R-13

Population pharmacokinetic study of lacosamide in children and adults with epilepsy

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Purpose:

- Lacosamide is an antiepileptic drug recommended for the treatment of partial seizures with or without secondary generalization in patients ≥ 4 years old.
- Lacosamide is subject to an important interindividual pharmacokinetic (PK) variability, increasing the risk of under- or overdosing.

Objective: To evaluate recommended and alternative dosing regimens for specific populations to achieve the target therapeutic concentration range using a population pharmacokinetic (popPK) approach.

Methods:

- ✓ Development of a popPK model from 136 plasma concentrations (111 adult observations + 25 pediatric observations) collected during routine therapeutic monitoring at the University Hospital of Lausanne (CHUV).
- ✓ IV and per os administration
- ✓ Analysis of biologically relevant covariates (e.g. creatinine clearance, body weight).
- ✓ Simulations under different dosing regimens for adults and infants to obtain the best percentage of patients with an average concentration within the target therapeutic range : [10 mg/L, 20 mg/L] [1]

Results:

Table 1. *Population description*

Patients characteristics	Adults (n=48) n (%) or median (min, max)	Children (n=8) n (%) or median (min, max)
Women	21 (43 %)	7 (87%)
Age (years)	67 (22, 94)	10 (4, 14)
BW (kg)	70 (40, 128)	41 (16, 52)
CrCL (Cockcroft-Gault formula, mL/min)	75 (16, 184)	-
CrCL (Schwartz formula, mL/min/1.73m²)	-	167 (106, 338)
Maintenance doses (mg/day)	400 (50, 400)	200 (40, 400)
Loading doses (mg)	400 (200, 800)	-

BW: body weight, CrCL : Creatinine clearance

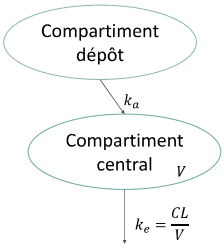

Figure 1. *Schematic representation of the structural popPK model*

Table 2. *PK parameters of the final popPK model*

Parameter	Final popPK model Estimate (RSE %)
θ_{CL} (L/h)	1.41 (5.9)
θ_{CrCL}	0.31 (46.3)
θ_V (L)	39.7 (14.2)
k_a (h⁻¹)	2.11 Fixed
F_1	1 Fixed
IIV_{CL} (%)	32.4 (14)

RSE: standard relative error, θ_{CL}: population clearance, θ_V: population volume of distribution, k_a : absorption constant rate, F_1 : relative bioavailability, θ_{CrCL}: effect of creatinine clearance on clearance, IIV_{CL} : inter-individual variability of clearance, expressed as CV (%)

Final equations : $CL = \theta_{CL} * \left(1 + \theta_{CrCL} * \frac{CrCL-75}{75}\right) * \left(\frac{BW}{70}\right)^{0.75*I_{pop}} * exp(IIV_{CL})$; $I_{pop} = \begin{cases} 0 \text{ if adult} \\ 1 \text{ if children} \end{cases}$; $V = \theta_V * \left(\frac{BW}{70}\right)^{1*I_{pop}}$

Dosing regimens optimization

➢ Adults

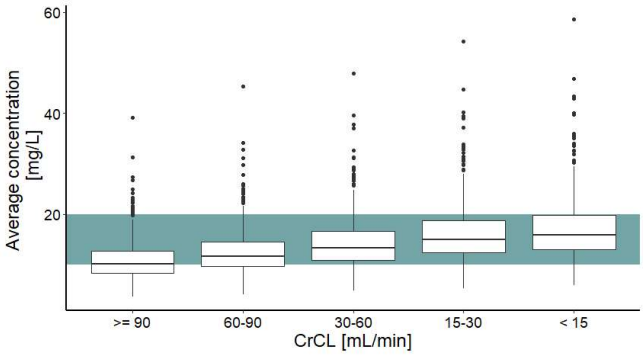

Figure 2. *Simulated adults average concentrations under usual dosing regimen (200 mg/12h) as a function of creatinine clearance.* The green shape represents the targeted therapeutic range

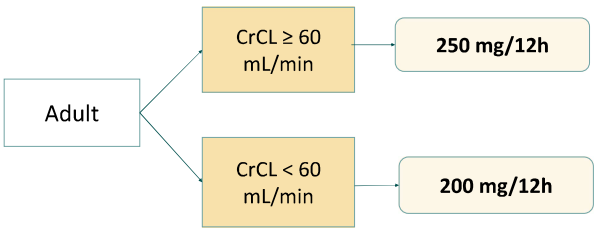

Figure 4. *Proposed adult doses for best target concentration achievement as a function of CrCL*

➢ Children

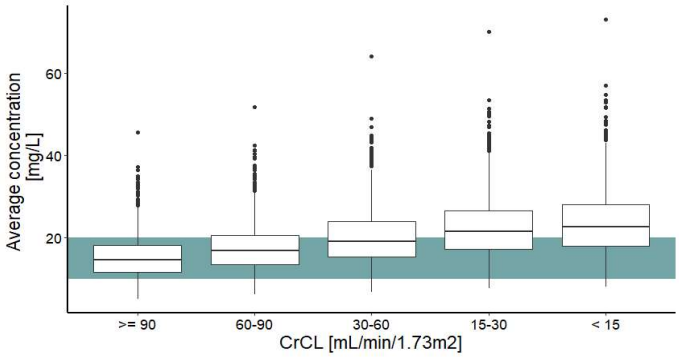

Figure 3. *Simulated pediatric average concentrations under maximum approved dose (6 mg/kg/12h) for children under 20 kg as a function of creatinine clearance.* The green shape represents the targeted therapeutic range

Table 3. *Proposed children doses for best target concentration achievement as a function of CrCL and BW*

CrCL (mL/min/1.73m²) \ BW (kg)	< 20	20-30	30-50	≥ 50
≥ 90	6 mg/kg/12h	5 mg/kg/12h	4 mg/kg/12h	250 mg/12h
60-90	5 mg/kg/12h	4 mg/kg/12h		
30-60			3 mg/kg	200 mg/12h
15-30	4 mg/kg/12h	3 mg/kg/12h		
< 15				

Conclusion:

- **The simulations showed a discrepancy between the target therapeutic range and the currently recommended doses of 200 mg/12h in adult patients with normal renal function**
- **Need for clinical studies to verify efficacy and toxicity of proposed dosage regimens**

1. Patsalos, P. N., et al. (2018). "Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy: A 2018 Update." Therapeutic Drug Monitoring 40(5): 526-548.