Population pharmacokinetics of oxcarbazepine and its metabolite 10-hydroxycarbazepine in healthy subjects

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Introduction

Oxcarbazepine is indicated as monotherapy or adjunctive therapy in the treatment of partial and generalized tonic-clonic seizures in adults and children (Verrotti et al., 2010; Wellington and Goa, 2001). Oxcarbazepine undergoes rapid pre-systemic reduction metabolism resulting in the formation of its active monohydroxy metabolite 10-hydroxycarbazepine (MHD). MHD has a chiral centre yielding two enantiomers (S-(+)- and R-(-)-MHD), which show similar effects *in vitro* and in animal models for anticonvulsant activity (May et al., 2003; Schmutz et al., 1994; Volosoc et al., 2000, 1999). The absolute bioavailability of oxcarbazepine assessed from MHD plasma data is 99% (Flesch et al., 2011) and its apparent volume of distribution (V/F) is 7.8 to 12.5 L/kg in epileptic patients (Dickinson et al., 1989). Protein binding is approximately 59% for oxcarbazepine (Patsalos et al., 1990), whereas even lower values were found for R-(-)-MHD and S-(+)-MHD (20 and 23%, respectively) (Fortuna et al., 2010). Most of the administered dose of oxcarbazepine (79%) is eventually excreted through the kidneys as glucuronide conjugate MHD and as unchanged MHD (Flesch et al., 2011). Less than 1% is excreted as unchanged oxcarbazepine and 9% as inactive glucuronide conjugates of oxcarbazepine (Tecoma, 1999; Wellington and Goa, 2001). In addition, about 4% of MHD is oxidized with formation of the inactive metabolite 10,11-dihydro-10,11-trans-dihydroxycarbazepine (DHD) (Flesch et al., 2011; Paglia et al., 2007; Schütz et al., 1986; Volosoc et al., 2000).

The extensive metabolic conversion to MHD is supported by data in healthy subjects who were administered a single 250-mg MHD infusion over 30 min. In these subjects, volume of distribution estimates were found to be 9.0 and 8.4 L for R-(-)-MHD and S-(+)-MHD, respectively (Flesch et al., 2011).In addition, enantioselective elimination was observed, as indicated by mean clearance (CL) values of 4.3 L/h for R-(-)-MHD and 3.1 L/h for S-(+)-MHD. These differences result in plasma accumulation of the S-(+)-MHD enantiomer relatively to the other enantiomer, with area under the plasma concentration *vs*. time curve (AUC) of 119.5 *vs.* 166.8 μmol.h/L. Similar findings were observed after oral administration of oxcarbazepine to healthy subjects, with AUC values of 63.9 μmol.h/L for R-(-)-MHD and 241.0 for S-(+)-MHD μmol.h/L (Flesch et al., 2011).

Previous studies have shown that oxcarbazepine and MHD are substrates of the P-glycoprotein (P-gp) efflux transporter (Clinckers et al., 2008, 2005; Zhang et al., 2011). P-gp can have major influence on the processes of absorption, distribution and elimination of drugs (Marzolini et al., 2004). P-gp may also affect the absorption rate and bioavailability of drugs administered orally (Estudante et al., 2013; Fortuna et al., 2012; Shugarts and Benet, 2009). On the other hand, the expression of P-gp in the blood brain-barrier limits the penetration of (substrate) moieties into the central nervous system (CNS), thereby potentially reducing their pharmacological effects (Yamamoto et al., 2016). Changes in the expression of P-gp in the brain are associated with differences in antiepileptic drug levels in the brain parenchyma. It has also been shown that seizures in mice increase the MDR1 expression in the hippocampus and reduce the brain/plasma concentration ratios of phenytoin (Marchi et al., 2005; Rizzi et al., 2002). Considering the possible involvement of the P-gp over-expression on the mechanisms underlying pharmacoresistance to epilepsy treatment, the inhibition of P-gp function by selective blockers may become a viable strategy to facilitate the distribution of drugs into the CNS. However, from a clinical safety perspective, implementation of such a strategy requires further understanding of the impact of P-gp inhibition on systemic exposure. Verapamil is a known P-gp inhibitor in various tissues including the brain (Clinckers et al., 2008), gut (Lemma et al., 2006) and liver (Lemma et al., 2006). Moreover, verapamil was found to potentiate the anticonvulsant activity of oxcarbazepine in an experimental seizure model in rats. This effect was associated with increased MHD levels in the rat brain (Clinckers et al., 2008, 2005). The current study aimed to characterize the pharmacokinetics of oxcarbazepine and the MHD enantiomers in the presence and absence of verapamil in humans using a model-based population pharmacokinetic approach. This investigation will allow the assessment of the impact of P-gp inhibition on systemic drug exposure and provide the basis for further investigation of the use of oxcarbazepine in combination with P-gp inhibitors in patients.

1. Materials and methods

2.1 Clinical trial protocol

Details of the clinical trial used in this analysis have been described previously (de Jesus Antunes et al., 2016). Briefly, 12 (8 female and 4 male) healthy subjects were enrolled into an open label, randomized, two-way crossover pharmacokinetic study. The study protocol was approved by the local research ethics committee. Individual subjects were enrolled into the study after signing an informed consent form. Only non-obese, non-smokers healthy adult subjects with clinical laboratory results within normal limits were included. Patient characteristics are shown in **Table 1**.

Subjects received repeated doses of either oxcarbazepine alone (defined as occasion O) or oxcarbazepine and verapamil (defined as occasion O+V). There was a washout period of 30 days between treatments. On occasion O, oxcarbazepine was administered as oral dose of 300 mg every 12 hours for 5 days. On the fifth day, a 9th dose of the drug was administered and steady state blood samples were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 h post oxcarbazepine dose. On occasion O+V, the subjects received oral dose of 300 mg of oxcarbazepine every 12 hours and oral dose of 80 mg of verapamil every 8 hours, at the same time. On the fifth day, after fasting for at least 10 h, the 13th dose of verapamil was administered and after 1 h the 9th dose of OXC. Serial blood samples were collected as described above for the O occasion. 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), and is summarized as supplemental material.

2.2 Pharmacokinetic modelling

Nonlinear mixed effects modelling was performed in NONMEM (version 7.2) using the first-order conditional estimation method with the interaction option. Model building criteria included a decrease in the objective function value (OFV), a successful minimisation, adequate standard error of estimates and number of significant digits, and evaluation of parameter correlation.

2.2.1 Pharmacokinetic model development for oxcarbazepine

Two and three-compartment disposition models with first order elimination were considered to describe the pharmacokinetics of oxcarbazepine. We evaluated both a first order absorption process and a transit compartment model (Eq. 1) (Savic et al., 2007).

$$K_{tr} = \frac{n+1}{MTT} \quad (1)$$

where K_{tr} is a transfer rate constant from n^{th}-1 compartment to the n^{th} compartment with n being the number of transit compartments, and MTT is the mean transit time (Savic et al., 2007).

2.2.2. Integrated model for oxcarbazepine and MHD enantiomers

The parameter estimates obtained for oxcarbazepine were fixed for the subsequent steps during which an integrated model was developed to account for the disposition of the metabolite enantiomers (Zhang et al., 2003). One and two compartment models were evaluated for describing the concentration-time profiles of the MHD enantiomers.

The absolute formation rates of MHD were not available from the same subjects due to a lack of urine data. Therefore, we fixed the fraction of oxcarbazepine metabolized to MHD (F_{MET}) to a previously published value of 0.79 (Schütz et al., 1986), in order to estimate the total clearance to the MHD enantiomers (CL_m). We then used the relative fraction of the MHD formation clearances for R-(-)-MHD (*CLmR*) and S-(+)-MHD (*CLmS*) on the AUC fractions of each enantiomer relative to the total metabolite AUC calculated by non-compartmental analysis (Eq. 2-5).

$$\text{CLm} = F_{MET} * CL_{total} \quad (2)$$

$$\text{FRS} = \frac{(\text{AUC}_{\text{R}-(-)-\text{MHD}})}{(\text{AUC}_{\text{R}-(-)-\text{MHD}})+(\text{AUC}_{\text{S}-(+)-\text{MHD}})} \quad (3)$$

$$\text{CLmR} = \text{CLm} * \text{FRS} \quad (4)$$

$$\mathrm{CLmS} = \mathrm{CLm} * (1 - \mathrm{FRS}) \quad (5)$$

Model building procedures and criteria, including the evaluation of covariate factors, inter-individual variability (IIV) and residual variability models were implemented as described previously for oxcarbazepine.

2.2.3. Covariate model development

Verapamil co-administration was treated as a discrete covariate, and was tested the parameters for absorption, bioavailability (F), CL/F and V/F. It was hypothesised that increased uptake of oxcarbazepine and MHD could occur after administration of verapamil due to the decrease in transport of drugs back into the intestinal lumen (Clinckers et al., 2008, 2005; Lemma et al., 2006).

Because of the small sample size of this dataset (N=12) and a considerably homogeneous population in terms of their baseline demographic characteristics, additional data-driven covariate modelling as potential predictors for IIV was not considered feasible. Instead, *a priori* allometric scaling of CL/F and V/F was implemented for both oxcarbazepine and MHD enantiomers using the following relationship:

$$\theta_i = \theta_p * (\frac{BW_i}{68})^m \quad (6)$$

in which θ_i is the parameter value of the i^{th} subject with body weight BW_i, θ_p the typical value of the parameter in the population with a body weight of 68 Kg, BW_i is the body weight of the i^{th} subject, *m* is the exponent value fixed to 0.75 for CL/F and 1 for V/F (Anderson and Holford, 2008).

2.2.4. Statistical model development

The IIV of the PK parameters was estimated using an exponential model expressed as:

$$\theta_i = \theta_p * e^{\eta_i} \quad (7)$$

where θ_i represents the parameter value of the i^{th} subject, θ_p the typical value of the parameter in the population, and η_i normally distributed with mean 0 and variance ω^2.

Inter-occasion variability (IOV) was tested on absorption parameters, distribution volumes, and clearance (CL/F) and was included as follows:

$$\theta_i = \theta_p * e^{\eta_i + \kappa_o} \quad (8)$$

where κ_o represents occasion *o* normally distributed with mean 0 and variance π^2.

We evaluated proportional, additive and combined residual error models, for each enantiomer of OXC and MHD separately:

$$C_{ij,obs} = C_{ij,pred} * (1 + \varepsilon_{ij,prop}) + \varepsilon_{ij,add} \quad (9)$$

where $C_{ij,obs}$ and $C_{ij,pred}$ are the observed and predicted concentration for the i^{th} individual and the j^{th} observation, $\varepsilon_{ij,add}$ and $\varepsilon_{ij,prop}$ are normally distributed with mean 0 and variance σ^2, and where $\varepsilon_{ij,add}$ = 0 for a proportional error model, and $\varepsilon_{ij,prop}$=0 for an additive error model.

2.2.5. Model evaluation

Model evaluation was based on graphical and statistical methods, including goodness of fit, correlation matrix for fixed vs. random effects, correlation matrix between parameters and covariates, mirror plots, visual predictive check (VPC), normalised prediction distribution errors (NPDE) and the posterior predictive check (PPC)(Nguyen et al., 2016). Comparison of hierarchical models was based on the likelihood ratio test, with a decrease in objective function value (OFV) of 3.84 corresponding to a *p*-value of <0.05 at 1 degree of freedom.

3. Results

A total of 185 plasma samples were included into the analysis, with a mean number of 16 samples per subject. Non-compartmental analysis (NCA, **Table 2**) indicated rapid absorption of oxcarbazepine (t_{max} 0.9-1.2 h) and conversion into MHD enantiomers (t_{max} 2.8-3.5 h) (de Jesus Antunes et al., 2016). Oxcarbazepine was rapidly absorbed and its majority directly converted

to the MHD enantiomers (**Figure 1**). MHD elimination was slow ($t_{1/2}$ 11.7-13.5 h). The administration of verapamil increased exposure with approximately 10 %, based on the AUC_{0-12}.

A two-compartment disposition model (**Figure 2**) with three absorption transit compartments and first order elimination best described the plasma concentration profiles of oxcarbazepine (**Table 3**). In addition, IIV was identified for MTT, F, central V/F, and CL/F. Whereas fixed effect parameters were estimated with good precision (RSE <21.9%), IIV estimates showed high RSE values. This is probably related to the low number of patients included in this study. Given the differences in the absorption profiles observed between the treatment periods, IOV was used to describe the variability in MTT. Overall, co-administration of verapamil caused a small increase (12%) in the relative apparent bioavailability of oxcarbazepine. It was not identified as a significant factor on other parameters (e.g., CL, V, absorption rate constant) during the covariate analysis.

Metabolite formation and elimination kinetics was characterised by two additional one compartment models both R-(-)-MHD and S-(+)-MHD, respectively. Separate clearances for the enantiomers were not uniquely identifiable. As only a study in which the metabolite enantiomers are administered separately would allow estimation of independent enantiomer CL/F estimates, the model was parameterised using single CL/F parameter for both moieties. On the other hand, we were able to estimate separate V/F values for both enantiomers, including a shared random effect parameter describing IIV, i.e. assuming the same distribution characteristics of each enantiomer. The estimation of FRS based on the AUC_{0-12h} was the best possible estimate that we could obtain given the available data.

For both oxcarbazepine and its metabolite, a proportional error model was used to describe the residual variability. The detailed model building steps are presented in **Table S1**. No effect of verapamil co-administration on metabolite PK parameters (clearance, volume) was identified.

Model diagnostics indicated adequate goodness-of-fit for the final model (**Figure 3**). In addition, the simulation-based NPDE analysis revealed acceptable differences in model predictions and observations (**Figure S1**). The plots in **Figure 4** describe the visual predictive check obtained for the final model. The plots show good model performance relative to the observed data, even

though a slight over-prediction occurs for both MHD enantiomers. Mirror plots revealed that the variance-covariance structure was well characterised, as the simulated datasets reproduced the dispersion pattern observed in the original data (**Figure S2**). The final step in the evaluation of the performance of the final model included posterior predictive checks (PPC) based on a secondary pharmacokinetic parameter (i.e., AUC_{0-12}). As shown in **Figure 5**, the model adequately predicted AUC_{0-12} for both the parent drug and its MHD enantiomers.

4. Discussion

Effective treatment and management of epileptic seizures remains a challenging objective in clinical practice (Piana et al, 2014). Whilst variation in response to treatment is often assigned to the heterogeneity in the underlying disease progression and other clinical and genetic factors, interindividual differences in drug exposure also result in treatment failure. Population modelling approaches offer an opportunity to assess drug disposition properties taking into account pharmacokinetic variability. We have developed an integrated population model to describe the pharmacokinetics of oxcarbazepine and its MHD enantiomers in healthy subjects after oral administration of oxcarbazepine alone and in combination with verapamil. The pharmacokinetic model adequately characterized the absorption and disposition of oxcarbazepine and the formation of its active metabolite enantiomers, including the identification of the associated IIV. To our knowledge, it is the first time a population pharmacokinetic model is developed for both moieties.

In agreement with a previous study (Dickinson et al., 1989), the absorption of oxcarbazepine did not follow first-order kinetics. Instead, a transit compartment was required to allow accurate description of the upswing phase of the concentration profile in plasma. The approach is an attractive alternative for characterizing delayed absorption profiles, especially when IIV in the rate and extent of absorption is high (Savic et al., 2007).

Even though the pharmacokinetics of MHD as racemic mixture has been previously described in adult epileptic patients (Park et al., 2012; Yu et al., 2016), no data are available that provides

insight into the formation rate of the MHD enantiomers after oral administration. Here we showed that the disposition characteristics of both MHD enantiomers can be accurately described by a one-compartment model. Given the relevance of active metabolite for the overall clinical response to oxcarbazepine, it is important to show whether formation clearance represents a rate limiting step in the disposition of the MHD enantiomers. Flesch and collaborators have studied the pharmacokinetics of MHD after intravenous administration and reported total clearance values of 4.3 L/h for R-(-)-MHD and 3.1 L/h for S-(+)-MHD, whereas our estimates for CL/F were 2.01 L/h for both enantiomers (Flesch et al., 2011). These differences clearly suggest that formation rate does reduce the total clearance of MHD *in vivo*. Distribution properties of parent drug and metabolites were also found to differ after intravenous and oral administration. A rather large V/F at steady-state was obtained after oral administration of oxcarbazepine (587 L). These findings are in agreement with the results reported by (Dickinson et al., 1989) in patients with epilepsy (523-839 L). The estimates of V/F for the active metabolites showed somewhat limited distribution of the enantiomers, with estimates of 23.6 L and 31.7 L for R-(-)- and S-(+)-MHD respectively. Previously, higher values have been reported for volume of distribution, with estimates of 54.7 L and 45.9 L for R-(-)- and S-(+)-MHD, respectively (Flesch et al., 2011).

Despite its inhibitory P-gp activity, our analysis reveals that verapamil has limited impact on the systemic pharmacokinetics of oxcarbazepine. Co-administration of verapamil resulted in an increase of the oxcarbazepine relative bioavailability of only 12 % (**Table 3**). This small difference reflects previous findings in pre-clinical species, where co-administration of verapamil and oxcarbazepine resulted in limited changes to systemic pharmacokinetics despite a major increase in the concentrations of MHD in the brain (Clinckers et al., 2008).

Unfortunately, verapamil pharmacokinetic data was not collected in our study and consequently, no information is available regarding the time course of P-gp inhibition. Yet, at steady state it can be anticipated that inhibitory effects are relatively constant, justifying the rationale for treating verapamil co-administration as a discrete covariate factor.

We acknowledge some limitations in our analysis, which are worth mentioning. First, apparent parameter estimates have been obtained due to the lack of urine data for each of the moieties.

Second, full characterisation of enantioselective metabolism would also benefit from a larger population size, but recruitment of a larger group of subjects was not feasible. Instead, we have resorted to published data whenever possible. Given the longer half life of MHD, of note is also the use of individual ratios of AUC_{0-12} for the calculation of FRS. An attempt to derive FRS based on mean AUC estimates over an interval of 48 h (AUC_{0-48h}) (Flesch et al., 2011) resulted in unsuccessful minimisation. Lastly, additional factors, such as co-medications would have to be included in a covariate analysis if patients were to be considered (Park et al., 2012).

5. Conclusion

An integrated population model has been identified that describes the pharmacokinetics of oxcarbazepine, including the formation and disposition of its active metabolite enantiomers. Concurrent estimation of clearances suggested that MHD formation may be rate limiting. As such, this process represents a critical step for the onset of the antiepileptic effects of MHD. Verapamil co-administration was associated with a modest 12% increase of the oxcarbazepine relative bioavailability, but not on any other parameter describing the disposition of oxcarbazepine of MHD enantiomers. The overall clinical relevance of this effect is likely to be negligible. However, assuming that inhibition of P-gp transport along the blood-brain barrier is comparable to preclinical findings (Clinckers et al., 2008), integration of this pharmacokinetic with functional measures of cerebral perfusion could shed light on the pharmacodynamic effect**s** of oxcarbazepine and MHD in the brain and the potential role of P-gp inhibitors as therapeutic adjuvant.

Competing interests

The authors declare no conflict of interest.

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Table legends

Table 1 Demographic and biochemical data of the healthy subjects (n=12).

Table 2 Non-compartmental estimates of oxcarbazepine (OXC) and the 10-hydroxycarbazepine (MHD) enantiomers in plasma of healthy volunteers (n=12) after oxcarbazepine alone treatment (Occasion O) or OXC + verapamil treatment (Occasion O+V).

Table 3 Population pharmacokinetic parameter estimates for oxcarbazepine (OXC) and the 10-hydroxycarbazepine (MHD) enantiomers.

Figure Legends

Figure 1 Pharmacokinetics of oxcarbazepine (OXC), R-(-)-MHD and S-(+)-MHD in plasma. The data are expressed as mean ± standard deviation, with and without verapamil (VER) co-administration.

Figure 2 A schematic overview of the population pharmacokinetic model for oxcarbazepine (OXC) and 10-hydroxycarbazepine (MHD) enantiomers. V, volume of distribution; V_c, central distribution volume; V_p, peripheral distribution volume; V_{RMHD}, central distribution volume R-(-)-MHD; V_{SMHD}, central distribution volume S-(+)-MHD; CLmR, formation clearance for R-(-)-MHD; CLmS, formation clearance for S-(+)-MHD; CL_{other}, formation clearance for other metabolites or elimination of unchanged OXC; F1, relative bioavailability; Ktr, transfer rate constant; Q, inter-compartmental clearance.

Figure 3 Goodness-of-fit of final population pharmacokinetic model of oxcarbazepine (OXC), R-(-)-MHD and S-(+)-MHD – Observed (DV) versus population predicted and individual predicted concentrations (PRED, IPRED), conditional weighted residuals (CWRES) versus PRED. ○, Occasion O (OXC alone treatment); ●, Occasion O+V (OXC+verapamil treatment).

Figure 4 Visual predictive check (VPC) for final PK model for oxcarbazepine (OXC), R-(-)-MHD and S-(+)-MHD. The dashed lines represent the 5^{th}, and 95^{th} percentiles of simulated data (n=1000). The solid lines represent the 50^{th} of simulated data (n=1000). Occasion O (OXC alone treatment); Occasion O+V (OXC+verapamil treatment).

Figure 5 Exposure distribution of oxcarbazepine (OXC), R-(-)-MHD and S-(+)-MHD in healthy subjects. The histograms represent the simulated $AUC_{0\text{-}12}$ distribution, the continuous line represent the median of the observed $AUC_{0\text{-}12}$. Occasion O (OXC alone treatment); Occasion O+V (OXC+verapamil treatment).