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Model-based analysis of the relationship between the pharmacokinetics and cerebral perfusion of oxcarbazepine and its metabolite 10-monohydroxy oxcarbazepine in plasma of healthy volunteers

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Oxcarbazepine (OXC) and its active metabolite 10-monohydroxy oxcarbazepine (MHD) enantiomers are P-glycoprotein (P-gp) substrates. This study aimed to evaluate the pharmacokinetic-pharmacodynamic relationship of OXC and MHD in the presence and absence of verapamil, a P-gp inhibitor. Healthy subjects (n=12) received for 5 days doses of 300 mg/12h OXC alone or combined with 80 mg/8 h verapamil. Blood samples were collected during 12 hours in conjunction with single-photon emission computed tomography for the assessment of drug concentrations and changes in cerebral perfusion. An integrated population pharmacokinetic model was developed using nonlinear mixed effects modelling, as implemented in NONMEM. A three-compartment model with first-order elimination and a set of transit compartments to describe the absorption profile best described the OXC pharmacokinetics. The MHD enantiomers disposition was characterised by one-compartment model. Clearance estimates (95% CI) was 84.9 L/h (69.5-100.3) for OXC and 2.0 L/h (1.9-2.1) for MHD. The volume of distribution was 131 L (97-165) for OXC, 23.6 L (14.4-32.8) for R-(-)- and 31.7 L (22.5-40.9) for S-(+)-MHD. Co-administration of verapamil was found to increase the bioavailability of OXC by 12% (10-28). This increase is most likely related to inhibition of P-gp in the intestinal tract. Based on allometric scaling from rat data, there appears to be a significant increase of R-(-)-MHD and S-(+)-MHD concentrations in the brain without clinically relevant changes to the circulating levels of either enantiomer. These estimates are in line with the changes in cerebral blood flow, as assessed by SPECT, which were observed after the verapamil co-administration.

Biography

Natalícia de Jesus Antunes has completed her Master degree at age 27 years from School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo. She is PhD student at the School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo. She did a PhD internship at the Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden University. She has worked with PK/PD modelling and pharmacokinetics studies of antihypertensive drugs during the pregnancy.

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