Supplemental material

Bioanalytical methods

A detailed description of the analysis of oxcarbazepine and MHD enantiomers can be found in a previous publication by our group (Antunes et al. 2013). Briefly, the plasma concentrations of OXC and MHD enantiomers were analysed by high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) coupled to a stationary phase chiral column Chiralcel® OD-H using a mixture of hexane: ethanol: isopropanol (80:15:5, v/v/v) as mobile phase. The calibration curves constructed using the ratios of areas vs. concentration of oxcarbazepine (12.5 ng/mL - 5 µg/mL plasma) and MHD enantiomers (31.25 ng-12.5 µg of each enantiomer/mL plasma) showed linearity in the reported ranges, with correlation coefficients higher than 0.99. OXC and MHD enantiomers demonstrated stability in plasma during three freezing and thawing cycles, with coefficients of variation and bias estimates lower than 15%. The limit of quantification in plasma was 12.5 ng/mL for OXC and 31.25 ng/mL for each MHD enantiomer.

Reference:

1. Antunes, N.D.E.J., Wichert-ana, L., Coelho, E.B., Pasqua, O. Della, Veriano, A., Takayanagui, O.M., Tozatto, E., Lanchote, V.L., 2013. Analysis of Oxcarbazepine and the 10-Hydroxycarbazepine Enantiomers in Plasma by LC-MS / MS : Application in a Pharmacokinetic Study. Chirality 25, 897–903.

Table S1. Summary of the model building steps for oxcarbazepine and MHD enantiomers.

Model	Compartments	Absorption	Interindividual variability	Covariate effects	OFV	ΔOFV	Comment
OXCARBAZEPINE							-
1	2	1st order	CL5, V_C	-	-1007.83	-	-
2	2	1st order	CL5, V_C ,F1,MTT	-	-1029.86	-22.03	-
3	2	1st order + LAG 2	CL5, V_C ,F1,MTT	-	-1130.28	-122.44	-
4	2	Transit 3*	CL5, V_C ,F1,MTT	-	-1176.21	-168.38	-
5	2	Transit 3*	CL5, V_C ,F1,MTT	VER in F1	-1189.98	-182.15	-
6	2	Transit 3*	CL5, V_C ,F1,MTT	V ER in V_C	-1184.26	-176.43	-
7	2	Transit 3*	CL5, V_C ,F1,MTT	VER in CL5	-184.95	-177.12	-
8	2	Transit 3*	CL5, V_C ,F1,MTT +IOV in MTT	VER in F1	-1228.07	-220.87	-
9	2	Transit 3*	CL5, V_C ,F1,MTT +IOV in MTT	VER in F1 + AS in CL5, V_C , V_P	-1229.78	-1.70	-

Model	Compartments	Absorption	Interindividual variability	Covariate effects	OFV	ΔOFV	Comment
MHD							
1	1 (R-(-)-MHD) +1 (S-(+)-MHD)	-	-	-	-1260.60	-	-
2	1 (R-(-)-MHD) +1 (S-(+)-MHD)	-	V_{RMHD}	-	-1266.58	-5.98	-
3	1 (R-(-)-MHD) +1 (S-(+)-MHD)	-	V_{SMHD}	-	-1261.86	-1.27	-
4	1 (R-(-)-MHD) +1 (S-(+)-MHD)	-	V_{RMHD} , V_{SMHD}	-	-1278.85	-18.25	Same IIV V_{RMHD}, V_{SMHD}
5	1 (R-(-)-MHD) +1 (S-(+)-MHD)	-	V_{RMHD} , V_{SMHD}	AS in CL_{RMHD}, CL_{SMHD}, V_{RMHD}, V_{SMHD}	-1277.96	-17.36	Same IIV V_{RMHD}, V_{SMHD}
6	1 (R-(-)-MHD) +1(S-(+)-MHD)	-	V_{RMHD} , V_{SMHD}	AS in CL_{RMHD}, CL_{SMHD}, V_{RMHD}, V_{SMHD}	-1274.87	-14.27	Same IIV V_{RMHD}, V_{SMHD}; Same THETA CL_{RMHD}, CL_{SMHD}

* Optimised number of transit compartments

IIV, interindividual variability; OFV**,** decrease in the objective function value; cmt, compartment; AS, allometric scaling; VER, verapamil covariate effect.

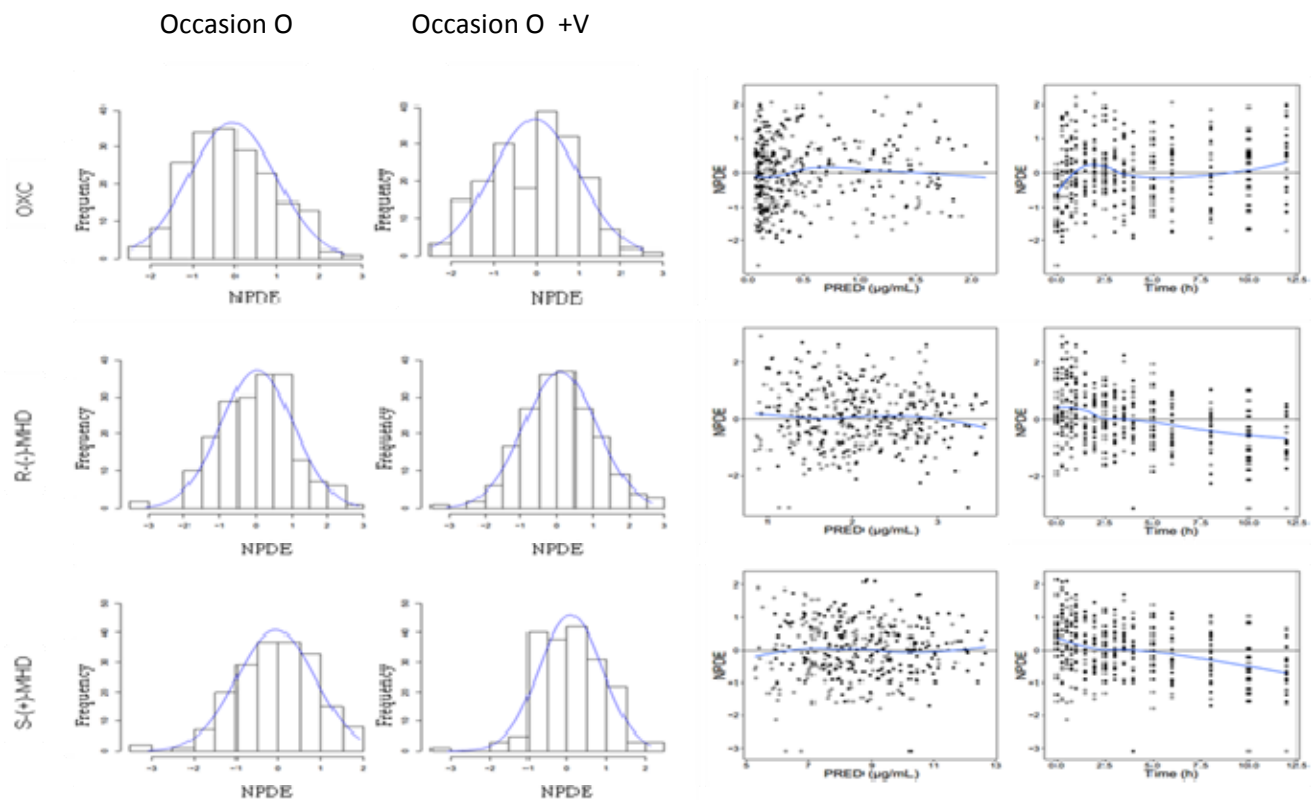

Figure S1. Normalised Prediction Distribution Errors (NPDE) for OXC, R-(-)-MHD and S-(+)-MHD. Left panels: Histogram of the distribution of the NPDE along with the density of the standard Gaussian distribution. Right panels: NPDE *versus* population prediction (PRED) and NPDE *versus* time; ○, occasion O (OXC alone); ●, occasion O+V (OXC+verapamil).

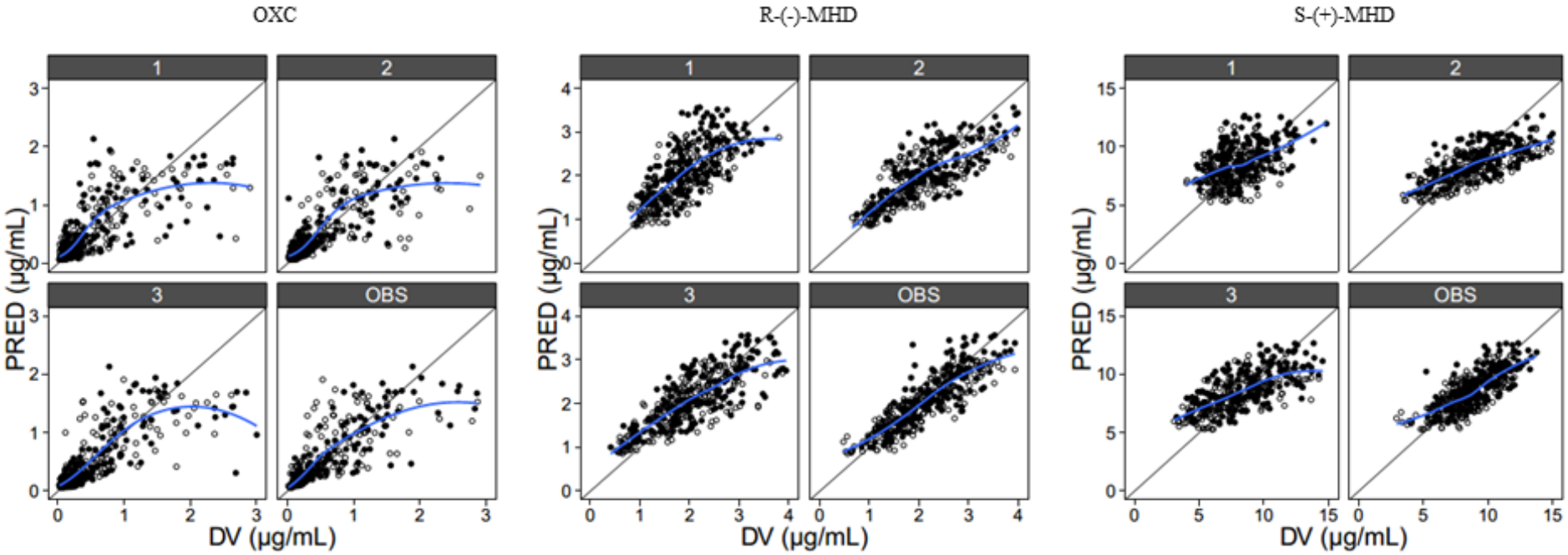

Figure S2 Mirror plots showing goodness-of-fit for simulated and observed concentrations of OXC, R-(-)-MHD and S-(+)-MHD. Panels show the correlation between observed (DV) *versus* population predicted (PRED) data. 1, 2 and 3 refer to randomly selected simulated data sets, whereas OBS depicts the original data used in this analysis. ○, occasion O (OXC alone); ●, occasion O+V (OXC+verapamil).