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Paediatric PBPK modelling: Prediction of drug exposure following oral dosing of different paracetamol formulations in fasted and fed states

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In recent years, physiologically-based pharmacokinetic (PBPK) models have been increasingly used in paediatric drug development. Moreover, the value of such approach has been recognized by the regulatory authorities (1).

The aim of this study was to evaluate paracetamol absorption and disposition in children following oral administration of sustained-release hot-melt coated (HMC) granules and tablets made of HMC granules (2,3) in comparison to immediate-release uncoated granules and tablets made of uncoated granules, using PBPK modelling. Paracetamol-specific PBPK model was firstly developed and validated for adults, and then extrapolated to five paediatric age groups: neonates/12 days, infants/18 months, children/2 years, children/6 years, and adolescents/12 years. Simulations were performed for fasted and fed states (different age-appropriate meal types). The simulated plasma concentration-time profiles indicated delayed paracetamol absorption from HMC formulations in comparison to immediate-release formulations. Also, the simulations revealed that co-administration of food is not expected to affect paracetamol absorption following oral administration of HMC formulations, in contrast to immediate-release formulations whereas marked food effect was anticipated.

According to the simulations results, HMC granules and tablets made of HMC granules can provide prolonged drug effect, irrespective of the presence of food, and consequently better compliance of paediatric patients.

References

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