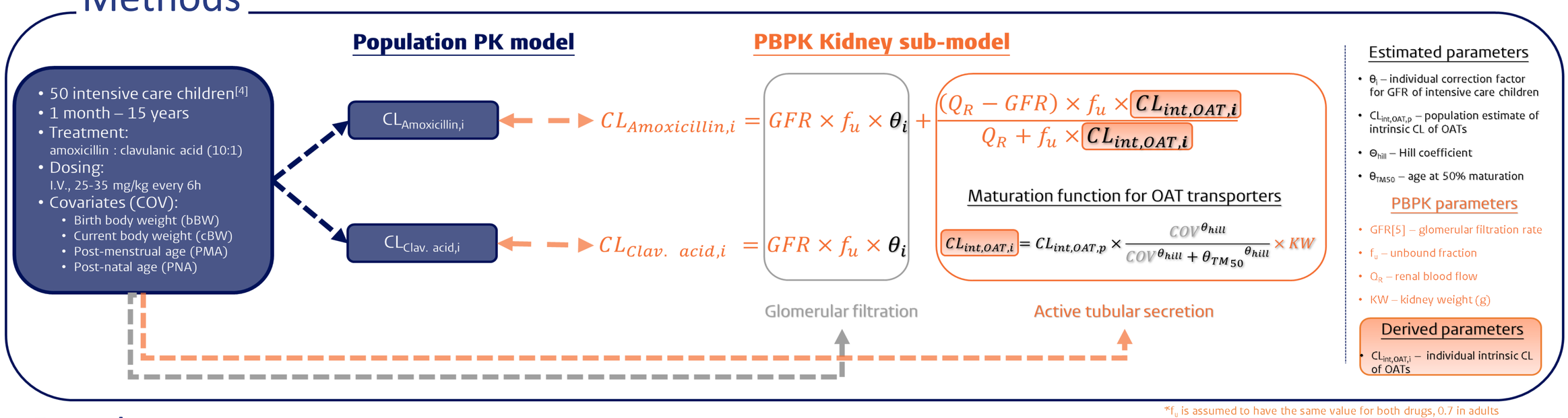
Introduction

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 maturation 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.

Aim

Characterize the maturation of the organic anion transporters 1 and 3 system (OATs) throughout the paediatric age range using clinical PK data from children aged 1 month to 15 years receiving simultaneously clavulanic acid (cleared by glomerular filtration (GF) [2]) and amoxicillin (cleared by GF and active tubular secretion [3]) analysed in a combined population PK and PBPK approach.

Methods

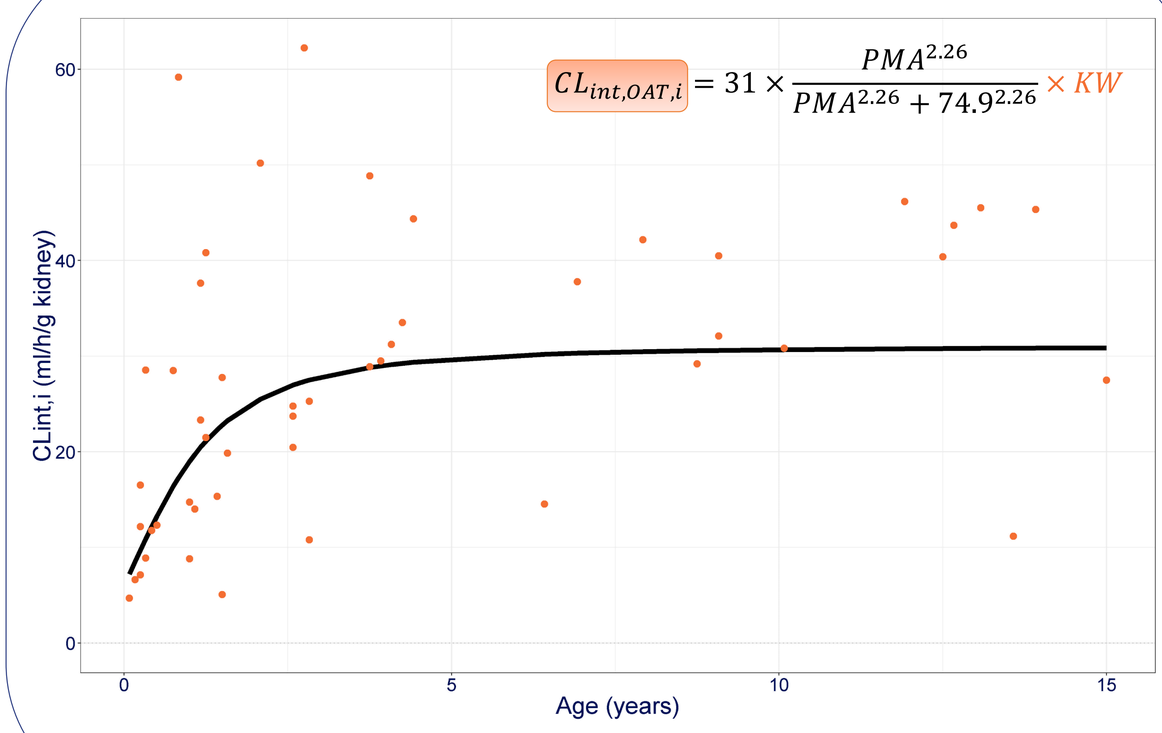


*f_u is assumed to have the same value for both drugs, 0.7 in adults

Results

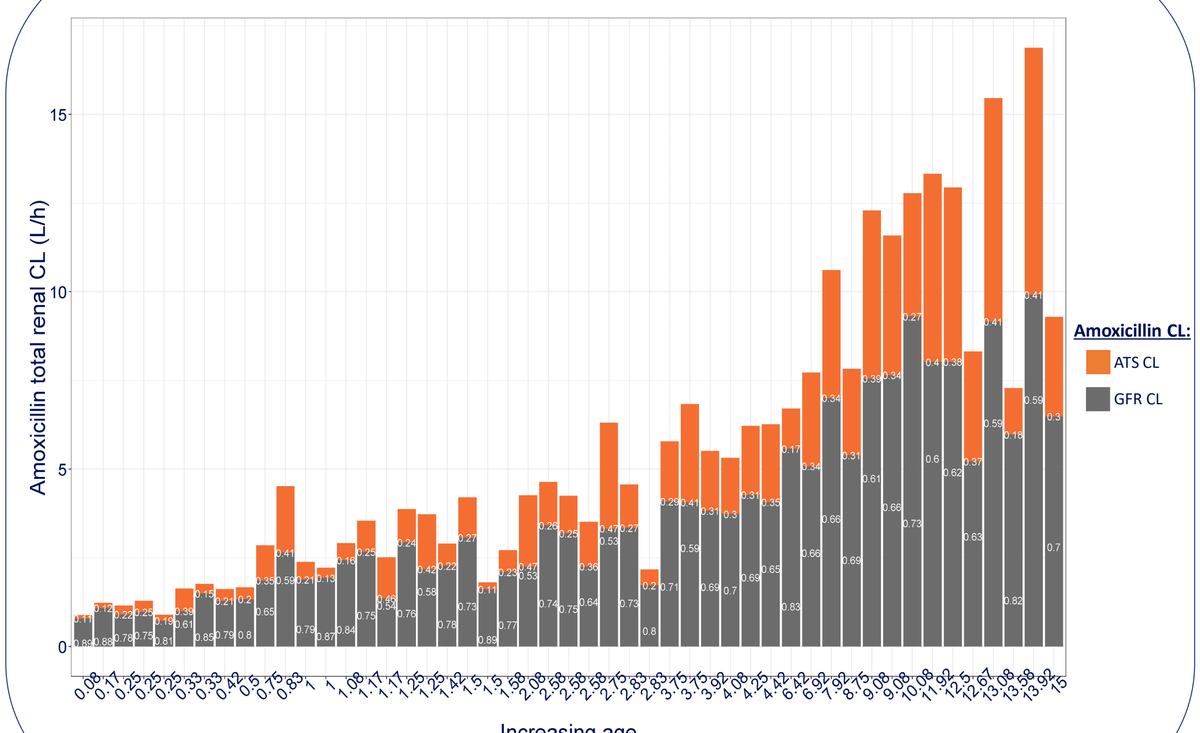
- The maturation profile for OAT transporters (i.e., $CL_{int,OAT,i}$) is best described by a sigmoid E_{max} relationship on the basis of PMA as a covariate (Figure 1).
  - The mature $CL_{int,OAT,p}$ value is 31 ml/h/g kidney (RSE% of 17%).
  - Half of the mature $Cl_{int,OAT,p}$ value (θ_{TM50}) is reached at PMA of 74.9 weeks (~8 months) (RSE% of 9%).
- Figure 2 shows the total renal CL of amoxicillin ($CL_{Amoxicillin,i}$) where:
  - The contribution of GFR changes with cBW , PMA and the estimated individual correction factor θ_i (Figure 2).
  - The median contribution of active tubular secretion is 29% (range: 11% -47%) (Figure 2).
- The individual correction factor for GFR (θ_i) of intensive care children is 2.04 (RSE% of 8%).

Figure 1



Individual intrinsic clearance values (orange) of amoxicillin and maturation function of OATs based on PMA (black) displayed throughout the pediatric age-range.

Figure 2



Contribution of CL through GFR (grey) and through ATS (orange) to total renal CL of amoxicillin for each individual pediatric patient.

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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