Population pharmacokinetics of the sustained-release granule formulation of valproic acid in epileptic children

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Introduction

Since its serendipitous discovery, valproic acid (VPA) has been widely used in multiple seizure types and various neurological and psychiatric disorders [1].

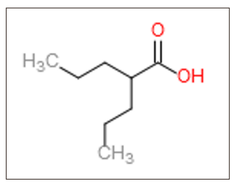

Figure 1. Valproic acid

VPA is almost completely absorbed and has a relatively small volume of distribution (0.15 - 0.4 L/kg) due to its extensive plasma protein binding (over 90%). Its metabolism is extensive and involve numerous pathways (principally glucuronidation, mitochondrial β-oxidation and ω-oxidation) [1,2].

A prolonged-release granule formulation facilitating drug intake was developed for children and is currently available at a recommended mean daily dose between 20 and 30 mg/kg [3,4].

Objectives

1. To develop a population pharmacokinetic model for this SR-granule formulation in epileptic children
2. To evaluate if dosage recommendations are adequate with the trough concentration (C_{trough}) target window of 50-100 mg/L [5] and, if not, which doses would be more suitable

Materials & Methods

Patients and Study Design
- Data obtained from two clinical studies (Table 1)
- VPA assayed by a fluorescence polarization immunoassay kit

Population pharmacokinetics analysis
- Nonlinear mixed effect model built in NONMEM 7.3 ® using the FOCE method with interaction
- Likelihood ratio test for model building
- Continuous covariates (body weight and total daily dose) included via allometric models
- Evaluation by NPDE and prediction and variability corrected VPC

Dose evaluation
- Monte Carlo simulations
- 1000 children of 10 to 70 kg
- Doses of 20, 30 and 40 mg/kg/day
- For each combination dose/weight, probabilities to be within the target range were calculated

Table 1. Description of the two studies

Study 1	Study 2
0.5 – 15 years	0.5 – 18 years
0 – 2 concomitant AEDs	Associated to clobazam and stiripentol
20 – 30 mg/kg/day, adjustable by clinician	20 – 30 mg/kg/day, adjustable by clinician
3 blood samples at steady-state	4 blood samples at steady-state

Results

Population
- 98 epileptic children (1 – 17,6 y) were included, providing 325 sampling points

Model development
- One compartment with first-order absorption and elimination
- Proportional residual error
- Flip-flop parametrization [6]:
  - Ka constrained to be higher than Ke
  - Ka = Ke + C
  - C is a constant to estimate
- Covariate analysis:
  - Body weight (BW)
    - Initially empirical : coefficients of 0.764 and 0.985 for CL/F and V/F
    - Loss of V/F IIV
    - Application of theoretical coefficients of 0.75 and 1 [7]
  - Total daily dose (TDD)
    - Saturation of protein binding
    - Nonlinear relationship between VPA clearance and dose

Final model (Table 2):

$$Ka = 0.15\ h^{-1}$$

$$\mathrm{CL/F} = 0.672 \times \left(\frac{\mathrm{BW}}{70}\right)^{0.75} \times \left(\frac{\mathrm{TDD}}{21.88}\right)^{0.371}\ \mathrm{L/h}$$

$$\mathrm{V/F} = 13.2 \times \left(\frac{\mathrm{BW}}{70}\right)\ \mathrm{L}$$

Model Evaluation
- No bias observed (Figure 2 & Figure 3)

Table 2. Values and precision of the parameters of the final model

Parameter	Final model parameters	
	Estimate	RSE (%)
C* (h^{-1})	0.0988	32.1
CL/F (L/h)	0.672	2.3
θ $BW_{CL/F}$	0.75 (Fixed)	-
θ $TDD_{CL/F}$	0.371	16.9
V/F (L)	13.2	12.0
θ $BW_{V/F}$	1 (Fixed)	-
ω^2 CL/F	0.0404	16.9
σ^2	0.0244	15.6

*C = Ka-Ke
BW body weight (kg), TDD total daily dose (mg/kg)

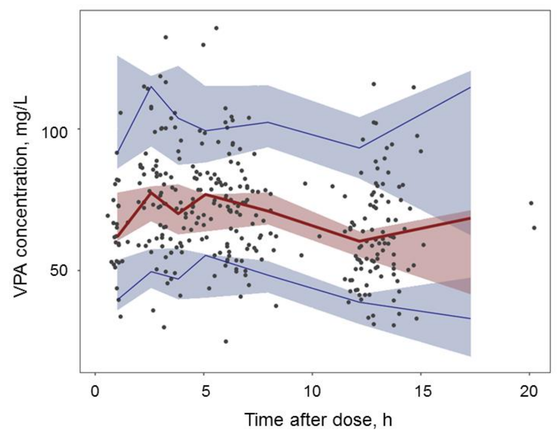

Figure 2. Prediction and variability corrected visual predictive checks obtained with the final model. Black dots represent the observed concentrations; red line represents de 50th empirical percentile of the observed plasma concentration; blue lines represent 5th and 95th empirical percentiles of the observations; upper and lower semitransparent blue areas represent the simulation-based 95% confidence interval of the predicted 95th and 5th percentiles respectively; semitransparent red area represents the simulation-based 95% confidence interval of the 50th percentile

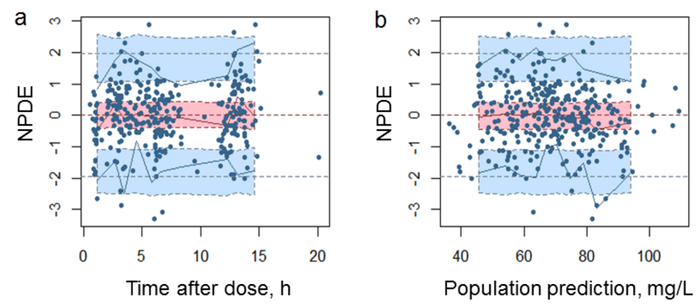

Figure 3. a. NPDE versus time after dose; **b.** NPDE versus population predictions.

Results (continuation)

Dose evaluation
- Probability of C_{trough} to be within the target range increases with increasing doses for smaller children but decreases with increasing doses for bigger children (Figure 4)
- Dose requirements decrease with increasing BW (Figure 5): a 40 mg/kg daily dose was needed for 10 kg children to obtain a C_{trough} within the target range, whereas current recommendations were found appropriate for ≥ 20 kg children

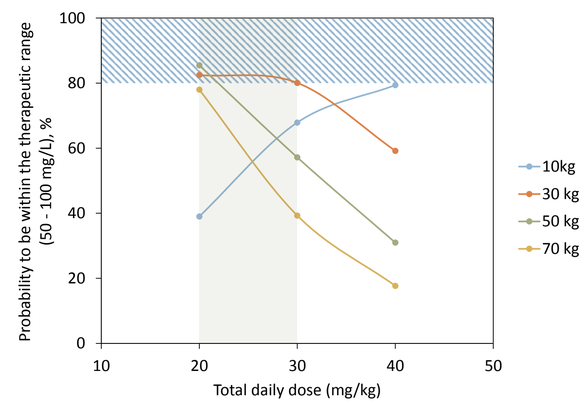

Figure 4. Probability to obtain a trough concentration within the therapeutic range per daily dose for 10, 30, 50 and 70 kg children. The green semi-transparent area represents the dose recommendations. The hatched blue area represents a probability over 80% to be within the therapeutic range

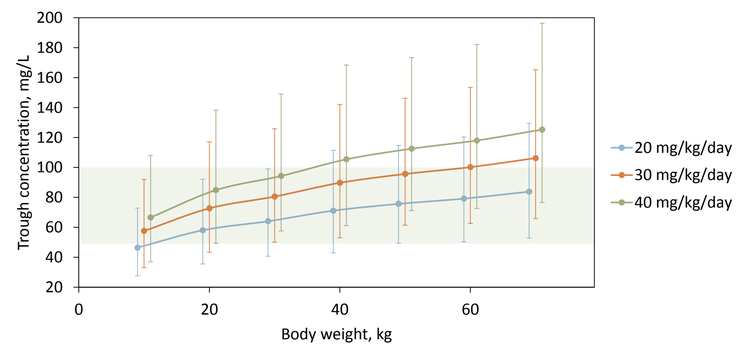

Figure 5. Median and 95% confidence intervals of VPA trough concentrations predicted by the final model with respect to dose and body weight. Semitransparent green field represents the target therapeutic range (50-100 mg/L)

Discussion & Conclusion

- The first population model of the SR granule formulation of VPA was developed, evidencing flip-flop occurrence
- BW influence VPA pharmacokinetic parameters in an allometric manner
- Protein binding is accounted for by the presence of the total daily dose as a covariate on VPA clearance, not to the confounded with the TDM effect [8]
- Smaller children need higher weight-normalized doses than bigger children
- Dose recommendations are adequate except for children < 20kg who may need a dose of 40mg/kg

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