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_{max}) from clinical studies in paediatrics.

Aim

To compare three methods of CL_{int} determination in paediatrics and choose the best method from:

- *in vitro* kinetic data (V_{max}, K_m)
- *in vivo* data using a retrograde model
- Combination of *in vitro- in vivo* model

Methodology

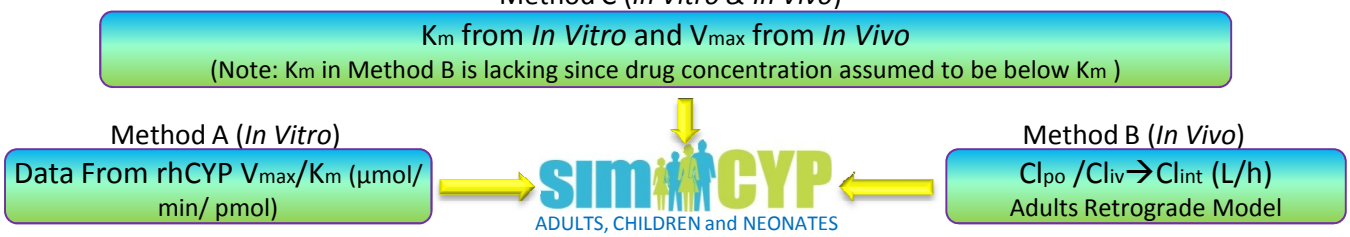

Figure 1. Summary of the 3 methods used to calculate CL_{int} values for use in the minimal paediatric PBPK model.

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

$$CL_{\text{int}\,H} = \frac{Q_H \times CL_{metH}}{fu_B \times (Q_H - CL_{metH})} \qquad CL_{\text{int}\,H} = \frac{CL_{po} \times F_G \times F_a}{fu_B}$$

Results

Figure 2 shows the results from comparison of observed and predicted AUC and Cmax. The studies for predictive performance were different than those used in model building under retrograde calculations from adult values. Bubble sizes reflect the weight of study in terms of subject numbers.

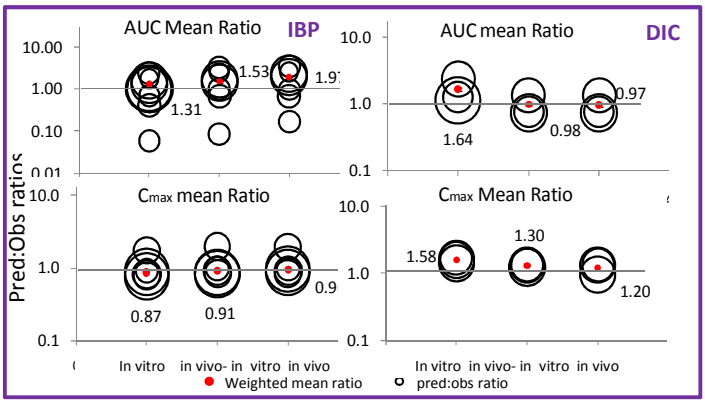

Figure 2. AUC and Cmax ratio arithmetic mean for ibuprofen and Diclofenac in paediatrics using a full PBPK model.

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 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 Cmax more accurate.

Full evaluation of the different CL_{int} input methods requires extension of the current analysis to incorporate a range of drugs metabolised by different CYP enzymes.

References

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