

oxcarbazepine and its 10-monohydroxy derivative in epileptic children

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Background

- Oxcarbazepine (OXC) is an antiepileptic drug (AED) used in focal seizures in both children and adults.
- Oxcarbazepine is almost completely transformed into its main metabolite, 10-hydroxy-carbazepine (MHD), which is principally eliminated through glucuronidation [1].
- Factors accounting for pharmacokinetic variability of OXC and MHD are age and association with enzyme-inducing antiepileptic drugs [2].

Objective: to develop the first parent-metabolite pop-PK model and to evaluate whether the recommended pediatric doses (from 10 to 60 mg/kg/day) allow to achieve a trough concentration of MHD (C_{trough}) within the target window (3 – 35 mg/L [4]).

Methods

Patients and study design

- Data from a clinical trial in epileptic children (previously analyzed using a non-compartmental approach [3])
- 31 epileptic children (2-12y) randomized to receive a single oral dose of 5 or 15 mg/kg
- Blood samples collected at times 0, 1, 2, 4, 6, 8, 12, 24, 36 and 48h
- MHD and OXC assayed using a HPLC method.
- LOQ for OXC and MHD were 0.05 mg/L and 0.1 mg/L, respectively

Population pharmacokinetics analysis

- Nonlinear mixed effect model built in Monolix 4.3.2
- Model built using the likelihood ratio test
- Continuous covariate (body weight) included via an allometric equation
- Categorical covariate (enzyme-inducing antiepileptic drugs (EIAEDs)) included via an exponential equation
- For each patient, the first value below the limit of quantification (BLQ) was kept in the dataset

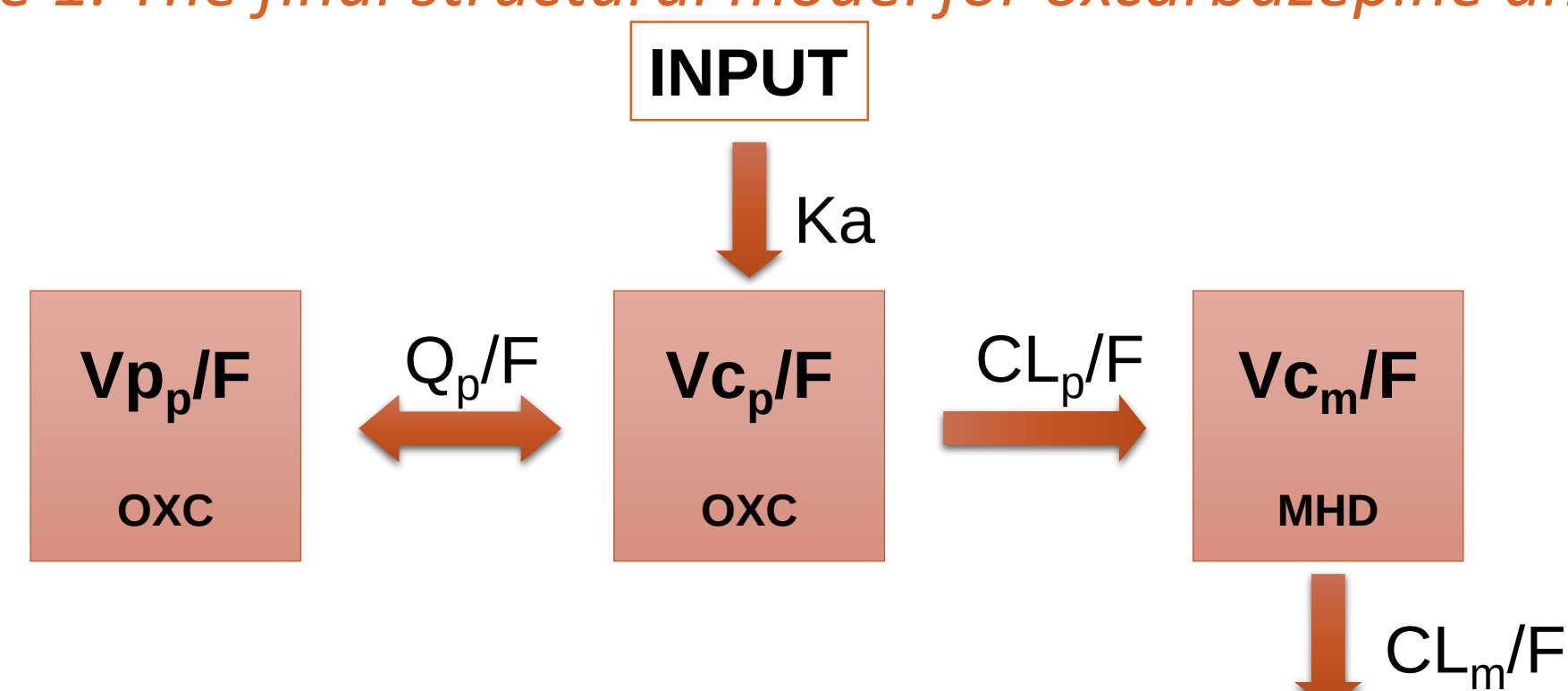
Monte Carlo Simulations

- Monte Carlo simulations realized with NONMEM 7.3
- 1000 children of 10 to 50 kg, with and without EIAEDs
- Doses of 10, 20, 25, 30, 40, 50, 60 and 90 mg/kg/day
- For each combination dose/weight/co-medication, probabilities to be within the target range were calculated

Results

- A total of 277 and 279 sampling points were obtained for OXC and MHD, respectively.
- 13.7% and 6.5% of the data were BLQ for OXC and MHD
- A parent-metabolite model with two compartments for oxcarbazepine and one compartment for MHD was the best to describe the pharmacokinetics of the two compounds (Figure 1)

Figure 1. The final structural model for oxcarbazepine and MHD



- The estimated parameters are reported in Table I.

Table I. Values and precision of the parameters of the final model

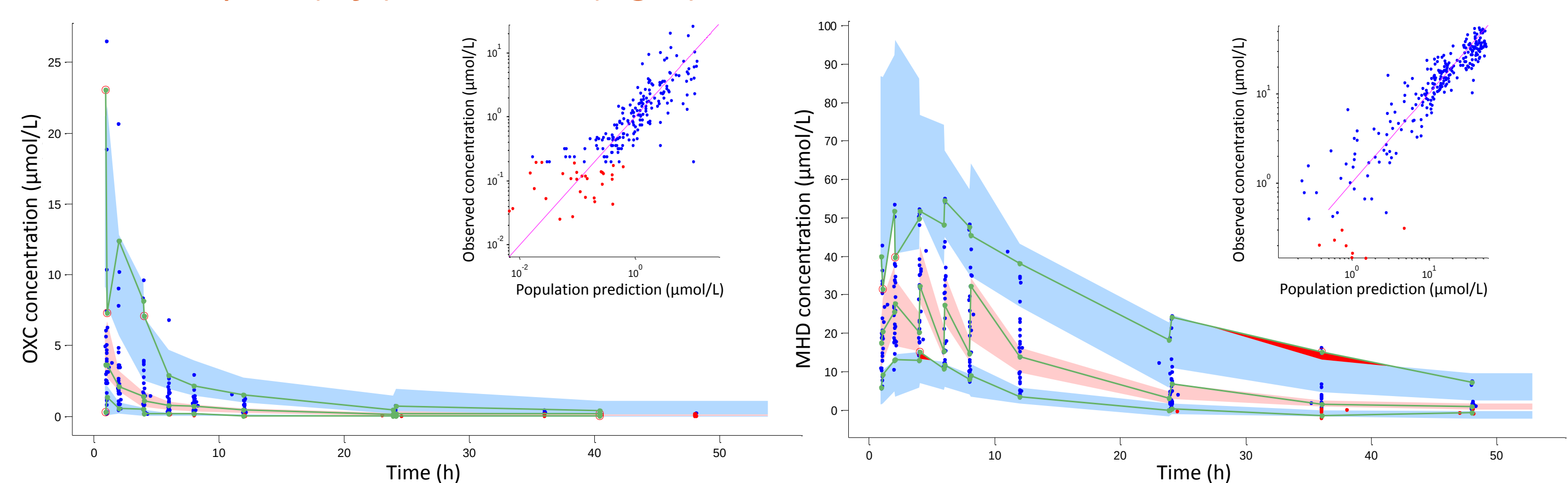
Parameter	Mean estimate	RSD (%)	Variability (ω)	RSD (%)
K_a (h^{-1})	2.19	15	0.75	13
CL_p/F (L/h)	$37.2 * (WT/23)^{0.457}$	7	0.387	15
V_{c_p}/F (L)	$43.6 * (WT/23)^{1.72}$	10	0.21	55
Q_p/F (L/h)	44.7	15	0.767	14
V_{p_p}/F (L)	$183 * (WT/23)^{1.03}$	11	0.498	15
CL_m/F (L/h)	$2.19 * e^{-0.191 * MED} * (WT/23)^{0.541}$	5	0.231	14
V_{c_m}/F (L)	$10 * (WT/23)^{0.803}$	6	0.244	22
σ_{OXC}	0.346	7		
σ_{MHD}	0.964	13		
σ_{MHD}	0.0336	24		

Where WT is body weight, MED is 1 if co-treated with non inducing AEDs and 0 if co-treated with inducing AEDs

Results (continuation)

- Model evaluation :

Figure 2. Visual predictive checks and goodness-of-fit of final population model of oxcarbazepine (left) and MHD (right)



Blue dots represent the observed concentrations; red dots represent the BLQ data; 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 represent outliers.

- Monte Carlo Simulations :

- Probability to be within the target range increased with increasing doses for smaller children but decreased for bigger children (Figure 3A)
- For the same dose, probability to be within target range was lower for patients taking EIAEDs (Figure 3B)

Figure 3. Probability of MHD trough concentration to be within the target range vs. dose per body weight

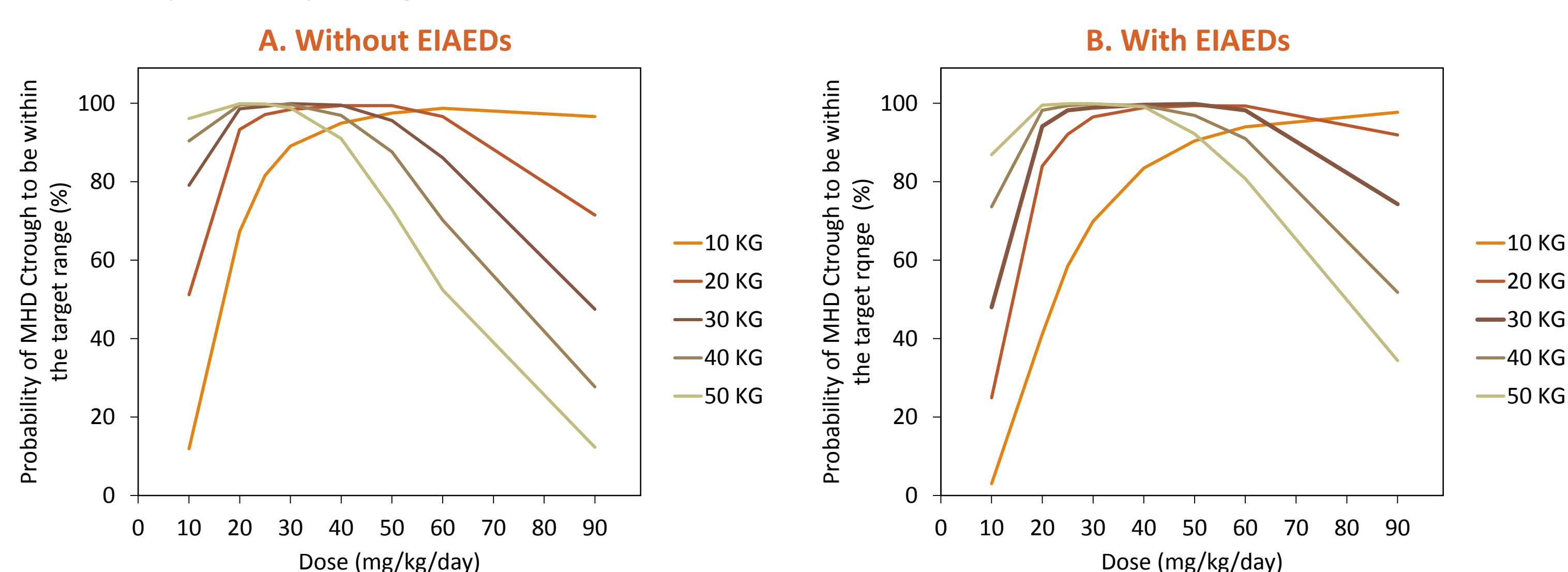
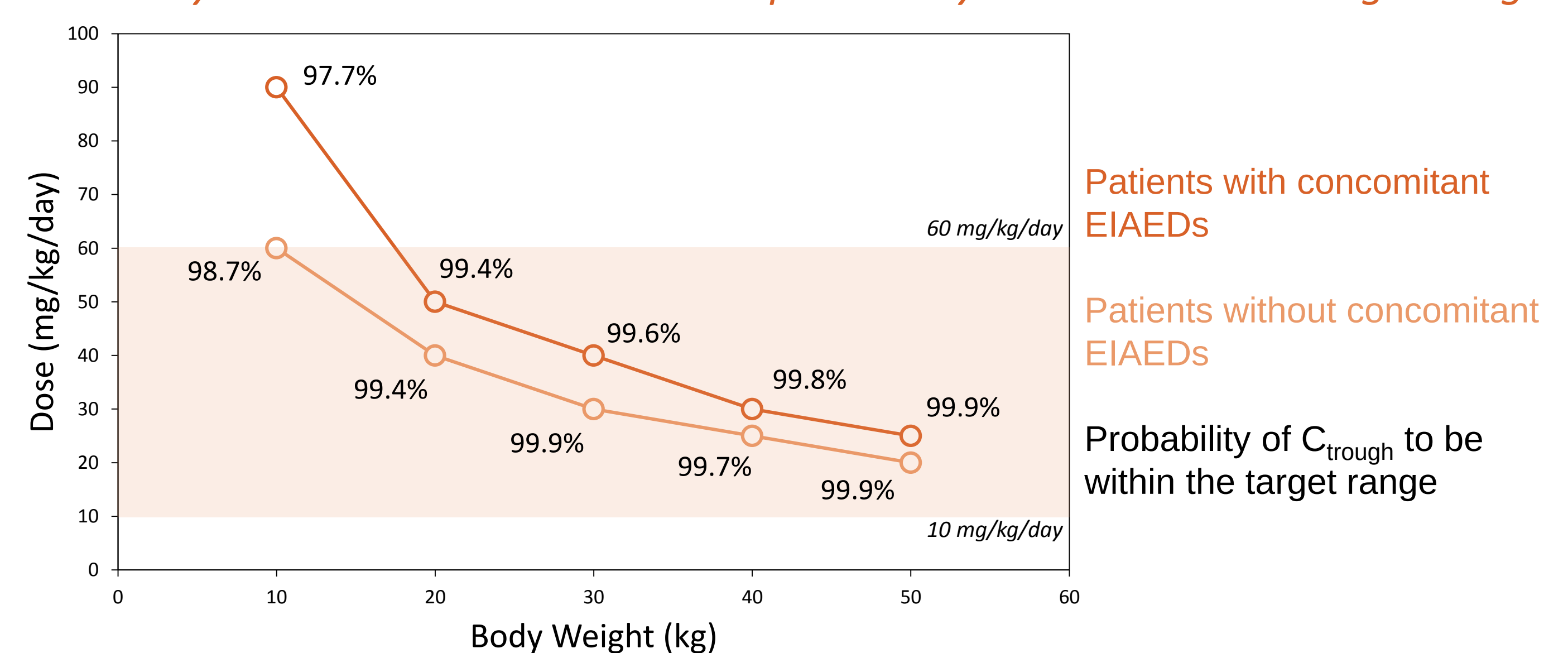


Figure 4. Daily doses to obtain a maximum probability to be within the target range



Discussion & Conclusion

- The first parent-metabolite population pharmacokinetic model of oxcarbazepine and its 10-monohydroxy derivative in epileptic children was developed.
- Body weight and concomitant enzyme-inducing AEDs were identified as important covariates.
- Monte Carlo simulations showed that smaller children need higher doses than bigger children to obtain MHD C_{trough} within the target range (Figure 4).
- Simulations also showed that children taking concomitant EIAEDs need higher doses than children not taking them to obtain MHD C_{trough} within the target range (Figure 4).
- This model evidenced that the doses currently used by clinicians are appropriate to obtain trough concentrations of MHD within the recommended target range, except for 10 kg children with concomitant EIAEDs.
- Because of the lack of PK/PD data, only clinical responsiveness can allow clinicians to decide which dose their patients require.