Predicting pharmacokinetics for two NSAIDs commonly used in paediatrics using a physiologically-based model: Comparing in vitro data, in vivo data from adults, or their combination as input parameters

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Introduction
Modelling and simulation is becoming an important part of the drug development process and may prevent unnecessary clinical studies or allow their more rational design. This approach has great potential in populations where conducting clinical studies is more difficult such as in paediatrics. In vitro- in vivo (IVIVE) extrapolation of drug clearance (CL) is combined with a physiologically based pharmacokinetic (PBPK) model to allow PK predictions with associated variability. Ibuprofen and diclofenac (two commonly used NSAIDs) are used here to predict pharmacokinetic parameters (AUC and C\text{\text{max}}) from clinical studies in paediatrics.

Aim
To compare three methods of CL\text{\text{int}} determination in paediatrics and choose the best method from:
- in vitro kinetic data (V\text{\text{max}}, K\text{\text{m}})
- in vivo data using a retrograde model
- Combination of in vitro- in vivo model

Methodology

Method C (In Vitro & In Vivo)

K\text{\text{m}} from In Vitro and V\text{\text{max}} from In Vivo
(Note: K\text{\text{m}} in Method B is lacking since drug concentration assumed to be below K\text{\text{m}})

Method A (In Vitro)

Data From rhCYP V\text{\text{max}}/K\text{\text{m}} (\text{\mu mol/ min/ pmol})

Method B (In Vivo)

C\text{\text{max}} /\text{\text{CL}} \rightarrow \text{\text{CL}}\text{\text{int}} (L/h)

Adults Retrograde Model

Figure 1. Summary of the 3 methods used to calculate CL\text{\text{int}} values for use in the minimal paediatric PBPK model.

The studies used for simulation are paediatric studies. Weighted pred: obs ratios are used to compare methods. The following equations were used to calculate CL\text{\text{int}} from iv and Oral in vivo CL values respectively (Method B) are shown below:

\[ CL_{\text{int,IV}} = \frac{Q_{\text{iv}} \times CL_{\text{iv}}}{f_{\text{u,v}} \times (Q_{\text{iv}} - CL_{\text{iv}})} \]

\[ CL_{\text{int,Oral}} = \frac{CL_{\text{po}} \times F_{\text{G}} \times F_{\text{a}}}{f_{\text{u,v}}} \]

Results
Figure 2 shows the results from comparison of observed and predicted AUC and C\text{\text{max}}. The studies for predictive performance were different than those used in model building under retrograde calculations from adult values. Bubble sizes reflect in IBP study- surgery and rheumatoid arthritis in DIC (a factor not accounted for in the model).

- In the paediatric population the in vivo method can predict C\text{\text{max}} more accurately.
Full evaluation of the different CL\text{\text{int}} input methods requires extension of the current analysis to incorporate a range of drugs metabolised by different CYP enzymes.

Conclusion
- The use of the in vitro method was more successful in the prediction of AUC (ratio closest to 1). This suggests that the in vitro metabolic input values used are accurate for IBP and DIC. The discrepancy between observed and predicted values could be resulted from the fact that children under investigation had a concurrent illness (cystic fibrosis

References