CERTARA

Assessing Different Formulations for Pediatric Patients Using Modeling and Simulation

Pharmaceutical companies face a challenge when developing drugs that may be used to treat newborns, infants, and children due to the ethical concerns of including these groups in clinical trials. Modeling and simulation can accelerate the development of pediatric medicines

Background

Quetiapine is an atypical antipsychotic drug for the treatment of schizophrenia, bipolar disorder, major depressive disorder and generalized anxiety disorder. An immediate-release (IR) formulation of quetiapine was first approved by the FDA in 1997 and has been extensively studied in adults, children and adolescents. Regulatory approval for the extended-release (XR) formulation was granted for use in adults, with the requirement that pediatric studies must be carried out for children over the age of 12.

Challenge

Various factors influence the bioavailability of different formulations including the release of the active ingredient, its dissolution and permeability across the gastrointestinal tract as well as intestinal metabolism. Furthermore, alterations in pharmacokinetics in children can be due to differences in absorption and transit rate, organ size, blood flow, tissue composition and metabolic capacity at various developmental stages. The challenge was to integrate the available *in vitro* ADME, physiochemical and clinical data into physiological-based pharmacokinetic (PBPK) models to predict the effects of age and formulation on the pharmacokinetics (PKs) of quetiapine in young subjects.

Solution

Scientists at Simcyp (part of Certara) and AstraZeneca developed PBPK models that predicted, with reasonable accuracy, the effects of CYP3A4 inhibition and induction on the PK of quetiapine, the PK profile of quetiapine IR in both children and adults, and the PK profile of quetiapine XR in adults.

Challenge

Quetiapine IR formulations have been studied in both adults and children, but the XR formulation was only tested in adults. Scientists at AstraZeneca sought to model the pharmacokinetic profile of the XR formulation in both children and adolescents to inform dosing regimens in pediatric groups.

Solution

PBPK models for quetiapine were developed for both adults and children. Simulations were in good agreement with observed data for the IR formulation providing a solid foundation to extend the model to predict the PKs of XR dosing in children and adolescents.

These validated models were then used to simulate relative exposure following XR formulation in adolescents (age 13-17) and children (age 10-12). In both groups, the predicted exposure to quetiapine XR followed a similar pattern to the IR formulation, with 300 mg XR once daily being comparable with 150 mg IR twice a day.[1]

Benefit

The results of this study helped a major pharmaceutical company to determine dosing regimens for adolescents and older children using quetiapine XR formulations. This provides an example of how a "learn-and-confirm" approach can be applied for studying pediatric PKs which can be adapted to other medicines that have already received market approval as well as those that are currently in development.

Impact

As well as being a regulatory requirement, successfully developing a drug that can be safely used in the pediatric population can gain additional marketing exclusivity. This can be extremely lucrative, particularly for 'blockbuster' drugs where competition from generics is likely to be high. Furthermore, a new formulation for a pediatric indication for an "off-patent" drug can secure 10 years of market protection, offering further incentives for pharmaceutical companies to focus on developing medicines for children.

Benefit

The results were used to inform the dosing regimens for quetiapine ER formulations in adolescents and older children, improving safety for this group of patients.

References

1. Johnson TN, Zhou D, Bui KH. Development of physiologically-based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents. *Biopharmaceutics and Drug Disposition*. 2014; 35(6):341-52.

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