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Toward an improved understanding of oral drug absorption in the paediatric population through physiologically based pharmacokinetic models

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Master thesis, Therapeutic Technology
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INTRODUCTION

In recent years, an increased interest in research into paediatric drug development has highlighted the important role played by physiologically based pharmacokinetic (PBPK) models in conjunction with other biopharmaceutical tools such as *in vitro* tests. Such technology supports development of age-appropriate medicines and helps to ensure that development of paediatric medicines is supported by the tools already available for adult medicines [1]. However, there are many gaps in our knowledge of age-specific changes in gastrointestinal (GI) physiology and a lack of published examples leads to uncertainty on the reliability of PBPK-based predictions of oral drug exposure for the paediatric population (newborns: 0-28 days, infants: 1-23 months, children: 2-12 years). By developing and validating paediatric PBPK models for oral drugs we enrich our knowledge of which extrinsic (drug, food and formulation) or intrinsic (GI physiology) variables are influential and uncover the limitations in our ability to predict [1][2][3].

Goal

The aim of this work is to identify age-specific differences and knowledge gaps in the GI anatomy and physiology that give rise to differences in absorption in the paediatric population compared to adults. A secondary goal is to increase the understanding in the anatomy and physiology of the GI tract in paediatric populations using physiologically based pharmacokinetic (PBPK) modelling, parameter sensitivity analysis (PSA) and in vitro dissolution testing. A further goal in this study is to improve the prediction of drug release and absorption in paediatric patients by optimizing PBPK modelling relevant to paediatric age groups.

Method

A systematic literature research was done to collect the current knowledge regarding: GI pH, volume of GI fluid, bile acids, enzymes, GI surface morphology, GI transit time and permeability. The experimental part in this study was carried out using software GastroPlus (G$^+$). This study was restricted to BCS 1 class compounds. Moreover, the drug products have to be available as an immediate release formulation. An immediate release, a high solubility and permeability allowed us to focus, without additional influence of the drug and drug formulation, on the age-specific GI parameters and processes which affecting the drug absorption. First of all the research platforms was screened for PK studies in adults and in the paediatric population. Once the PK profiles were found, an adult PBPK model was developed and validated using the clinical PK data. Adult models were developed for intravenous (IV) and peroral (PO) application. The developed and precise validated adult PBPK model was extrapolated to the paediatric age range (0-12 years). The simulations were initially run in children, then in infants and finally in newborns. A simulation in the paediatric population means that the adult model was kept, by using the incorporated age-specific scaling in G$^+$. The resulting paediatric PBPK models were evaluated using PK data in the specific population; a discrepancy between the simulation and the *in vivo* data was analysed using PSA and *in vitro* dissolution testing. We carried out *in vitro* dissolution testing to evaluate the influence of volume and composition of gastric and intestinal fluids on the kinetics of drug solubilisation of BCS class 1 compounds. The analysis may help to increase the understanding of the age-specific change in GI parameters and will improve the prediction of drug release and absorption by optimizing the paediatric PBPK model.

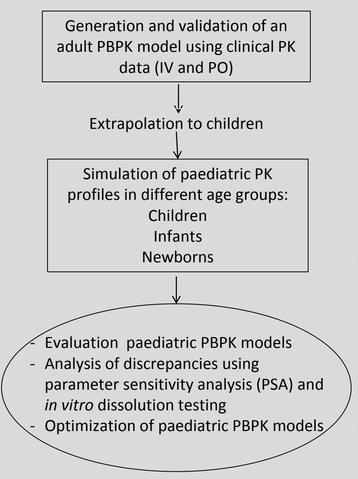

Fig. 1: Schematic workflow for PBPK modelling and simulation.

RESULTS

The prediction of oral absorption of BCS 1 compounds using PBPK modelling is accurate in adults (C_p ratio$_{(Obs/Pred)}$ 0.86-1.31, AUC_{0-t} ratio$_{(Obs/Pred)}$ 0.83-1.05) and 2-12 years old children (C_{max} ratio$_{(Obs/Pred)}$ 0.78-1.34, AUC_{0-t} ratio$_{(Obs/Pred)}$ 0.94-1.50 and t_{max} ratio$_{(Obs/Pred)}$ 0.92-1.43) over a various dose range (Fig. 2). However, a poor prediction was obtained in newborn and infants (0-2 years), as can be seen in Fig. 3 (red line) (C_{max} ratio$_{(Obs/Pred)}$ 0.5-1.49, AUC_{0-t} ratio$_{(Obs/Pred)}$ 0.82-1.64 and t_{max} ratio$_{(Obs/Pred)}$ 0.13-5.40).

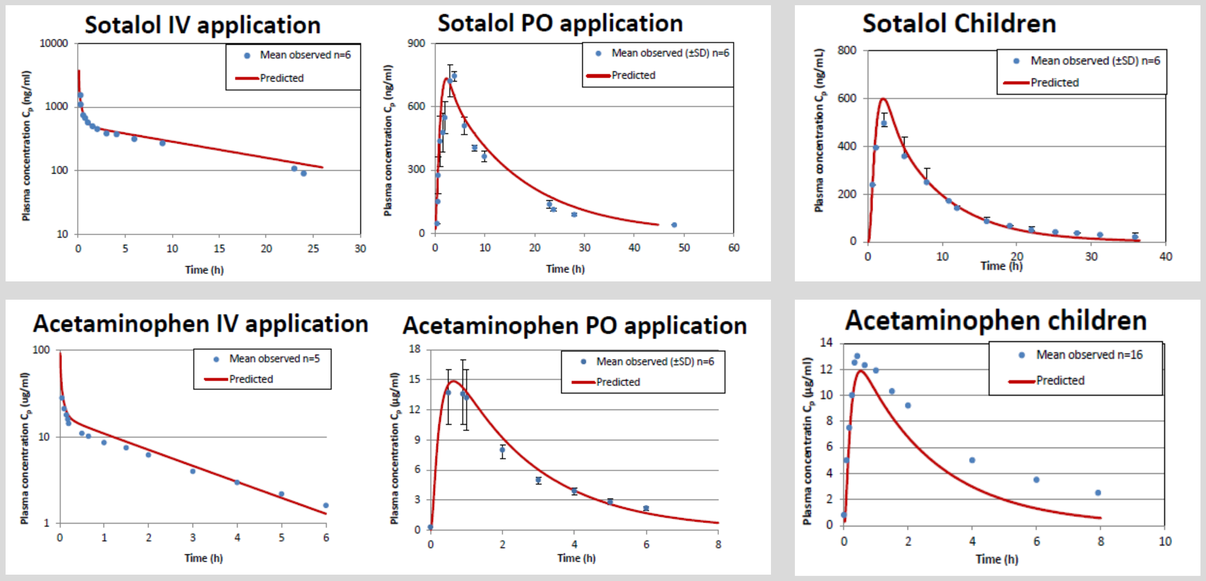

Fig. 2: Comparison of predicted (lines) and observed (dots ±SD) concentrations of IV and PO sotalol and acetaminophen after dosing in adults and PO sotalol and acetaminophen in children.

PSA of the mean ratio of gastric emptying time (GET), stomach pH, duodenal pH, jejunal pH, small intestinal transit time (SITT), permeability, small intestine (SI) radius, SI length, SI fluid volume, dose volume of the drug products, and bile salt solubilisation ratio were carried out. As can be seen in Fig. 3, GET showed a substantial influence on C_{max} and t_{max}, but not on AUC_{0-t} . A prolonged GET leads to a decreased C_{max} and to a increased t_{max}. The other physiological and anatomical parameters showed no influence on drug absorption. Furthermore, over 90% of acetaminophen and sotalol were solubilized within 5 min. No difference was observed between dissolution kinetics in SGF_{sp}, FaSSIF, FeSSIF and formula milk. Therefore, the slower drug absorption in newborns and infants is not related to slower dissolution kinetics. Including the prolonged GET improved the accuracy of the PBPK models in infants and newborns (C_{max} ratio$_{(Obs/Pred)}$ 0.83-1.24, AUC_{0-t} ratio$_{(Obs/Pred)}$ 0.83-1.63 and t_{max} ratio$_{(Obs/Pred)}$ 0.82-1.12).

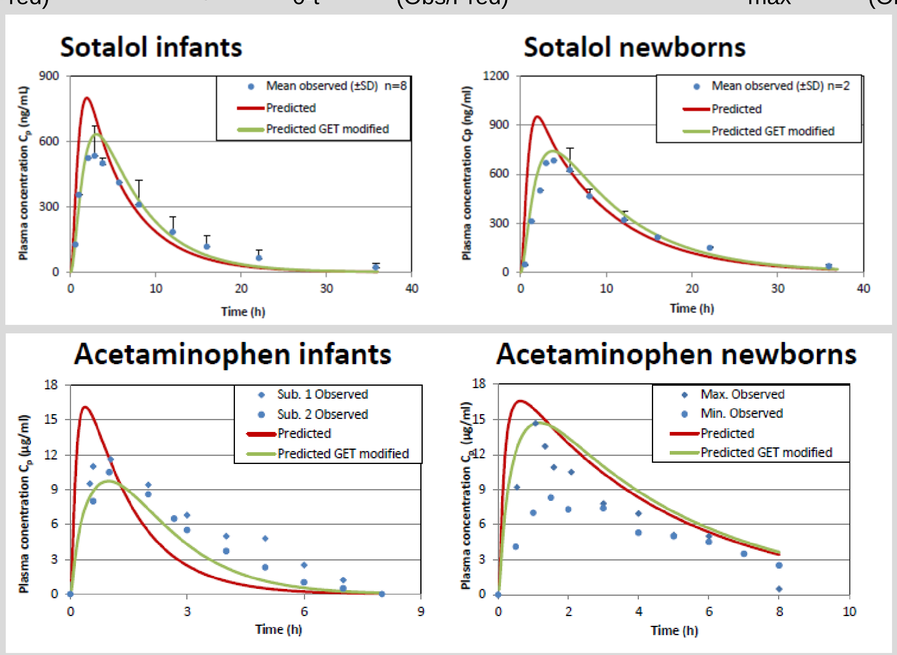

Fig. 3: Comparison of predicted (lines) and observed (dots) plasma concentrations of PO sotalol and acetaminophen after various dosing. Different GET were applied in these simulations, i.e. 0.5 h (red), 0.8 – 1.5 h (orange).

CONCLUSION

There exist significant knowledge gaps in paediatric GI physiology and anatomy. Furthermore, the use of PBPK modelling together with in vitro dissolution testing is an effective strategy for characterizing the anatomical and physiological GI parameters that affect oral drug absorption. The prediction of oral absorption of BCS 1 compounds using PBPK modelling is accurate in adults and 2-12 years old children; However, a poor prediction was obtained in newborn and infants (0-2 years). Including the prolonged GET improved the accuracy of the model. PBPK models simulating the paediatric population need to be further optimized and validated. Evaluating compounds with more complex physico-chemical properties (e.g., poorly water soluble APIs, weak acids/bases) may further increase the understanding of the physiological parameters affecting oral absorption in children.

Reference

[1] Batchelor et al. (2013)
[2] Mooij et al. (2012)
[3] Kaye et al. (2011)