

## Abstract

Oxcarbazepine is indicated for the treatment of partial or generalized tonic-clonic seizures. The majority of the oxcarbazepine is converted into its active metabolite, 10-hydroxycarbazepine (MHD), which can exist as R-(-)- and S-(+)-MHD enantiomers. Here we describe the influence of the P-glycoprotein (P-gp) inhibitor verapamil, on the disposition of oxcarbazepine and MHD enantiomers, both of which are P-gp substrates. Healthy subjects (n=12) were randomised to oxcarbazepine or oxcarbazepine combined with verapamil at doses of 300 mg b.i.d. and 80 mg t.i.d., respectively. Blood samples (n=185) were collected over a period of 12 h post oxcarbazepine dose. An integrated PK model was developed using nonlinear mixed effects modelling using a sequential approach. The pharmacokinetics of oxcarbazepine was described by a two-compartment model with absorption transit compartments and first-order elimination. The concentration-time profiles of both MHD enantiomers were characterised by a one-compartment distribution model. Clearance estimates (95% CI) were 84.9 L/h (69.5-100.3) for oxcarbazepine and 2.0 L/h (1.9-2.1) for both MHD enantiomers. Volume of distribution was much larger for oxcarbazepine (131 L (97-165) as compared to R-(-)- and S-(+)-MHD (23.6 L (14.4-32.8) vs. 31.7 L (22.5-40.9), respectively). Co-administration of verapamil resulted in a modest increase of the apparent bioavailability of oxcarbazepine by 12% (10-28), but did not affect parent or metabolite clearances. Despite the evidence of comparable systemic levels of OXC and MHD following administration of verapamil, differences in brain exposure to both moieties cannot be excluded after P-glycoprotein inhibition.