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Development of a physiologically based model to support the choice of paediatric enalapril dosing regimen for orodispersible minitablets

Khalil F., Läer S.
Clinical Pharmacy and Pharmacotherapy, Heinrich-Heine-University of Düsseldorf, Germany

Introduction: Efforts have been increasingly dedicated towards paediatric clinical trials since the EU-paediatric regulation in 2007. The EU's Seventh Framework Programme under grant agreement n°602295 will perform paediatric clinical trials aiming at the safety and the pharmacokinetics of enalapril in children with heart failure using an innovative formulation of orodispersible minitablets. The paediatric committee (PDCO) of the European Medicines Agency required in silico simulations using physiologically based pharmacokinetic (PBPK) models to inform the dosing regimen of these paediatric trials and to be included into the paediatric investigation plan.
Methods: Drug-specific parameters as well as PK experimental data were collected from the literature for model parameterization and evaluation. A coupled PBPK-model of enalapril and its active metabolite was then developed using Simcyp®. The model was evaluated and refined in adults before scaling to children on physiological basis. The ontogeny profile of the main metabolising enzyme, carboxyesterase 1 (CES1), was additionally assigned based on protein expression data. Using the scaled model, drug exposure in different pediatric age groups was predicted and the generated information were used to support the design of the dosing schedule.
Results: Model predictions in adults were comparable with the observed data for both enalapril and enalaprilat, which indicate the model ability to capture the drug PK behavior. The relative precentage error of expoure predictions were <10%. The collected information of relative CES1 expression at different pediatric ages indicated that CES1 reaches about 50% of the adult activity within the first 6 months of life. The pediatric simulations showed an age dependent differences of drug exposure, with high variability in young children. The data generated were used to derive a proposed dosing regimen for the paediatric clinical trials according to the requirements, which was accepted by the PDCO.
Conclusion: Simulations of drug exposure in virtual subjects delivered valuable information on the expected drug pharmacokinetic behaviour in the paediatric population on the basis of already available data in adults and thus safeguard the designed dosing regimen. PBPK-models can save time, effort, and resources when planning paediatric clinical trials, however, simulation informed decisions should yet be confirmed by experimentally obtained data.