Introduction: Oxycodone undergoes a relatively complicated metabolism producing 3 main metabolites: noroxycodone, oxymorphone, and noroxymorphone. Among these metabolites, oxymorphone is highly related to the pharmacodynamic effect of oxycodone. It is 14 times more potent than the parent compound, and its affinity for the μ opioid receptor is 3 times higher than morphine. Development of a whole-body physiologically based pharmacokinetic (PK) model is an approach to predict in vivo metabolism of oxycodone and PK profile of each metabolite in different drug–drug interaction (DDI) scenarios.

Patients (or Materials) and Methods: The Simcyp simulator was used as a platform and database for simulation of oxycodone’s metabolism in virtual healthy populations. Prior in vitro and in vivo data were combined to build an oxycodone model which was used to predict the PK profile in healthy volunteers. The incorporated parameters were optimized by a top-down approach based on the clinical trial conducted by Samer et al, where PK profile of 0.2 mg/kg single dose were closely matched with the clinical trial and the virtual population. The incorporated parameters combined to build an oxycodone model which was used to predict the metabolism of oxycodone and main metabolites, and to simulate DDI involving CYP3A and 2D6.

Results: Pharmacokinetic profiles of oxycodone and 2 predominant metabolites (oxymorphone and noroxycodone) were closely simulated by the model.

Mean values (SD).

Oxycodone, noroxycodone, and oxymorphone PK profiles were also concordant with the clinical study according to CYP2D6 phenotypic groups. Obtained DDI magnitudes were also in agreement with the clinical data. Noroxymorphone PK profile was less accurately predicted by the model.

Conclusion: The Simcyp developed model for oxycodone is valuable to predict the metabolism of oxycodone and main metabolites, and to simulate DDI involving CYP3A and 2D6.

Disclosure of Interest: None declared.

PP191—INFLUENCE OF VERAPAMIL ON THE PHARMACOKINETICS OF OXCARBAZEPINE AND 10-HYDROXYCARBAZEPINE ENANTIOMERS IN HEALTHY VOLUNTEERS

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Introduction: Oxcarbazepine (OXC) is a drug indicated for the treatment of partial seizures or generalized tonic-clonic seizures in adults and children. It undergoes rapid presystemic reduction with formation of 10-hydroxyoxcarbazepine (MHD), which has a chiral center at position 10, with the enantiomers (S)-(+)- and (R)-(-)-MHD with similar antiepileptic effects. OXC and MHD are substrates of P-glycoprotein (Pgp), whereas verapamil is an inhibitor of Pgp expressed in various tissues, including the brain. This study aims to evaluate the influence of verapamil on the pharmacokinetics of OXC and MHD enantiomers in healthy volunteers.

Patients (or Materials) and Methods: The study was conducted in 2 phases and included 12 adult healthy volunteers. In the Phase I, they were treated with 300 mg/12 hours OXC during 5 days. On the fifth day, after the last dose, serial blood samples were collected up to 12 hours. In the Phase II, the same healthy volunteers were treated with OXC (300 mg/12 hours during 5 days) associated with verapamil (80 mg/8 hours during 5 days). On the fifth day, after the last OXC dose, serial blood samples were collected up to 12 hours. Plasma concentrations of OXC and MHD enantiomers were evaluated by LC-MS/MS coupled with a chiral phase Chiralcel® OD-H column. Pharmacokinetic analysis was performed using the software WinNonlin and statistical tests were conducted with the significance level set at P < 0.05.

Results: The following pharmacokinetic parameters for OXC were obtained in Phase I (median; maximum plasma concentration (Cmax) of 1.35 mg/mL in 1.0 hour, area under the plasma concentration versus time curve (AUC0–12) of 3.98 μg·h/mL and half-life of 2.45 hours. The kinetic disposition of MHD was enantioselective, with observation of a higher proportion for the enantiomer 5-(+)-MHD compared with R-(−)-MHD (AUC0–12S(+)/R-(−) of 4.10). Verapamil treatment (Phase II) decreased the mean residence time (3.83 vs 4.71 hours) and the apparent volume of distribution (Vd/τ) (2.86 vs 3.78 L/kg) of OXC. Concerning MHD enantiomers, the verapamil treatment increased Cmax, AUC and Css for both enantiomers.

Conclusion: Verapamil treatment reduced OXC Vd/τ and increased AUC of both MHD enantiomers probably due to the Pgp inhibition.

Disclosure of Interest: None declared.