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Predicting Drug Exposure over the Entire Pediatric Age Range

Physiologically-based pharmacokinetic (PBPK) modeling and simulation using Simcyp Pediatric is increasingly being used to accelerate drug development and inform clinical dosing decisions in children

Background

Caution surrounding the routine adoption of pediatric PBPK modeling and simulation is being overcome by the growing appreciation that this approach is not intended as a complete substitute for clinical investigation, but instead is an essential tool to maximize the value of prior information as part of a 'learn-and-confirm' strategy.[1] Increasingly, validation studies are being published highlighting the power of PBPK and its applications in drug development, as well as guiding best practice.

Challenge

Researchers at the University of Florida, working with colleagues at The Children's Hospital of Philadelphia and the US FDA, set out to mechanistically understand APAP metabolism in children and provide a framework for the development and validation of pediatric PBPK models.

Solution

A PBPK model was developed using the Simcyp Simulator, incorporating compound-specific data, pharmacogenetic information and *in vitro* and clinical PK data for adult populations. Using additional clinical data, the adult model was evaluated and shown to consistently represent the dose-exposure relationship following administration of different intravenous and oral formulations. The model was then modified to account for the maturation, growth and age-dependency of many anatomical and physiological processes from birth. The ability to accurately predict pediatric PK was assessed using clinical data. Simulations performed well for all ages, from neonates through to adolescents, following different intravenous and oral dosing regimens. The impact of changes in metabolite formation and elimination was also reasonably predicted.[2]

Challenge

To develop pediatric PBPK models that can accurately predict drug exposure in neonates, infants, children and adolescents.

Solution

Independent researchers developed and qualified a PBPK model for acetaminophen (APAP) in adults. This was then expanded to children, accounting for maturational changes from birth. Simulations reliably predicted intravenous and oral PK for children of all ages, validating the use of PBPK modeling to predict drug exposure in pediatric subpopulations.

Benefit

A PBPK modeling strategy has been established which can assist with dose selection and clinical trial design, potentially saving significant resources and improving safety in drug development.

Since the study was undertaken, a major advance in pediatric modeling and simulation has been achieved through the ability to incorporate developmental changes which may occur over the time course of a study.[3] This reflects the rapid changes that occur during development, anticipating the varying pharmacokinetics and drug-drug interactions that may be observed over even fairly short treatment periods – a particular concern in newborn babies. Certara scientists have also recently implemented the first pediatric oral drug absorption model as well as undertaken a re-evaluation and validation of ontogeny functions for CYP1A2 and CYP3A4.[4] These are important steps in ensuring that PBPK models are continually updated as information on relevant parameters becomes available.

Benefit

Pediatric PBPK models have been developed and validated, clearly demonstrating their utility in evaluating the efficacy and safety of drugs, and informing appropriate dosing regimens. Simulations can also assist with the design of studies, such as indicating optimal sampling times and study power.[5]

Impact

A robust framework for using pediatric PBPK modeling and simulation is now in place with the potential to save significant time, effort and resources in drug development.

References

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About Certara

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