Population pharmacokinetics of oxcarbazepine and its monohydroxy derivative in epileptic children

Christelle Rodrigues, Catherine Chiron, Elisabeth Rey, Olivier Dulac, Emmanuelle Comets, Gérard Pons, Vincent Jullien

Title: Population pharmacokinetics of oxcarbazepine and its monohydroxy derivative in epileptic children

Running head: Population pharmacokinetics of oxcarbazepine in epileptic children

Authors

Christelle Rodrigues[1], Catherine Chiron[1], Elisabeth Rey[1], Olivier Dulac[1], Emmanuelle Comets[2, 3], Gérard Pons[1], Vincent Jullien[1, 4]

[1] INSERM U1129, Paris, France; Paris Descartes University; CEA, Gif-sur-Yvette, France

[2] INSERM, IAME, UMR1137, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

[3] INSERM, CIC 1414, Université Rennes 1, Rennes, France

[4] Service de Pharmacologie, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France

Submitting author: Christelle RODRIGUES, christelle.spr@gmail.com

Corresponding author: Vincent JULLIEN, Service de Pharmacologie, Hôpital européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France. Tel : +33 1 56 09 39 77

vincent.jullien@aphp.fr

Word count: 5216

Number of tables: 6

Number of figures: 7

Conflict of interest

Summary

Aims: Oxcarbazepine is an antiepileptic drug with an activity mostly due to its monohydroxy derivative metabolite (MHD). A parent-metabolite population pharmacokinetic model in children was developed in order to evaluate the consistency between the recommended pediatric doses and the reference range for trough concentration (C_{trough}) of MHD (3-35 mg/L).

Methods: A total of 279 plasma samples were obtained from 31 epileptic children (2-12y) after a single dose of oxcarbazepine. Concentration-time data were analyzed with Monolix 4.3.2. The probability to obtain C_{trough} between 3-35 mg/L was determined by Monte Carlo simulations for doses ranging from 10 to 90 mg/kg/day.

Results: A parent-metabolite model with two compartments for oxcarbazepine and one compartment for MHD best described the data. Typical values for oxcarbazepine clearance, central and peripheral distribution volume and distribution clearance were 140 L/h/70kg, 337 L/70kg, 60.7 L, and 62.5 L/h respectively. Typical values for MHD clearance and distribution volume were 4.11 L/h/70kg and 54.8 L/70kg respectively. Clearances and distribution volumes of oxcarbazepine and MHD were related to body weight via empirical allometric models. Enzyme-inducing antiepileptic drugs (EIAEDs) increased MHD clearance by 29.3%. Fifty kg children without EIAEDs may need 20-30 mg/kg/day instead of the recommended target maintenance dose (30-45 mg/kg/day) to obtain C_{trough} within the reference range. By contrast, 10kg children with EIAEDs would need 90 mg/kg/day instead of the maximum recommended dose of 60 mg/kg/day.

Conclusion: This population pharmacokinetic model of oxcarbazepine supports current dose recommendations, except for 10kg children with concomitant EIAEDS and 50kg children without EIAEDs.

What is already known about this subject?

- Oxcarbazepine is an antiepileptic compound with an activity mainly due to its monohydroxy metabolite (Monohydroxy Derivative: MHD).

- Enzyme inducing antiepileptic drugs increase the metabolism of both oxcarbazepine and MHD.

- Younger children present a higher weight-normalized MHD clearance than older children.

What this study adds?

- A new parent-metabolite population model of oxcarbazepine was developed.

- 10 kg children may need higher doses than recommended if they are taking concomitant enzyme inducing antiepileptic drugs.

- 50 kg children not taking any inducing co-medication may need lower doses than recommended.

Introduction

(OXC) is an antiepileptic drug (AED) indicated for the treatment of partial

onset seizures, with or without secondary generalization, as monotherapy or in combination,

in adults and children from 2 or 6 years of age (in the US and EU respectively). It acts by

blocking voltage-gated sodium channels in excitatory glutamatergic neurons. This stabilizes

hyper-excited neuronal membranes and inhibits repeated neuronal firing and its spread. OXC

also modulates potassium and calcium activities, and reduces glutamatergic transmission [1].

Administered orally, OXC is well absorbed and rapidly and almost completely transformed in

its monohydroxy derivative (MHD), by cytosolic arylcetone reductases [2]. The formation of

MHD is enantioselective with a predominance of the (S)-enantiomer [3,4]. Despite this

difference in exposition (the ratio of the area under the curve (AUC) values of (S)-MHD over

(R)-MHD is 3,8 when OXC is administered orally [4]), other pharmacokinetic (PK)

parameters of the two enantiomers, such as the half-lives, are similar and they both present a

similar pharmacological activity [3,4]. In fact, MHD, as the sum of the two enantiomers, is

the main responsible for oxcarbazepine antiepileptic action and exposure to MHD is about 15

times higher than exposure to OXC [5]. MHD is principally eliminated by glucuronidation

(about 45%), by renal clearance (about 28%), and minor amounts are eliminated by

dihydroxylation leading to the formation of its dihydroxy derivative (DHD) [4,6]. An

equilibrium between OXC and MHD is established with the back-transformation of the

metabolite in its oxidized form [4].

For 4-16 years old children, it is recommended to start oxcarbazepine at 8-10 mg/kg/day,

divided into two intakes, and to increase it by 5 mg/kg/day every third day until reaching the

target maintenance dose of 30-45 mg/kg/day (900 mg/day for 20-29 kg children, 1200

mg/day for 29.1-39 kg children and 1800 mg/day for children over 39 kg). For 2-4 years old

children, recommendations indicate to initiate the medication at 16-20 mg/kg/day, divided into two intakes, achieving maintenance dose over two to four weeks, not to exceed 60 mg/kg/day [1].

Therapeutic drug monitoring can be a tool for physicians to adapt the dose for each of their patients. In 2008, ILAE Commission on Therapeutic Strategies created guidelines for the therapeutic drug monitoring of antiepileptic drugs [7]. They concluded that the reference range of MHD trough (C_{trough}) concentrations should be 3-35 mg/L, since it corresponded to trough concentrations of responding patients [7]. Indeed, it is well established that toxic concentrations begin between 35-40 mg/L [8–10], and some studies have shown data of responding children with MHD trough concentrations below 5 mg/L [11,12].

Factors accounting for pharmacokinetic variability of oxcarbazepine in children are age and association with enzyme-inducing antiepileptic drugs (EIAEDs) [13]. It was demonstrated that young children (2 to 5 years) presented a higher MHD clearance, so a shorter half-life (30% lower), and that they required a greater dose per body weight [11]. Co-medication with EIAEDs, such as carbamazepine, phenobarbital and phenytoin, were intensively investigated and it was established that these drugs were able to induce MHD metabolism [14–17].

To date, OXC and MHD pharmacokinetics in children have only been studied partially by non-compartmental approaches, that did not consider the continuous effect of age or body weight [3–5,14,18–20]. Some studies investigated population pharmacokinetics in children [15–17,21–24], modeling MHD directly from OXC administration. This method does not allow to distinguish pharmacokinetic changes related to OXC transformation to MHD from those related to MHD clearance. Thus, it does not permit a correct estimation of MHD pharmacokinetic parameters.

The aim of the present study was to develop a parent-metabolite population pharmacokinetic model and to use this model to evaluate whether the recommended pediatric doses allow to obtain C_{trough} of MHD within the reference range (3-35 mg/L) for therapeutic drug monitoring.

Materials and methods

Patients

This population analysis was performed using data collected for a previously published ancillary pharmacokinetic (PK) study with a non-compartmental analysis of oxcarbazepine and MHD [11]. The study included pediatric patients aged 2 to 12 years. Because the main objective of the clinical trial was to evaluate the efficacy of OXC as add-on medication, only children with inadequately controlled partial-onset and/or generalized atonic, tonic, or tonic-clonic seizures were included. Thus patients were only eligible if they experienced at least one seizure per week despite being treated by one to three AEDs that remained unchanged for at least one month before inclusion into the study.

The exclusion criteria were as follows : (1) contraindications to treatment with oxcarbazepine, such as atrioventricular disorders, blood pressure disorders or hypersensitivity to carbamazepine or tricyclic antidepressants; (2) conditions likely to modify OXC pharmacokinetics, such as renal or hepatic failure, untreated known hypothyroidism, congenital metabolic diseases, abnormal body weight (more than two standard deviations), concomitant medication with an enzyme inducing or inhibiting drug (except for AEDs), alcoholism or drug abuse; (3) previous or current use of oxcarbazepine; and (4) no cooperation from the patient or his family.

Study design

Children were randomized to receive a single OXC dose of 5 or 15 mg/kg, administered as an oral suspension after an overnight fast. Blood samples of 1 mL were collected into heparinized tubes at baseline (before administration) and, approximately, 1, 2, 4, 6, 8, 12, 24, 36 and 48 hours after administration. Times of dosing and sampling were recorded, as were the investigated covariates (age, body weight, sex, comedications). The samples were centrifuged and the separated plasma was stored at -80°C until analysis.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and their protocol was approved by the ethical committee of Cochin, Saint-Vincent de Paul, and Saint-Anne hospitals. Written informed consent was provided by a parent or legal guardian for all participating children.

Analytical method

Total MHD and OXC were assayed in plasma samples using a previously reported non-enantioselective high-performance liquid chromatography method [25]. (S) and (R) enantiomers were consequently not distinguished. Precision and inaccuracy were below 15%. The lower limits of quantification (LOQ) for OXC and MHD were 0.05 mg/L and 0.1 mg/L, respectively.

Population pharmacokinetic model development

The population pharmacokinetic analysis was performed using a non-linear mixed-effect approach, with the Monolix® software (version 4.3.2; Lixoft, Antony, France).

Model development

Population parameters for oxcarbazepine and MHD were estimated using the stochastic approximation expectation maximization (SAEM) algorithm. Data below the limit of quantification (BLQ) were handled as left-censored data, by an extended SAEM algorithm which simulate BLQ data with a right-truncated Gaussian distribution [26]. For each patient, only the first BLQ was kept in the dataset and was taken into account in the estimation via the CENS item in the database, corresponding to the M3 method [27].

For OXC, the structural PK models evaluated were composed by one, two or three compartments, and the absorption phases were evaluated with first- or zero-order models, with or without lag time. Based on previous results evidencing a bioavailability of OXC of 0.99, this parameter was fixed to 1[4]. For racemic MHD one- and two-compartment models were tested. Based on previous results showing that no OXC was found unchanged in the urine [4,28], it was assumed that all the parent was converted into MHD. Pre-systemic metabolite formation was investigated with a non-physiological model where the dose enters both parent and metabolite compartments with two independent absorption rate constants, with and without dose apportionment [29]. Elimination of OXC was tested with first- or zero-order models. Due to the linearity of MHD pharmacokinetics [6], its elimination was assumed to be ruled by a first-order process. A back-transformation of MHD into OXC was also tested, as it was evidenced that the enantiomers can be oxidized into the parent compound [4].

Exponential models were used to describe inter-individual variability, as illustrated bellow (Eq. 1):

(Eq.1)

Where θ_i is the estimated value of a parameter in an individual i, θ_{TV} is the typical value of this parameter in the population and η_i is the individual deviation from this typical value, i e, the inter-individual variability, that is assumed to be normally distributed with a mean of 0 and a variance of ω^2.

Additive, proportional and mixed residual error models were tested for each dependent variable.

Covariate analysis

Demographic variables (weight, age and sex) and co-medication with enzyme inducing antiepileptic drugs (EIAEDs), such as carbamazepine, phenobarbital and phenytoin, were tested as potential covariates. First, variables were added one by one and were selected if their addition was able to cause a significant drop of the log-likelihood (LL). Because the reduction in LL follows a chi-square distribution, a decrease of 3.84 was considered significant at the 5% level ($p < 0.05$, one degree of freedom). Once all the covariates were tested, the significant ones were added to the model, obtaining the full model, and a backward elimination was performed. Covariates were retained if their elimination resulted in an augmentation greater than 6.63 ($p < 0.01$, one degree of freedom) of the LL. After all non-significant covariates were removed, the final model was obtained.

The continuous covariates were included in the model using a power function equation (Eq. 2):

$$\overline{} \qquad\qquad\qquad \text{(Eq. 2)}$$

where cov is the value of the covariate, cov_{median} is its median and θ_{cov} is the factor describing the relationship between the covariate and the parameter.

For body weight, cov_{median} was fixed to the standard adult value of 70kg and several models were tested:

1. θ_{cov} was empirically estimated

2. θ_{cov} was fixed to the theoretical values of 0.75 for clearance and to 1 for volume

3. two independents θ_{cov} were empirically estimated for children > 6 years and children < 6 years, for MHD clearance

4. the body-weight dependent exponent (BDE) model was also tested for MHD clearance [30]. In this model the allometric exponent changes in a sigmoidal fashion with respect to bodyweight:

$$\underline{\hspace{2cm}} \qquad \text{(Eq.3)}$$

Where k_0 is the value of the exponent at a theoretical bodyweight of 0 kg, k_{max} is the maximum decrease of the exponent, k_{50} is the bodyweight at which 50 % of the maximum decrease of the exponent is attained, and γ is the Hill coefficient.

In the case of theoretical allometry, age was additionally tested as a covariate in two different ways: with Eq.2 and with a maturation function (Eq. 4):

$$\underline{\hspace{2cm}} \qquad \text{(Eq. 4)}$$

where γ represents the Hill coefficient and Age_{50} the age at which half of the maturation is reached.

Categorical covariates (sex and EIAEDs) were incorporated using a similar model (Eq. 5), as illustrated bellow:

$$\qquad \text{(Eq. 5)}$$

where cov is 1 or 0 in the presence or absence of the covariate.

Comparison of the tested models

The possible difference between the empirical allometry model and the theory-based allometry model was assessed by normalized prediction distribution errors (NPDE) and prediction and variability corrected visual predictive checks (pvcVPC) against body weight. These NPDE were realized with an add-on package on R [31] using 1000 simulation of the dataset. pvcVPC were also performed using 1000 simulations with the design of the original dataset and the investigated model using Perl-speaks for NONMEM ® (PsN,version 4.4.8; SourceForge) [32].

External evaluation of the tested models and comparison with previous models

In order to evaluate the reliability of the investigated models, the steady-state MHD trough concentrations reported in children by Li et al. [33] were compared to the population trough concentrations predicted by the models for similar doses and body weights. In their study, Li and colleagues collected blood samples from 52 children aged from 0.58 to 15 years, and provided age, weight-normalized doses and individual MHD steady-state trough concentrations for each child [33]. Since their paper did not provide any, body weights were estimated using the Advanced Paediatric Life Support (APLS) manual formulae [34], which are (2 x age in years) + 8 for 1 to 5 years old patients and (3 x age in years) + 7 for 6 to 12 years old children. Patients without concomitant medication and whose age was not included in the 2 to 12 years interval were excluded from the analysis. Using these calculated body weights and the corresponding doses, trough MHD concentrations at steady-state were calculated using the empirical model, the theory-based allometry model, as well as previously published population PK models [15–17,22]. Adequacy between actual and predicted concentrations was investigated by calculating precision (RMSE) and bias (MPE) using the following formulae:

where, C_{OBS} is the observed concentration and C_{PRED} is the predicted concentration of the subject i and n is the total number of subjects.

<u>Evaluation of the final model</u>

Lack of bias of the final model was investigated by visual inspection of goodness of fit curves (population prediction (PRED) versus observed concentration (DV), individual weighted residuals (IWRES) and NPDE versus PRED or time after administration). Prediction-corrected visual predictive checks (pcVPC), stratified by the categorical covariate EIAED or not, were also performed using 500 simulations of the original dataset.

Dose evaluation

Monte Carlo simulations were performed with NONMEM 7.3 using the final model in order to obtain steady-state areas under the curve (AUC_{0-12}) and steady-state trough concentrations (C_{trough}) of MHD, at different daily doses in a bid regimen. One thousand children per body weight, dose and co-treatment were simulated. Investigated body weights were 10, 20, 30, 40 and 50 kg. Investigated doses were 10, 20, 25, 30, 40, 50, 60 and 90 mg/kg per day, divided into two intakes. The presence or absence of EIAEDs was also explored. Then, for each combination dose/body weight/co-medication, the probabilities to obtain steady-state C_{trough} within the reference range (3-35 mg/L) and to reach the toxicity threshold (>35 mg/L) [7] were calculated.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [35], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [36].

Results

Patient characteristics

Thirty-one children (13 girls and 18 boys) were included in the study, having a median (range) age of 8.08 (2.25 – 12.5) years and a median (range) body weight of 23 (12.7 – 56) kg. Of these children, fourteen received a dose of 5 mg/kg and seventeen received a dose of 15 mg/kg. Six patients were co-treated with one AED, nineteen with two AEDs and six with three AEDs. Concomitant AEDs are described in Table 1. Twenty-four of these patients were co-medicated with at least one EIAED. These thirty-one patients provided 277 and 279 sampling points for OXC and MHD, respectively. Two OXC sampling points were discarded because of analytical issues. Of these measured concentrations, 32% of OXC and 11.5% of MHD observations were below the LOQ. After keeping only the first BLQ of each patient, 13.7% and 6.5% of the observations remained BLQ for OXC and MHD, respectively.

Population pharmacokinetic modelling

The best base model was a two-compartment model with first-order absorption (without lag-time) and elimination for OXC, and a one compartment model with first-order elimination for MHD. Taking into account the equilibrium between OXC and its metabolite MHD via a constant representing the back-transformation of MHD into OXC improved the fit. The structural parameters for this model were the absorption rate constant of OXC (Ka), the apparent central and peripheral distribution volumes of OXC (Vc_{OXC}/F, where F is the

bioavailability, and Vp_{OXC}/F), the apparent elimination and distribution clearances of OXC (CL_{OXC}/F, Q_{OXC}/F), the apparent elimination clearance of MHD (CL_{MHD}/F), the apparent volume of distribution of MHD (Vc_{MHD}/F), and the back-transformation constant rate (K_{BT}) of MHD into OXC. The fraction of oxcarbazepine metabolized to MHD (Fm) was fixed to 1 and it was assumed that OXC was completely eliminated via metabolic conversion to MHD. The fraction of the dose that directly reached the metabolite compartment after oral absorption was estimated to 5.4% with the first-pass effect model. However, this model was not retained as it did not decrease significantly the LL. Inter-individual variability was estimated for all the parameters, except Ka. The residual error model used was proportional for OXC and combined for MHD.

The co-administration of EIAEDs was found to influence CL_{MHD}/F but no influence was found on CL_{OXC}/F. Addition of body weight as a covariate on CL_{OXC}/F, Vc_{OXC}/F, CL_{MHD}/F and Vc_{MHD}/F via an allometric function also significantly improved the fit with models 1 and 2. For model 3, where two separate allometric exponents for CL_{MHD} depending on the child age (over or under 6 years) were estimated, two very similar estimates were obtained for both age range (0.498 for children >6y and 0.541 for children <6y) and both values were very similar to the value obtained for the all population (0.549). The BDE model (model 4) on CL_{MHD} did not provide satisfying results (the -2LL increased and the parameters of the BDE were poorly estimated). Estimated exponents (model 1) allowed a better fit of the data than the theory-based allometric model (model 2), which was not improved by the addition of age via an allometric function or a maturation function. NPDE versus body weight and pvcVPC with body weight as the independent variable were performed for both models (with empirical allometric exponents and with fixed theoretical allometric exponents) (Figures 1 and 2). No significant bias was observed for each model, showing that they both described well the data across the range of body weights included in the study. However, the model

with estimated allometric exponents performed better on the external evaluation than the

model with fixed exponents, despite a slight over prediction of the concentrations. It also

performed better than formerly published models that included only MHD data (Table 2).

Thus, the empirical model was chosen as the final model and was considered reliable enough

to predict steady-state exposure of MHD.

The final model was then:

where MED is 0 or 1, if enzyme-inducing antiepileptic drugs were associated or not, and WT

is the patient body weight in kilograms.

The estimated values of the parameters of the final model and of the theory-based allometry

model and their precisions are reported on Table 3.

No significant bias was observed on the plot of observed versus population prediction for

OXC and MHD (data not shown). For OXC, IWRES versus time or PRED did not present

any bias (data not shown), whereas a small bias was seen in NPDE versus time graph for time

= 48h (Figure 3). Since almost all observations at this time were BLQ data, and the drug

intake is usually twice-a-day, it was considered that this bias would not penalize the prediction of PK profiles, for a bid regimen, with the model. No bias was observed for all the goodness of fit curves for MHD (Figure 3). pcVPC revealed no bias as the observed concentrations were homogeneously distributed around the 50th percentile of simulated concentrations (Figure 4). When stratified by the covariate EIAED, no bias was observed as well (data no shown).

Dose Evaluation

For a same dose, steady-state AUC_{0-12} of MHD increased with increasing body weight, and was lower in patients taking EIAEDs than in those without concomitant EIAEDs (Table 4). Similarly, MHD C_{trough} increased too with body weight and dose, and its value was also lower in patient co-treated with EIAEDs (Table 5).

For 10 kg children (i.e. children roughly 2 years old) without EIEADs, a probability > 95 % to be within the 3-35 mg/L reference range for MHD C_{trough} was obtained for 40-60 mg/kg daily doses (Figure 5B), which is in agreement with current recommendations.

For children with body weights between 20 and 40 kg, and without EIAEDs, a probability > 95% was obtained with daily doses between 20 and 40 mg/kg (Figure 5B), which is also consistent with current recommendations.

For 50 kg children without EIAEDs, a probability > 95% was obtained with daily doses between 20 and 30 mg/kg (Figure 5B). Of note, these doses are inferior to the target recommended maintenance dose of 30-45 mg/kg/day for 4-12 years old children. With such doses, around 10 % of the patients would reach the 35 mg/L toxicity threshold (Figure 5D).

In case of combined treatment with EIAEDs, the probability of target attainment was lower, so higher doses were needed. The most important impact of EIAEDs was observed for 10 kg

children, who may need doses up to 90 mg/kg/day (Figure 5A), which is 50% above the maximal recommended maintenance dose.

Discussion

This study was conducted with the aim to develop a parent-metabolite population model of OXC and MHD in order to characterize the pharmacokinetic parameters of both compounds and the covariates associated with their inter-individual variability. This model allows a better understanding of MHD pharmacokinetics resulting from its formation from OXC and its elimination and takes into account the back-transformation of MHD into its parent compound. Previous population PK studies directly related OXC dose to MHD concentration, without considering OXC concentration [15–17,21–24]. Such an approach can be supported by the high bioavailability of OXC and the fact that OXC is almost completely converted into MHD. However, since MHD concentration at a given time is the result of several phenomenon (MHD formation from OXC, MHD elimination, and MHD back-transformation to OXC), we believed a parent-metabolite model would allow a better prediction of the PK profile of MHD. Based on the results of the external evaluation displayed on Table 2, it appeared indeed that such a model provided a better prediction of MHD concentration at a given time.

The present model could not take into account the pre-systemic transformation of OXC into MHD [3], since the first-pass effect model investigated to describe this phenomenon [29] did not improve the fit. In fact, estimating all PK parameters could not be possible with oral data only and would require IV data as well [29,37]. However, a previous report determined that the fraction of the administered oxcarbazepine dose pre-systemically converted to MHD was only 6.5% (this fraction was estimated to 5.4% with our first-pass effect model), minimizing its impact [38].

A mean time to reach the maximum concentration (Tmax) of around 1h can be derived from our mean PK estimates for OXC, which is in accordance with the value provided by Flesch et al. [4]. OXC mean apparent weight-normalized clearance was 140 L/h/70kg. This value is in accordance with the reported value of 170,1 L/h/70kg in adults after a single dose [39]. Concerning MHD, apparent weight-normalized clearances were 4.11 L/h/70kg for children taking EIAEDs and 3.18 L/h/70kg for children not taking these medication. Those values are in agreement with the results of Sallas et al. (3.2 L/h/70kg) [15]. Flesch et al. [4] reported an absolute bioavailability of 99% after oral administration of OXC as well as a clearance of 3.5-5.5 L/h, for racemic MHD, in healthy volunteers after an intravenous administration of MHD. Considering that the bioavailability is almost total, our estimates are in accordance with these values.

MHD weight-normalized clearance decreased with increasing age (Figure 6). This was already evidenced in the non-compartmental study from Rey et al. [10] and some population approaches [15,16]. This phenomenon is frequent in children, and was already observed for other antiepileptic drugs like clobazam [40], carbamazepine [41], phenobarbital [42], felbamate [43] and valproic acid [44]. The main elimination route of MHD is glucuronidation, and the maturation of the hepatic abundance/activity depends on the UGT isoforms considered: it can sometimes reach adult levels two to three months after birth, while it can be upregulated beyond two years of age in other cases [45]. Of note, UGT isoform(s) responsible for MHD glucuronidation have not yet been identified. Renal excretion has a minor contribution in MHD elimination (less than 20% of the MHD dose administered intravenously was found unchanged in the urine [4]), nonetheless, as renal clearance follows the same allometric principles as metabolic clearance, it may also explain the decrease of weight-normalized clearance with age.

In the present study, OXC mean apparent volume of distribution was 397.7 L/70kg (5.7L/kg). This value is in agreement with the adult values described in the literature which are 3.9-12.5 L/kg (273-875 L/70kg) [6]. MHD mean apparent weight-normalized volume was 54.8 L/70kg. It differed greatly from the values displayed in some former population pharmacokinetic studies in children (285.6 L/70kg [16], 171.5 L/70kg [16] and 312.9 L/70kg [23]). However, according to the allometric principles, weight normalized-volume should be similar in all age groups [46]. Of note, the value we obtained in this study is similar to the values observed in adults, after an IV administration of MHD, that were 54,7 L for (R)-MHD and 45.9 L for (S)-MHD [4].

A summary of a size-standardized estimates and literature values is provided on Table 6.

In pediatric population pharmacokinetic studies, body weight is a factor reflecting changes in body size, and is related to clearance and volume via an allometric model with theoretical exponents of 0.75 or 0.67 for clearance and 1 for the volume [47]. Fixed and estimated allometric exponents were both tested. For oxcarbazepine, the estimated exponents for CL_{OXC}/F and Vc_{OXC}/F were 0.798 and 2.4, respectively. For MHD, those values were 0.549 and 1.09 for CL_{MHD}/F and Vc_{MHD}/F, respectively. Although the obtained values were not exactly similar to the theoretical exponents (principally the 2.4 exponent related to Vc_{OXC}/F), the model with estimated exponents performed better on the external evaluation (Table 2), as evidenced by the lower Mean Prediction Error obtained with the empirical model. The reason for this result is unclear to us. A possible explanation for the great difference between the exponent of 2.4 that was estimated for Vc_{OXC}/F and the theoretical value of 1 may result from the study design. Indeed, our PK parameters allow to calculate a distribution half-life of 0.53 h. It is therefore possible our study design did not include enough samples during the distribution phase, which may have penalized the estimation of this allometric factor. The estimated exponent for CL_{MHD}/F (0.549) is in accordance with the empirical allometric

exponent obtained by Sugiyama et al [16] in their population model of MHD (0.555). It was previously demonstrated that the theory-based allometric exponent of 0.75 for CL could be inaccurate in some situations [48–50]. Indeed, if this theory-based exponent accurately predicts CL in all cases in adolescents (from 12 to 18 years) [51], it may not be relevant for some drugs in younger children, especially < 5 years [48–50]. The fact that our population included children between 2 and 12 years and that half of them were below 6 years of age may explain the difference between the empirical allometric exponent of CL_{MHD}/F and the theoretical value of 0.75. Based on these results, we decided to use the empirical exponents to perform the dose evaluation. Nonetheless, because of the inconsistency with the allometric principles, we believe an important limitation of the present model is its inapplicability for children under 2 years.

Monte Carlo simulations were performed with the aim to evaluate the consistency between the recommended pediatric doses and the reference trough concentration of MHD (C_{trough}) for therapeutic drug monitoring. Older children, represented by higher body weights, achieved an AUC about 104.5% higher than younger patients (Table 4). This is consistent with the observation that weight-normalized clearance decreased with age. For 10 kg children, the probability for their MHD C_{trough} to be within the reference range increased from 23% to 98.3% with increasing doses (from 10 to 60 mg/kg/day) while, in 50 kg children, it decreased from 98.7% to 40.6% with increasing doses (for 10 and 60 mg/kg/day), as more C_{trough} exceeded the limit of 35 mg/L and reached possibly toxic concentrations (Supplementary data, Table 1). This confirms that older children need lower weight-normalized doses when compared to younger children.

Association with enzyme inducing drugs is another factor accounting for oxcarbazepine variability [13]. Most of the patients were on concomitant enzyme-inducing AEDs, so, MHD clearance was modelled as the clearance induced by EIAEDs and the covariate was the

absence of concomitant EIAEDs. Those AEDs increased MHD clearance by 29.3%. This phenomenon is well known and has been verified in most population models [15–17,23,24]. The drugs involved are carbamazepine, phenobarbital and phenytoin and it was demonstrated that they can reduce MHD concentration by 20 to 40% [14,52,53]. With our model, patients medicated with concomitant enzyme-inducing antiepileptic drugs had about 24% lower exposition to MHD than patients not co-treated with EIAEDs (Table 4). Therefore, it seems that children taking EIAEDs require greater weight-normalized doses to reach similar expositions. For these patients, probabilities to be within the reference range increased with dose/kg and weight and it was less likely for them to reach the toxicity threshold (Supplementary data, Table 2).

Figure 7 shows daily oxcarbazepine doses allowing the attainment of a maximum probability (> 95%) for MHD C_{trough} to be within the reference range with respect to body weight, with and without associated enzyme-inducing antiepileptic drugs. Recommended doses seem convenient, except for 50 kg children not co-medicated with EIAEDs, who would need less than the recommended target dose of 30-45 mg/kg/day, since a maximum probability of being within the reference range is attained between 20 and 30 mg/kg/day, and the risk of toxicity increases with higher doses. On the other hand, 10 kg children receiving concomitant EIAEDs would need more than the maximum recommendation of 60 mg/kg/day to have at least 95% chance to be within the reference range. It is not uncommon for clinicians to exceed the recommendations, as verified by Borusiak et al. in their retrospective study, where epileptic children were given oxcarbazepine doses from 19 to 123 mg/kg/day [9]. Considering a narrower reference range of 15-35 mg/L, as proposed by May et al. [6], the need for higher doses is, as expected, increased for 10kg children with EIAEDs who only have, for a 90 mg/kg/day dose, a 33.8% probability to be within this reference range

(Supplementary data, Tables 1 and 2). Nonetheless, despite smaller probabilities to reach therapeutic trough concentrations, the risk of toxicity remains the same.

The present model is only applicable to 2 to 12 years old epileptic patients and was developed based on oral suspension data. This formulation is optimal for young children (< 8 years) who may have swallowing issues, but the tablet formulation is preferable for older children. In adults, bioequivalence between the oral suspension and the film-coated tablet was evidenced [54,55], allowing us to assume that our model is applicable to the use of tablets in children. Due to exclusion criteria, this model cannot be applied neither to patients with body weights differing more than 2 SDs from normal body weight such as obese and malnourished children.

In conclusion, a parent-metabolite population pharmacokinetic model of oxcarbazepine and its monohydroxy derivative was developed in epileptic children. It identified body weight and concomitant enzyme-inducing antiepileptic drugs as important covariates explaining inter-individual pharmacokinetic variability of these two compounds. This model also allowed to evidence that the doses currently used by clinicians are appropriate to obtain trough concentrations of MHD within the recommended reference range [7], except for 10 kg children receiving concomitant enzyme-inducing antiepileptic drugs who could need doses higher than recommended, and 50 kg children without concomitant enzyme inducing drugs who may need doses lower than recommended. However, as this reference concentration range is wide and the correlation between MHD plasma concentration and its antiepileptic effect has not been well established [10], only clinical responsiveness and adverse events occurrence can ultimately allow the clinicians to decide which dose their patient requires. When the dose/effect relationship will be elucidated, this model could be useful to determine optimal dose regimens for children, especially the youngest ones.

Acknowledgment

The authors would like to acknowledge the contribution of the reviewers to this article.

References

1.   Full Prescribing Information. Trileptal. 2014.

2.   Flesch G. Overview of the Clinical Pharmacokinetics of Oxcarbazepine. Clin Drug Investig. 2004;24(4):185–203.

3.   Volosov A, Xiaodong S, Perucca E, Yagen B, Sintov A, Bialer M. Enantioselective pharmacokinetics of 10-hydrocarbazepine after oral administration of oxcarbazepine to healthy Chinese subjects. Clin Pharmacol Ther. 1999;66(6):547–53.

4.   Flesch G, Czendlik C, Renard D, Lloyd P. Pharmacokinetics of the Monohydroxy Derivative of Oxcarbazepine and Its Enantiomers after a Single Intravenous Dose Given as Racemate Compared with a Single Oral Dose of Oxcarbazepine. Drug Metab Dispos. 2011;39(6):1103–10.

5.   Kim DW, Gu N, Jang I, Chu K, Yu K, Cho JY, Yoon SH, Kim HS, Oh J, Lee SK. Efficacy, tolerability, and pharmacokinetics of oxcarbazepine oral loading in patients with epilepsy. Epilepsia. 2012;53(1):e9–12.

6.   May TW, Korn-Merker E, Rambeck B. Clinical Pharmacokinetics of Oxcarbazepine. Clin Pharmacokinet. 2003;42(12):1023–42.

7.   Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring : A position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239–76.

8.   Striano S, Striano P, Di Nocera P, Italiano D, Fasiello C, Ruosi P, Bilo L, Pisani F. Relationship between serum mono-hydroxy-carbazepine concentrations and adverse effects in patients with epilepsy on high-dose oxcarbazepine therapy. Epilepsy Res. 2006;69:170–6.

9.   Borusiak P, Korn-merker E, Holert N, Boenigk HE. A Survey in Treatment of Childhood Epilepsy: of 46 Children and Adolescents. J Epilepsy. 1998;11(6):355–60.

10.   Bring P, Ensom MH. Does Oxcarbazepine Warrant Therapeutic Drug Monitoring? A Critical Review. Clin Pharmacokinet. 2008;47(12):767–78.

11.   Rey E, Bulteau C, Motte J, Tran A, Sturm Y, D'Souza J, Markabi S, Pons G, Dulac O. Oxcarbazepine Pharmacokinetics and Tolerability in Children With Inadequately Controlled Epilepsy. J Clin Pharmacol. 2004;44:1290–300.

12.   Landmark CJ, Baftiu A, Tysse I, Valsø B, Larsson PG, Rytter E, Johannessen SI. Pharmacokinetic Variability of Four Newer Antiepileptic Drugs, Lamotrigine, Levetiracetam, Oxcarbazepine, and Topiramate: A Comparison of the Impact of Age and Comedication. Ther Drug Monit. 2012;34(4):440–5.

13.   Johannessen SI, Tomson T. Pharmacokinetic Variability of Newer Antiepileptic Drugs: When is Monitoring Needed ? Clin Pharmacokinet. 2006;45(11):1061–75.

14.   Tartara A, Galimberti CA, Manni R, Morini R, Limido G, Gatti G, Bartoli A, Strada G, Perucca E. The pharmacokinetics of oxcarbazepine and its active metabolite 10-hydroxy-carbazepine in healthy subjects and in epileptic patients treated with phenobarbitone or valproic acid. Br J Clin Pharmacol. 1993;36:366–8.

15.   Sallas WM, Milosavljev S, D'Souza J, Hossain M. Pharmacokinetic drug interactions in children taking oxcarbazepine. Clin Pharmacol Ther. 2003;74:138–49.

16.   Sugiyama I, Bouillon T, Yamaguchi M, Suzuki H, Hirota T, Fink M. Population pharmacokinetic analysis for 10-monohydroxy derivative of oxcarbazepine in pediatric epileptic patients shows no difference between Japanese and other ethnicities. Drug Metab Pharmacokinet. 2015;30(5):160–107.

17.   Wang Y, Zhang H, Niu C, Gao P, Chen Y, Peng J, Liu M, Xu H. Population pharmacokinetics modeling of oxcarbazepine to characterize drug interactions in Chinese children with epilepsy. Acta Pharmacol Sin. 2014;35:1342–50.

18.   Elger C, Bialer M, Falcão A, Vaz-da-Silva M, Nunes T, Almeida L, Soares-da-Silva P.

Pharmacokinetics and tolerability of eslicarbazepine acetate and oxcarbazepine at steady state in healthy volunteers. Epilepsia. 2013;54(8):1453–61.

19. Kristensen O, Klitgaard NA, Jonsson B, Sindrup S. Pharmacokinetics of 10-OH-carbazepine, the main metabolite of the antiepileptic oxcarbazepine, from serum and saliva concentrations. Acta Neurol Scand. 1983;68:145–50.

20. Lloyd P, Flesch G, Dieterle W. Clinical Pharmacology and Pharmacokinetics of Oxcarbazepine. Epilepsia. 1994;35(3):10–3.

21. Yu Y, Zhang Q, Xu W, Lv C, Hao G. Population pharmacokinetic modeling of oxcarbazepine active metabolite in Chinese patients with epilepsy. Eur J Drug Metab Pharmacokinet. 2015;

22. Peng J, Zhang H, Liu Z, Xu H, Wang Y. Population pharmacokinetics of oxcarbazepine active metabolite in Chinese children with epilepsy. Int J Clin Pharmacol Ther. 2014;52(8):684–92.

23. Northam RS, Hernandez AW, Litzinger MJ, Minecan DN, Glauser TA, Mangat S, Zheng C, Souppart C, Sturm Y. Oxcarbazepine in Infants and Young Children With Partial Seizures. Pediatr Neurol. 2005;33(5):337–44.

24. Park K, Kim J, Joo EY, Seo DW, Hong SB, Ko J, Kim S, Huh W, Lee S. Drug Interaction and Pharmacokinetic Modeling of Oxcarbazepine in Korean Patients With Epilepsy. Clin Neuropharmacol. 2012;35(1):40–4.

25. Rouan MC, Decherf M, Le Clanche V, Lecaillon JB, Godbillon J. Automated microanalysis of oxcarbazepine and its monohydroxy ans transdiol metabolites in plasma by liquid chromatography. J Chromatogr B. 1994;658:167–72.

26. Samson A, Lavielle M, Mentré F. Extension of the SAEM algorithm to left-censored data in nonlinear mixed-effects model: Application to HIV dynamics model. Comput Stat Data Anal. 2006;51:1562–74.

27. Beal SL. Ways to Fit a PK Model with Some Data Below the Quantification Limit. J Pharmacokinet Pharmacodyn. 2001;28(5):481–504.

28.   Schütz H, Feldmann KF, Faigle JW, Kriemler H-P, Winkler T. The metabolism of 14C-oxcarbazepine in man. Xenobiotica. 1986;16(8):769–78.

29.   Bertrand J, Laffont CM, Mentré F, Chenel M, Comets E. Development of a Complex Parent-Metabolite Joint Population Pharmacokinetic Model. AAPS J. 2011;13(3):390–404.

30.   Wang C, Peeters MYM, Allegaert K, van Oud-alblas HJB, Krekels EHJ, Tibboel D, Danhof M, Knibbe CAJ. A Bodyweight-Dependent Allometric Exponent for Scaling Clearance Across the Human Life-Span. Pharm Res. 2012;29(6):1570–81.

31.   Comets E, Brendel K, Mentré F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. Comput Methods Programs Biomed. 2008;90:154–66.

32.   Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-Corrected Visual Predictive Checks for Diagnosing Nonlinear Mixed-Effects Models. AAPS J. 2011;13(2):143–51.

33.   Li R, Sheng X, Ma L, Yao H, Cai L, Chen C, Zhu S, Zhou Y, Wu Y, Cui Y. Saliva and Plasma Monohydroxycarbamazepine Concentrations in Pediatric Patients with Epilepsy. Ther Drug Monit. 2016;38(8):365–70.

34.   Samuels M, Wieteska S, Eds. Advanced Paediatric Life Support: The Practical Approach. John Wiley & Sons Ltd, editor. West Sussex, UK; 2011.

35.   Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: Towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucleic Acids Res. 2016;44:D1054–D1D68.

36.   Alexander SPH, Catterall WA, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Southan C, Davies JA, CGTP Collaborators. The concise guide to PHARMACOLOGY 2015/16 : Voltage-gated ion channels CatSper and Two-Pore channels. Br J Pharmacol. 2015;172:5904–41.

37.   Cheng H, Juskot WJ. Pharmacokinetics of reversible metabolic systems. Biopharm Drug Dispos. 1993;14:721–66.

38.   Brar S, Bhattaram A, Kumi K, Zhu H. Clinical Pharmacology Review [Internet]. 2011. Available   from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ UCM328328.pdf

39.   Dickinson RG, Hooper WD, Dunstan PR, Eadie MJ. First dose and steady-state pharmacokinetics of oxcarbazepine and its 10-hydroxy metabolite. Eur J Clin Pharmacol. 1989;37:69–74.

40.   Jullien V, Chhun S, Rey E, Dulac O, Tod M, Chiron C, Pons G. Pharmacokinetics of Clobazam and N -Desmethylclobazam in Children with Dravet Syndrome Receiving Concomitant Stiripentol and Valproic Acid. Clin Pharmacokinet. 2015;54:527–36.

41.   Delgado Iribarnegaray MF, Santo Bueldga D, Garcia Sanchez MJ, Otero MJ, Falcao A, Dominguez-Gil A. Carbamazepine population pharmacokinetics in children: mixed-effect models. Ther Drug Monit. 1997;19(2):132–9.

42.   Yukawa E, Higuchi S, Aoyama T. Phenobarbitone population pharmacokinetics from routine clinical data: role of patient characteristics for estimating dosing regimens. J Pharm Pharmacol. 1992;44(9):755–60.

43.   Banfield CR, Zhu GR, Jen JF, Jensen PK, Schumaker RC, Perhach JL, Affrime MB, Glue P. The effect of age on the apparent clearance of felbamate: a retrospective analysis using nonlinear mixed-effects modeling. Ther Drug Monit. 1996;18(1):19–29.

44.   Cloyd JC, Fisher JH, Kriel RL, Kraus DM. Valproic acid pharmacokinetics in children. IV. Effects of age and antiepileptic drugs on protein binding and intrinsic clearance. Clin Pharmacol Ther. 1993;53(1):22–9.

45.   Strassburg CP, Strassburg A, Kneip S, Barut A, Tukey RH, Rodeck B, Manns MP.

Developmental aspects of human hepatic drug glucuronidation in young children and adults. Gut. 2002;50:259–65.

46.   Holford N, Heo Y-A, Anderson B. A Pharmacokinetic Standard for Babies and Adults. J Pharm Sci. 2013;102(9):2941–52.

47.   Anderson BJ, Holford NHG. Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303–32.

48.   Calvier EAM, Krekels EHJ, Välitalo PAJ, Rostami-Hodjegan A, Tibboel D, Danhof M, Knibbe CAJ. Allometric Scaling of Clearance in Paediatric Patients : When Does the Magic of 0.75 Fade ? Clin Pharmacokinet. 2017;56:273–85.

49.   Mahmood I. Dosing in Children: A Critical Review of the Pharmacokinetic Allometric Scaling and Modelling Approaches in Paediatric Drug Development and Clinical Settings. Clin Pharmacokinet. 2014;53:327–46.

50.   Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol. 2006;61(5):545–57.

51.   Momper JD, Mulugeta Y, Green DJ, Karesh A, Krudys KM, Sachs HC, Yao LP, Burckart GJ. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatr. 2013;167(10):926–32.

52.   McKee P, Blacklaw J, Forrest G, Gillham R, Walker S, Connelly D, Brodie M. A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. Br J Clin Pharmacol. 1994;37(1):27–32.

53.   Armijo J, Vega-Gil N, Shushtarian M, Adin J, Herranz J. 10-Hydroxycarbazepine serum concentration-to-oxcarbazepine dose ratio: influence of age and concomitant antiepileptic drugs. Ther Drug Monit. 2005;27(2):199–204.

54.   Souppart C, Yin Q, Merz M, Hu P, Jiang J, Appel-Dingemanse S. Bioequivalence of oxcarbazepine oral suspension vs . film-coated tablet in healthy Chinese male subjects. Int J

Clin Pharmacol Ther. 2008;46(10):538–44.

55.   Flesch G, Tudor D, Denouel J, Bonner J, Camisasca R. Assessment of the bioequivalence of two oxcarbazepine oral suspensions versus a film-coated tablet in healthy subjects. Int J Clin Pharmacol Ther. 2003;41(7):299–308.

Table 1. Concomitant antiepileptic drugs

Associated Antiepileptic Drug	Patients (%)	
Carbamazepine	19	(61.3 %)
Vigabatrin	14	(45.2 %)
Clobazam	8	(25.8 %)
Phenytoin	5	(16.1 %)
Valproic acid	4	(12.9 %)
Clonazepam	3	(9.7 %)
Lamotrigine	3	(9.7 %)
Diazepam	2	(6.5 %)
Phenobarbital	2	(6.5 %)
Ethosuccimide	1	(3.2 %)
Progabide	1	(3.2 %)

Table 2. Comparison between MHD steady-state trough concentrations obtained in therapeutic drug monitoring by Li et al. [29] and predicted by different models

Model	MPE	RMSE
Parent-metabolite model with back-transformation and estimated allometric coefficients	27.7%	7.2
Parent-metabolite model with back-transformation and fixed allometric coefficients	39 %	7.8
MHD model developed by Peng et al. [22]	44.1%	14.5
MHD model developed by Sallas et al. [15]	95.6%	14.2
MHD model developed by Sugiyama et al. [16]	69.1%	11.4
MHD model developed by Wang et al. [17]	145.1%	24.5

Table 3. Values and precision of the parameters of the estimated allometric exponent and fixed allometric exponent models

Parameter	Model with estimated allometric exponents		Model with fixed allometric exponents	
	Estimated value	RSE (%)	Estimated value	RSE (%)
K_a (h^{-1})	1.83	4	1.81	4
CL_{OXC}/F (L/h/70kg)	140	24	116	8
Vc_{OXC}/F (L/70kg)	337	41	55.7	22
Q_{OXC}/F (L/h)	62.5	21	119/70kg	21
Vp_{OXC}/F (L)	60.7	25	235/70kg	23
CL_{MHD}/F (L/h/70kg)	4.11	14	5.1	5
Vc_{MHD}/F (L/70kg)	54.8	16	47.7	6
K_{BT} (h^{-1})	0.0622	15	0.0476	16
θWT	0.798	26	0.75	FIXED
θWT	2.4	17	1	FIXED
θWT	-	-	0.75	FIXED
	-	-	1	FIXED
θn	-0.257	42	-0.276	40
θWT	0.549	21	0.75	FIXED
θWT	1.09	13	1	FIXED
$\omega CL_{OXC}/F$	0.393	15	0.361	16
$\omega Vc_{OXC}/F$	0.601	22	1.07	16
$\omega Q_{OXC}/F$	0.919	18	0.928	17
$\omega Vp_{OXC}/F$	1.26	15	1.11	15
$\omega CL_{MHD}/F$	0.235	14	0.247	15
$\omega Vc_{MHD}/F$	0.211	25	0.209	23
ωK_{BT}	0.63	16	0.587	17
σ_{OXC}	0.32	7	0.321	7
σ_{MHD} (a)	0.993	13	0.972	13
σ_{MHD} (b)	0.0398	21	0.0406	20

RSE relative standard error, Ka absorption rate constant, F bioavailability, Vc_{OXC} central volume of distribution of OXC, CL_{OXC} elimination clearance of OXC, Q_{OXC} intercompartmental clearance of OXC, Vp_{OXC} peripheral volume of distribution of OXC, CL_{MHD} elimination clearance of MHD, Vc_{MHD} central volume of distribution of MHD, K_{BT} back-transformation constant, θ factor describing the relationship between the covariate and the parameter, WT body weight, nEIAEDs absence of enzyme-inducing antiepileptic drug, ω inter-individual variability, σ residual error, (a) additive, (b) proportional, OXC oxcarbazepine, MHD monohydroxy derivative

Table 4. Median and non-parametric 95% confidence interval (95CI) of simulated steady-state AUC_{0-12} of MHD according to the daily dose of oxcarbazepine administered as a bid regimen

Body weight (kg)	Co-treatment	10 mg/kg/d Median [95CI]	20 mg/kg/d Median [95CI]	40 mg/kg/d Median [95CI]	60 mg/kg/d Median [95CI]	90 mg/kg/d Median [95CI]
10		46.5 [31.0 – 72.3]	92.9 [61.9 – 144.7]	185.8 [123.8 – 289.3]	278.8 [185.7 – 434.0]	412.1 [267.1 – 662.6]
20		62.2 [38.5 – 101.8]	124.4 [77.0 – 203.5]	248.7 [154.0 – 407.0]	373.1 [231.0 – 610.4]	561.3 [357.6 – 897.9]
30	Without EIAEDs	75.5 [48.0 – 119.8]	151.0 [96.1 – 239.6]	302.0 [192.1 – 479.2]	453.0 [288.2 – 718.7]	680.0 [420.2 – 1110.2]
40		84.9 [56.3 – 132.6]	169.9 [112.5 – 265.1]	339.7 [225.0 – 530.2]	509.6 [337.5 – 795.3]	771.3 [472.3 – 1232.7]
50		95.1 [60.4 – 148.4]	190.2 [120.9 – 296.9]	380.4 [241.8 – 593.8]	570.6 [362.7 – 890.6]	861.0 [538.1 – 1349.3]
10		35.5 [21.9 – 57.4]	71.1 [43.9 – 114.7]	142.2 [87.7 – 229.4]	213.3 [131.6 – 344.2]	317.6 [206.3 – 503.9]
20		48.7 [30.0 – 77.3]	97.3 [60.1 – 154.6]	194.6 [120.1 – 309.1]	291.9 [180.2 – 463.7]	432.8 [271.9 – 697.7]
30	With EIAEDS	58.3 [35.5 – 92.8]	116.5 [71.0 – 185.6]	233.1 [141.9 – 371.2]	349.6 [212.9 – 556.8]	519.9 [330.1 – 824.5]
40		66.3 [41.4 – 104.3]	132.6 [82.8 – 208.6]	265.2 [165.5 – 417.2]	397.8 [248.3 – 625.8]	602.0 [383.5 – 938.0]
50		72.3 [46.0 – 113.8]	144.6 [92.0 – 227.5]	289.1 [184.1 – 455.1]	433.7 [276.1 – 682.6]	673.2 [405.4 – 1033.0]

EIAEDS: Enzyme Inducing Anti-Epileptic Drugs; 95CI: non parametric 95% confidence Interval

Table 5. Median and non-parametric 95% confidence interval (95CI) of simulated steady-state MHD trough concentrations according to the daily dose of oxcarbazepine administered as a bid regimen

Body weight (kg)	Co-treatment	10 mg/kg/d Median [95CI]	20 mg/kg/d Median [95CI]	40 mg/kg/d Median [95CI]	60 mg/kg/d Median [95CI]	90 mg/kg/d Median [95CI]
10		2.2 [0.6 – 4.5]	4.4 [1.3 – 9.1]	8.9 [2.5 – 18.1]	13.3 [3.8 – 27.2]	19.2 [5.2 – 41.4]
20		3.3 [1.3 – 6.7]	6.6 [2.5 – 13.5]	13.2 [5.1 – 27.0]	19.7 [7.6 – 40.4]	29.6 [11.6 – 57.9]
30	Without EIAEDs	4.5 [1.9 – 8.0]	8.9 [3.8 – 16.0]	17.9 [7.7 – 32.0]	26.8 [11.5 – 48.0]	39.5 [16.4 – 74.0]
40		5.4 [2.7 – 9.4]	10.8 [5.3 – 18.7]	21.7 [10.6 – 37.5]	32.5 [16.0 – 56.2]	48.7 [22.8 – 87.9]
50		6.3 [3.4 – 10.9]	12.5 [6.7 – 21.9]	25.1 [13.5 – 43.7]	37.6 [20.2 – 65.6]	56.9 [28.6 – 96.9]
10		1.5 [0.3 – 3.4]	2.9 [0.6 – 6.9]	5.9 [1.1 – 13.7]	8.8 [1.7 – 20.6]	12.2 [2.8 – 29.2]
20		2.3 [0.7 – 4.7]	4.6 [1.4 – 9.3]	9.1 [2.9 – 18.7]	13.7 [4.3 – 28.0]	20.0 [5.8 – 42.2]
30	With EIAEDs	3.1 [1.2 – 5.9]	6.1 [2.5 – 11.7]	12.3 [5.0 – 23.5]	18.4 [7.5 – 35.2]	27.4 [10.5 – 53.6]
40		3.8 [1.6 – 7.1]	7.7 [3.3 – 14.2]	15.3 [6.6 – 28.4]	23.0 [9.9 – 42.6]	34.9 [14.5 – 62.9]
50		4.4 [2.1 – 7.9]	8.8 [4.1 – 15.9]	17.7 [8.3 – 31.8]	26.5 [12.4 – 47.6]	40.9 [18.4 – 72.1]

EIAEDs: Enzyme Inducing Anti-Epileptic Drugs; 95CI: non parametric 95% confidence Interval

Table 6. Comparison of size-standardized estimates and values reported in the literature.

Parameter	Estimate	Literature value	Ref.
CL_{OXC}/F	140 L/h/70kg	170,1 L/h/70kg	[39]
V_{OXC}/F	397.7 L/70kg	273-875 L/70kg	[6]
CL_{MHD}/F	3.18 L/h/70kg	3.2 L/h/70kg	[15]
		3.5-5.5 L/h*[a]	[4]
V_{MHD}/F	54.8 L/70kg	54.7 L (S)-MHD *[a]	[4]
		45.9 L (R)-MHD *[a]	[4]

* obtained from IV data
[a] no body weight was provided by the authors; study included 12 healthy volunteers (6 females and 6 males)
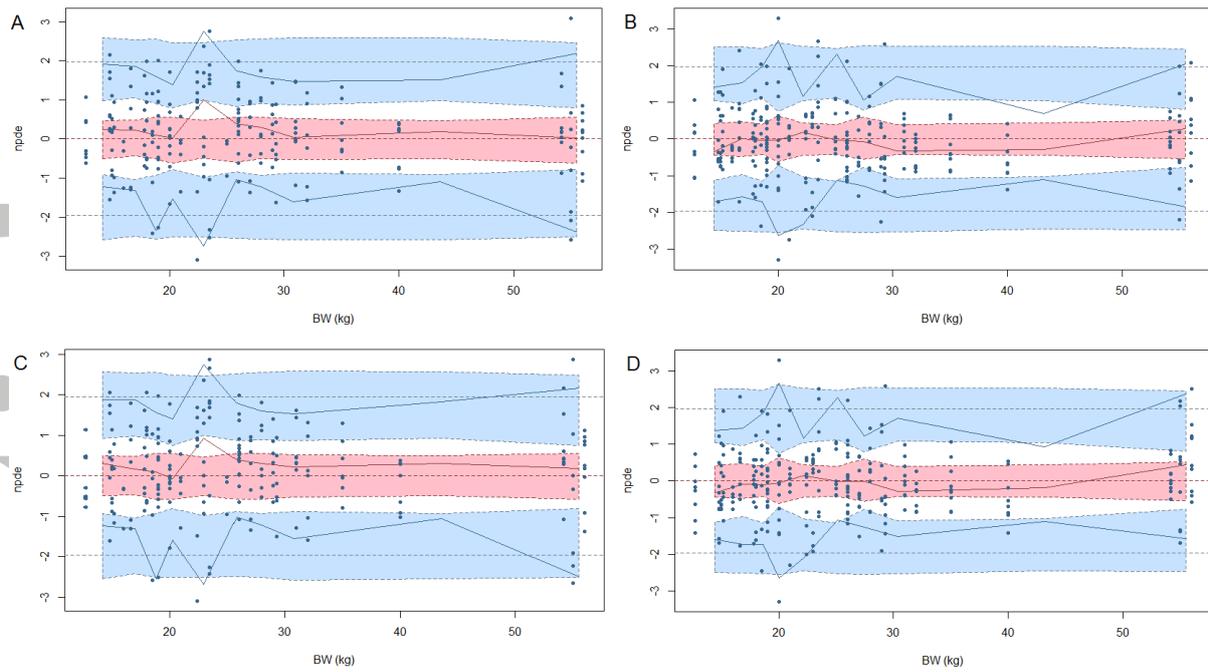
Figure 1. NPDE versus body weight (BW) of oxcarbazepine (A) and its monohydroxy

derivative (MHD) (B) for the empirical model and of oxcarbazepine (C) and MHD (D) for

the allometry theory based model. Upper blue area represents the simulation-based 95%

confidence interval of the 95th percentile; pink area represents the simulation-based 95%
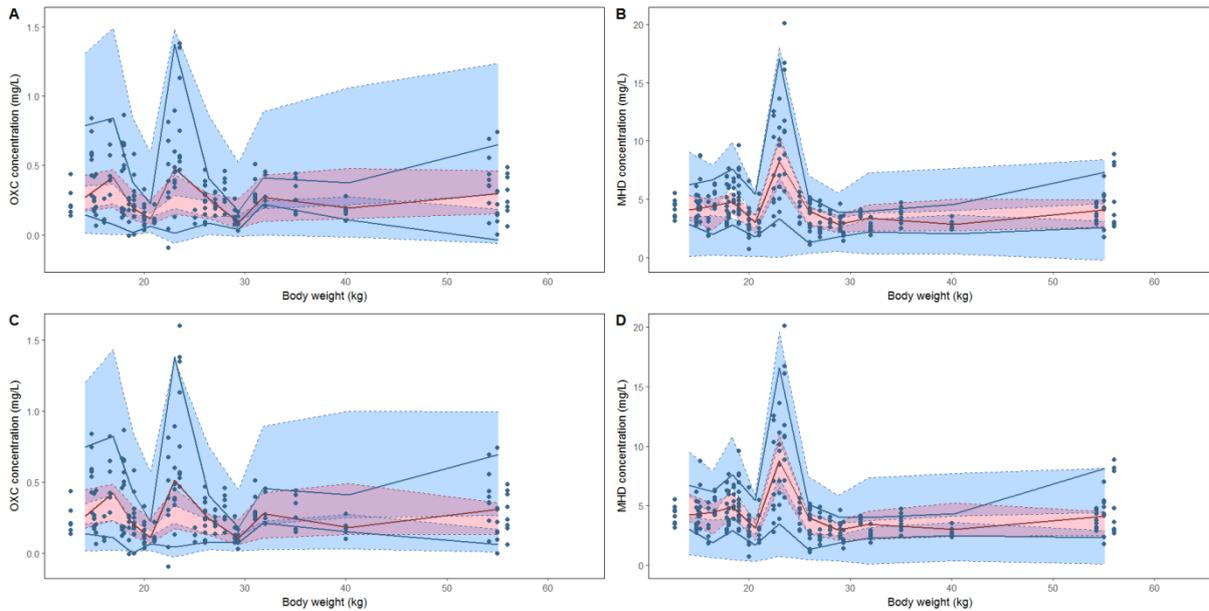
confidence interval of the 50th percentile; lower blue area represents the simulation-based

95% confidence interval of the 5th percentile

Figure 2. Prediction and variability corrected visual predictive checks against body weight obtained with the empirical model for oxcarbazepine (OXC) (A) and monohydroxy derivative (MHD) (B) and obtained for the theory-based allometry model for OXC (C) and MHD (D). Blue dots represent the predicted and variability corrected observed concentrations; upper blue area represents the simulation-based 95% confidence interval of the 95th percentile; pink area represents the simulation-based 95% confidence interval of the 50th percentile; lower blue area represents the simulation-based 95% confidence interval of the 5th percentile; upper and lower blue solid lines represent the 5th and 95th empirical percentiles of the observations; red solid line represents the 50th empirical percentile of the observations
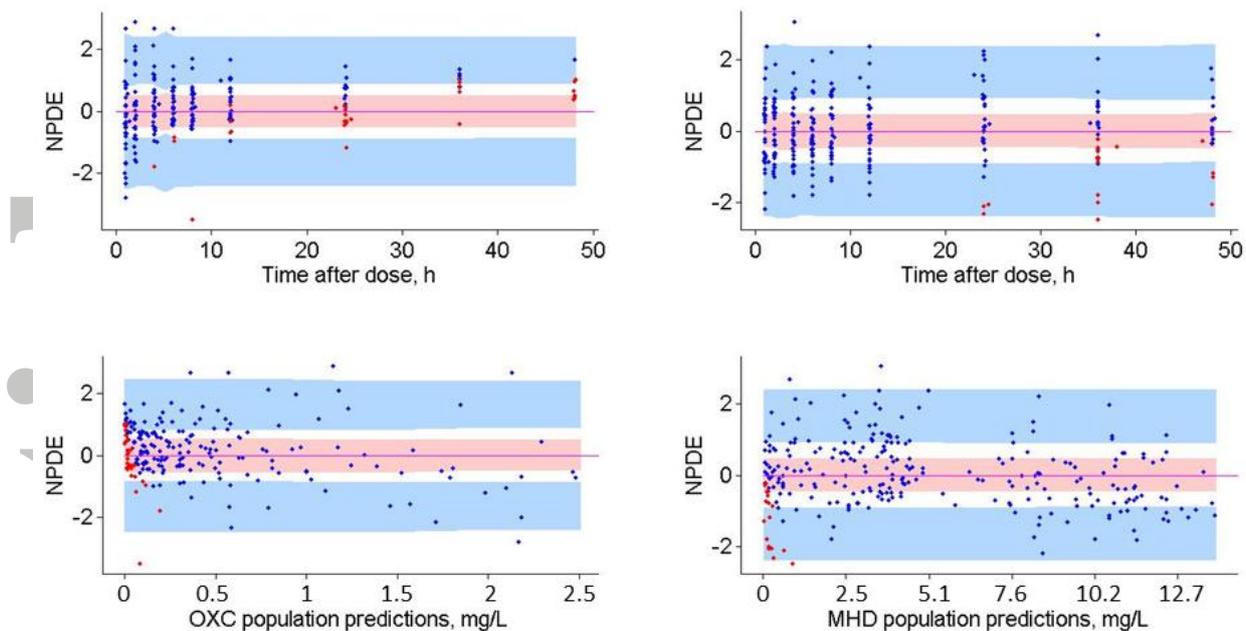
Figure 3. NPDE versus time (top) and population predictions (below) of oxcarbazepine (left) and its monohydroxy derivative (MHD) (right). Blue dots are observed data; red dots are BLQ data (sampled from the conditional distribution   ), where $\hat{\psi}$ and are the estimated individual and population parameters, respectively); upper blue area represents the simulation-based 90% confidence interval of the 90th percentile; pink area represents the simulation-based 90% confidence interval of the 50th percentile; lower blue area represents the simulation-based 90% confidence interval of the 10th percentile
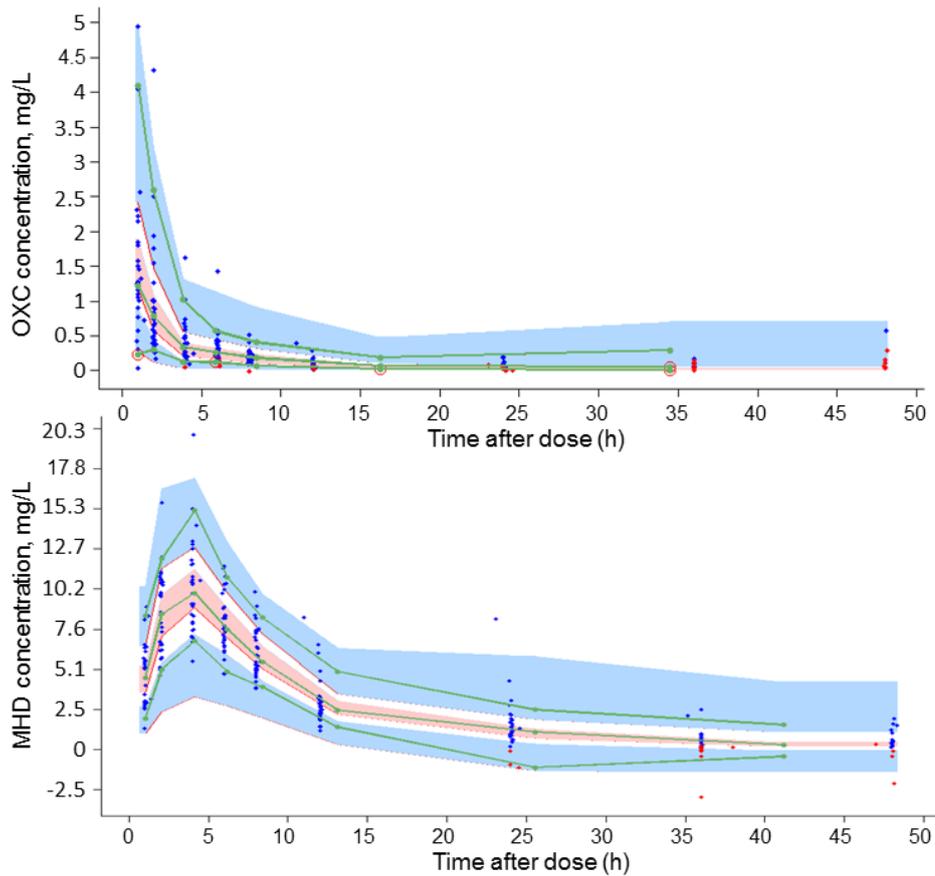
Figure 4. Prediction-corrected visual predictive checks obtained with the final model.

Oxcarbazepine (OXC) on top, monohydrody derivative (MHD) below. Blue dots represent

the observed concentrations; red dots represent the BLQ data (sampled from the conditional

distribution); green lines represent 5th, 50th and 95th empirical percentiles of the observations;

upper blue area represents the simulation-based 95% confidence interval of the 95th

percentile; pink area represents the simulation-based 95% confidence interval of the 50th

percentile; lower blue area represents the simulation-based 95% confidence interval of the 5th

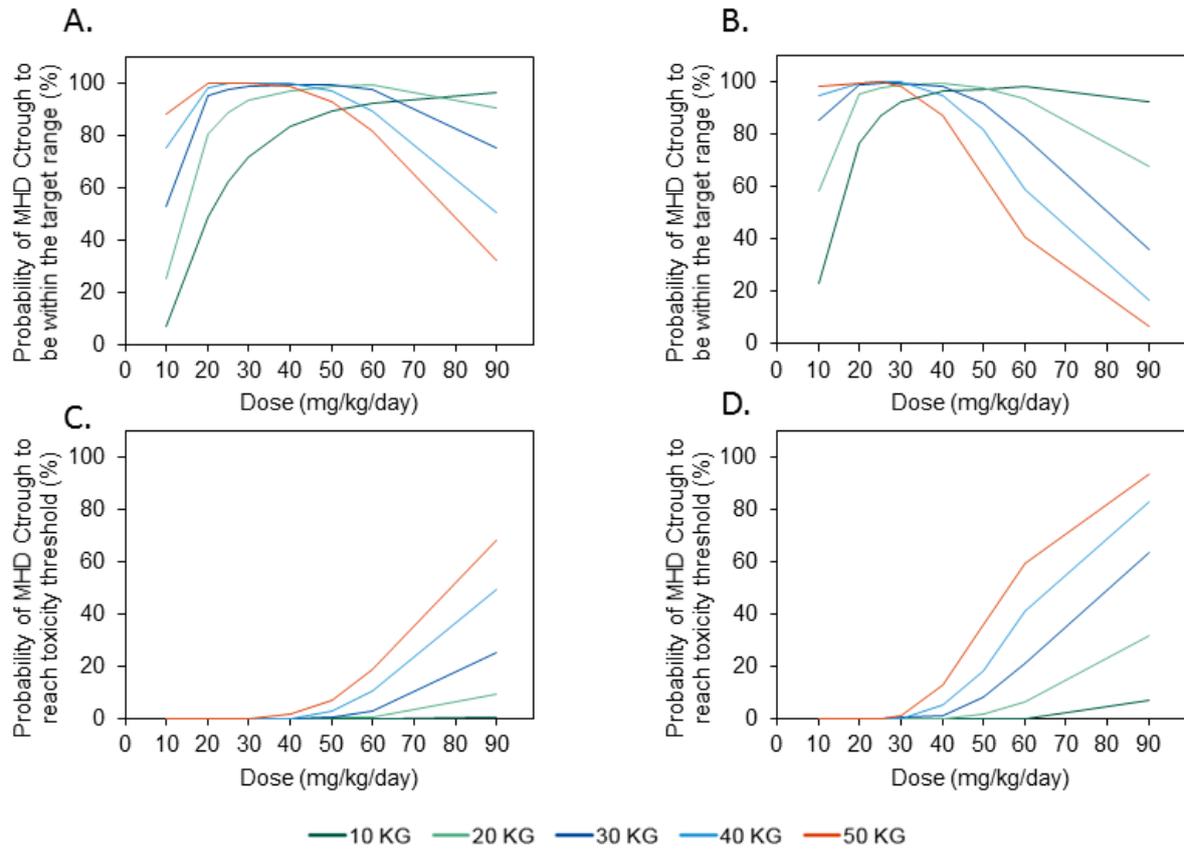percentile; red area represents outliers

Figure 5. Probability of steady-state MHD trough concentration to be within reference range (3-35 mg/L) depending on dose and body weight when enzyme-inducing antiepileptic drugs are associated (A) or not (B); Probability of steady-state MHD trough concentration to reach toxicity threshold (>35 mg/L) depending on dose and body weight when enzyme-inducing antiepileptic drugs are associated (C) or not (D)
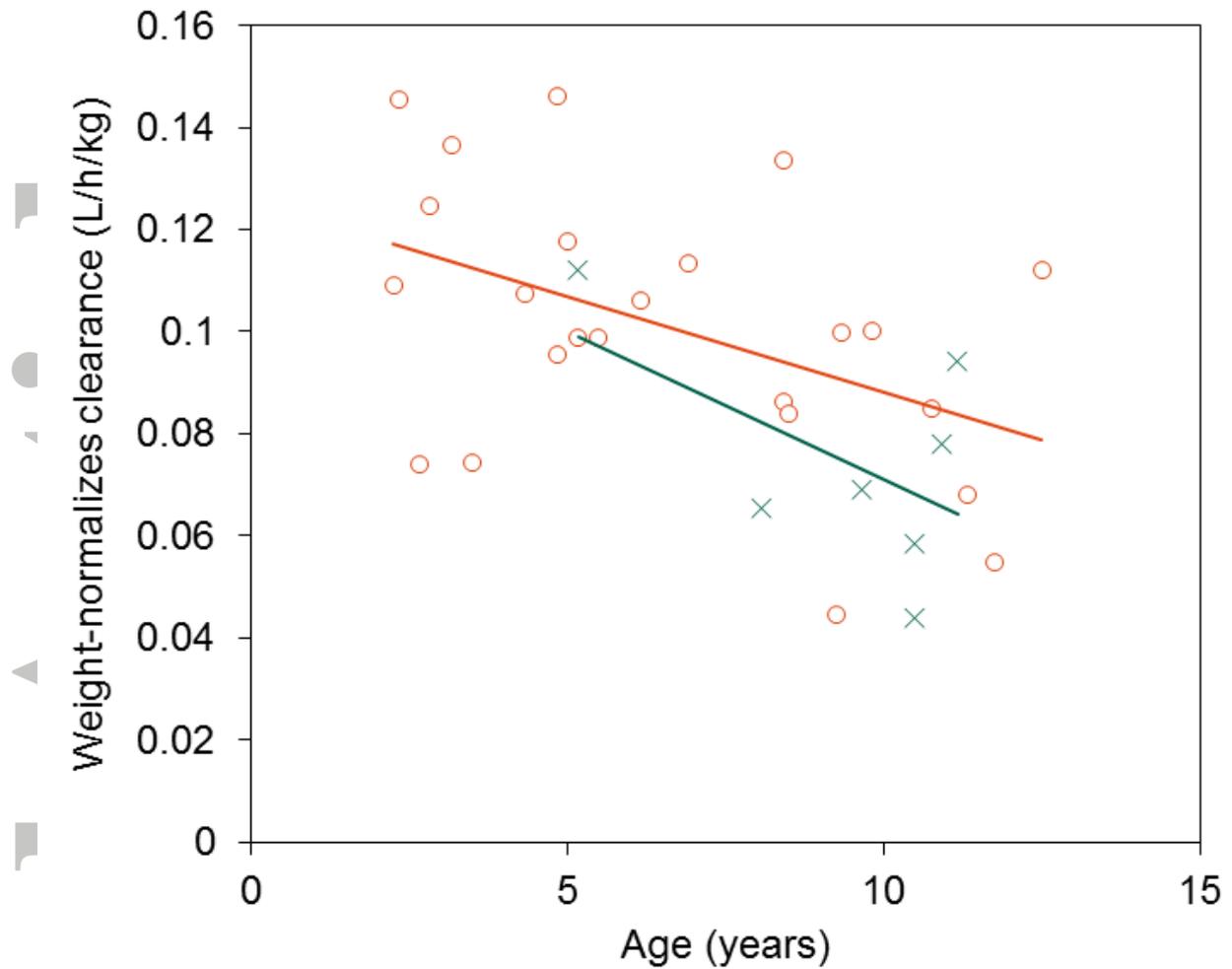
Figure 6. Relationship of monohydroxy derivative (MHD) weight-normalized clearance with respect to age. Orange circles represent children taking concomitant enzyme-inducing antiepileptic drugs; green crosses represent children not taking enzyme-inducing antiepileptic drugs
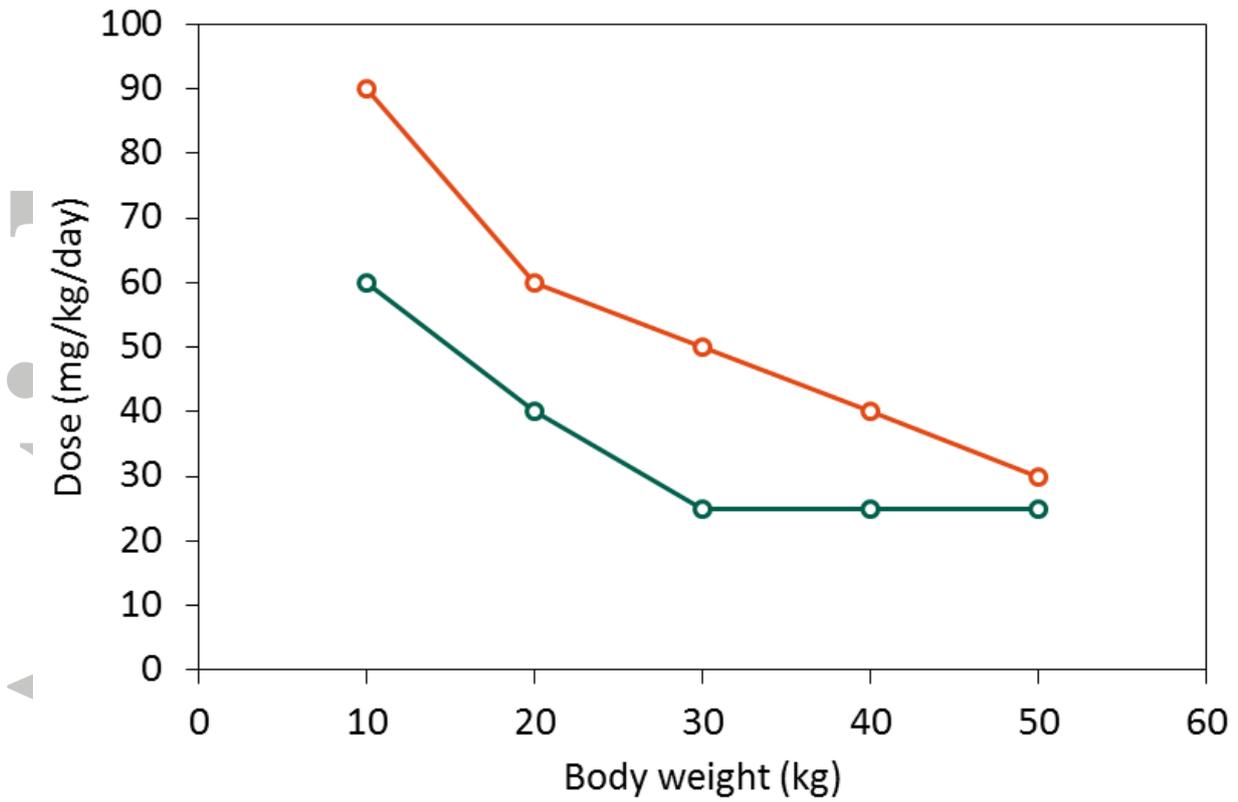
Figure 7. Daily doses to obtain a maximum probability (> 95%) to be within the reference range. Orange line represents doses for children taking concomitant enzyme-inducing antiepileptic drugs; green line represents doses for children not taking concomitant enzyme-inducing antiepileptic drugs

List of Hyperlinks for Crosschecking

Oxcarbazepine :
http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7254.

Voltage-gated sodium channels :
http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=82

Potassium:
http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=81

Calcium : http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=80