Assessment of CYP1A2 inductive potential of edaravone using PBPK model

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Objectives: To develop a PBPK model for a positive CYP1A2 inducer (omeprazole), to develop a PBPK model for edaravone and to prospectively assess the potential for edaravone to affect the pharmacokinetics of CYP1A2 substrate drugs when the two drugs are co-administered.

Methods: A PBPK model for a positive CYP1A2 inducer omeprazole was developed to recover the multiple-dose exposures by accounting for auto-inhibition of CYP2C19. Omeprazole CYP1A2 induction data determined in vitro were optimised using the observed induction effect on caffeine in vivo DDI data. Due to the uncertainty associated with the omeprazole CYP1A2 induction parameters determined in vitro, a sensitivity analysis on CYP1A2 IndMax was conducted to identify the range of values that allowed the recovery of the observed induction effect on pharmacokinetics of caffeine. A model for edaravone incorporating information on its physicochemistry, distribution and elimination was developed and verified using the observed clinical pharmacokinetic data. In vitro CYP1A2 induction data for edaravone were incorporated in the final PBPK model and calibrated against omeprazole data. Then the final edaravone model was applied to prospectively assess the potential for edaravone to affect the pharmacokinetics of CYP1A2 substrate drug caffeine. The Simcyp Population-Based Simulator was used for all simulations.

Results: Simulated plasma concentration-time profiles of omeprazole were reasonably consistent with observed data after oral single or multiple dosing. The sensitivity analysis focused on CYP1A2 IndMax indicated that CYP1A2 IndMax for omeprazole was a value of 290-fold. Simulated and observed plasma concentration time profiles and PK parameters were compared in order to verify the edaravone model. Mean simulated AUC values of edaravone were 0.79-1.58-fold of the observe values. The model was applied to assess the potential for edaravone to affect the pharmacokinetics of caffeine. The predicted caffeine DDI effects were negligible; the predicted caffeine AUC ratios ranged from 0.98 to 0.99.

Conclusions: We developed a PBPK model for a positive CYP1A2 inducer omeprazole. The DDI potential for edaravone to affect the pharmacokinetics of CYP1A2 substrate drugs was negligible.