A physiologically-based pharmacokinetic model of clopidogrel in populations of European and Japanese ancestry: an evaluation of CYP2C19 activity

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Abstract

Aims CYP2C19 activity is associated with treatment response to clopidogrel through the formation of the active H4 metabolite. The aims of this study were to develop a physiologically-based pharmacokinetic (PBPK) model of clopidogrel and its metabolites for populations of European ancestry, to predict pharmacokinetics in the Japanese population by CYP2C19 phenotype (extensive metaboliser, EM; intermediate metaboliser, IM; poor metaboliser, PM), and to investigate the effect of clinical and demographic factors. Methods A PBPK model (Simcyp® v18.2) was developed and verified (2-fold acceptance criteria) to describe the two metabolic pathways of clopidogrel (H4 metabolite, acyl glucuronide metabolite) for a population of European ancestry using plasma data from four published studies. Subsequently, model predictions in the Japanese population (2 studies) were evaluated. The effects of CYP2C19 activity, fluvoxamine coadministration (CYP2C19 inhibitor) and population-specific factors (age, sex, BMI, body weight, cancer, hepatic and renal dysfunction) on the pharmacokinetics of clopidogrel and its metabolites were investigated. Results The predicted/observed ratios for clopidogrel and metabolite exposure parameters were acceptable. For all CYP2C19 phenotypes, steady-state $AUC_{0\text{-}\tau}$ of the H4 metabolite was lower for the Japanese (e.g. EM, 7.69 [6.26 – 9.45] ng·h/mL; geometric mean [95% CI]) than European (EM, 24.8 [20.4 – 30.1] ng·h/mL, P <0.001) population. CYP2C19 PM phenotype, fluvoxamine co-administration, hepatic and renal dysfunction reduced H4 metabolite but not acyl glucuronide metabolite concentrations. Conclusion This is the first PBPK model developed to describe the two major metabolic pathways of clopidogrel which can be applied to populations of European and Japanese ancestry by CYP2C19 phenotype.

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