Development of a Physiologically Based Pharmacokinetic – Population Pharmacodynamic model for Oxycodone

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Objectives: To optimize Oxycodone therapy using a modeling framework which integrates the pharmacokinetics and pharmacodynamics of oxycodone and its active metabolites by linking genetics CYP2D6, in vitro receptor binding affinity, and pain on a physiological basis.

Methods: A physiologically-based pharmacokinetic (PBPK) model for oxycodone and its active metabolites was developed in GastroPlus (ADMET predictor, v.7.0) in a stepwise fashion and informed by IV and oral dose-ranging data in plasma and urine of healthy volunteers phenotyped as poor and extensive CYP2D6 metabolizers [1,2]. The model was qualified using literature datasets following a 10mg oral dose [2]. PBPK model simulated concentrations for oxycodone and its active metabolites were used as PK input into a semi-mechanistic PD model developed in NONMEM (v.7.3), where they were linked μ-opioid receptor affinity, electroencephalography, and pain data [3,4].

Results: The PBPK model was able to predict parent and metabolite plasma profiles, cumulative urinary excretion and pain relief for different CYP2D6 phenotypes and DDIs with strong CYP2D6 and CYP3A4 inhibitors. Bootstrap analysis of the PD model showed acceptable precision for the estimated parameters. Visual predictive checks plots also confirmed the stability of pharmacodynamic model.

Conclusions: The developed PBPK-PD model was able to characterize the pharmacokinetic profiles of Oxycodone and its major metabolites in plasma and assess the impact of DDIs and CYP2D6 activity on pain relief. The developed semi-mechanistic model will be further used as the initial building block to characterize opioid effects on pain relief.
