Oxcarbazepine and its active metabolite 10-monohydroxycarbamazepine clearance maturation in paediatric patients with epilepsy

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Background

Oxcarbazepine (OXC) is a second generation antiepileptic drug approved for treatment of partial seizures in adults and children as monotherapy or adjunctive therapy. The recommended initiation dosing regimen in children (2-16 years) is 8-10 mg/kg/day, given twice daily.

After oral administration OXC is rapidly absorbed and metabolized to its 10-monohydroxy derivative (MHD) which is mostly responsible for the pharmacological effects. MHD is further metabolised with glucuronidation, is eliminated renally and to minor extent by metabolism to dihidroxy derivative.

There is a potential benefit of TDM (reference range of MHD trough concentrations is 3-35 mg/L).

Pharmacokinetic studies with OXC and MHD in children (<2 years) are scarce. Consequently, there are no guidance on dosing in this age group.

Objectives

To develop OXC-MHD parent-metabolite population pharmacokinetic model in paediatric patients (0.5-3 years) to:

- assess the OXC and MHD clearance maturation and to
- avaluate the recommended dosing regimen in children in this age group.

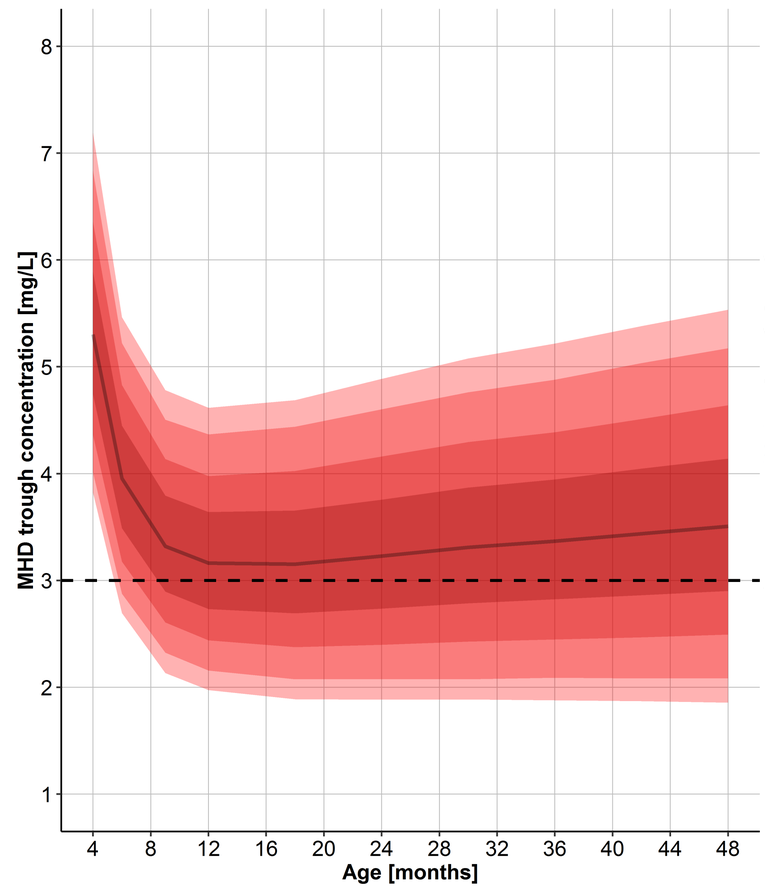
Conclusion

Our pharmacokinetic model confirms rapid maturation of OXC and MHD clearances, which during the first year of age approach the values in adults accounting for the difference in weight.

Nevertheless, the results of the simulation study indicate that the recommended dosing regimen in children (0.5-2 years) is safe.

Simulation

Simulated trough MHD concentration with 10 mg/kg/day bid (median, 50%, 75%, 90%, and 95% prediction interval).



Weight distributions in various age groups were obtained from WHO child growth standards available at: http://www.who.int/childgrowth/standards/weight_for_age/en/.

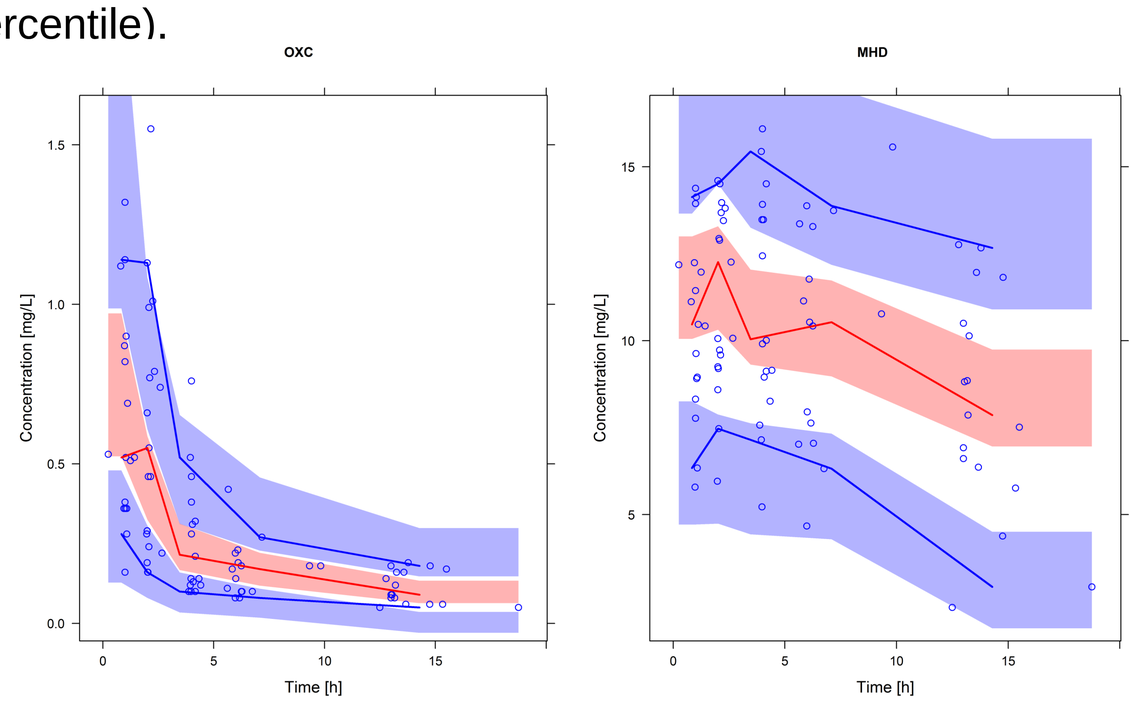
Dashed line is the lower limit of the reference range (3-35 mg/L).

Model

Parameters of the final model.

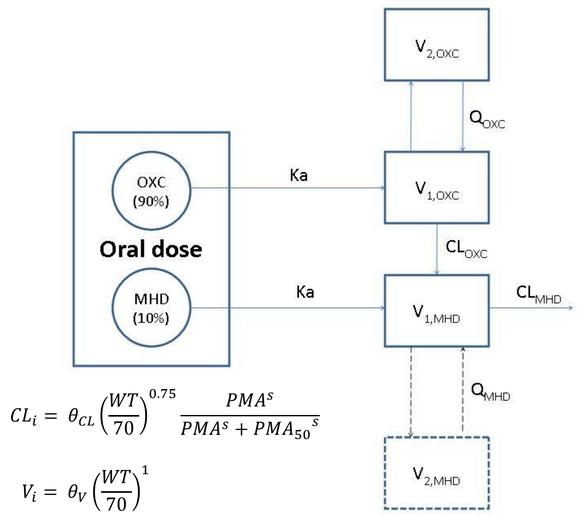
Parameter	Estimate [bootstrap 95% CI]	IIV, Shrinkage (%, %) [bootstrap95% CI]
K_a (h^{-1})	**0.863** [0.327, 1.24]	**75.0**, 22.3 [3.6, 161]
CL_{OXC} (L/h/70 kg)	**127** [112, 161]	**7.40**, 59.2 [0.2, 29.7]
$PMA_{50,OXC}$ (week)	**58.2** [49.2, 71.6]	
s_{OXC}	**4.57** [3.56, 16.8]	
$V_{1,OXC}$ (L/70 kg)	**141** [67.1, 316]	**206**, 31.4 [4.1, 682]
$V_{2,OXC}$ (L/70 kg)	**2260** [1100, 535000]	
Q_{OXC} (L/h/70 kg)	**103** [69.2, 135]	
CL_{MHD} (L/h/70 kg)	**0.489** [0.454, 0.537]	**12.7**, 7.20 [8.1, 17.0]
$PMA_{50,MHD}$ (week)	**55.1** [35.6, 71.4]	
s_{MHD}	**6.15** [3.57, 44.0]	
$V_{1,MHD}$ (L/70 kg)	**19.7** [13.4, 24.3]	
Residual variability (Shrinkage 10.1%)		
$\sigma_{additive,OXC}$ (mg/L)	**0.0259** [0.00041, 0.0381]	
$\sigma_{proportional,OXC}$ (%)	**34.5** [24.7, 43.9]	
$\sigma_{additive,MHD}$ (mg/L)	**0.907** [0.721, 1.10]	

Prediction and variabilty corrected VPC (5th, 50th, and 95th percentile).



Methods

Model structure.



$$CL_i = \theta_{CL}\left(\frac{WT}{70}\right)^{0.75}\frac{PMA^s}{PMA^s + PMA_{50}{}^s}$$

$$V_i = \theta_V\left(\frac{WT}{70}\right)^{1}$$

Characteristics of the patients.

Demographic data	
Number of patients (n)	18
Sex (female/male)	9 (50)/9 (50)
Age (years)	2.22 (0.49-3.59)
Gestational age (weeks)	39.5 (36-41)
Postmenstrual age (weeks)	155.4 (63.5-226.0)
Weight (kg)	12.84 (7.87-17)
Height (cm)	90.5 (71-106)
Body surface area (m^2)	0.56 (0.40-0.71)
OXC dose (mg/day)	375 (75-525)
Somatic diseases (Yes/No)	7 (39.9)/11 (61.1)
Co-medication	
Valproic acid (n)	2 (11.1)
Levetiracetam (n)	4 (22.2)
Vigabatrine (n)	1 (5.6)
Ethosuximide (n)	1 (5.6)
Topiramate (n)	1 (5.6)

n (%) or median (range)

The model was developed in NONMEM (ver. 7.3) using FOCe-I for parameter estimation. Initially, only OXC concentration measurements were analysed to develop a structural model for the parent drug. Subsequently a parent-metabolite model was developed. One and two compartments were tested for the disposition of MHD. Complete OXC absorption (first-order process) was assumed. Firs-pass metabolism was fixed to 10% to avoid non-identifiability. We further assumed that OXC is completely transformed to MHD. Patient weight (WT) and age were introduced into the model using a theoretical allometric relationship and a sigmoidal maturation function (MF) of post menstrual age (PMA).

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