

A population pharmacokinetic model taking into account protein binding for the sustained-release granule formulation of valproic acid in children with epilepsy



Rodrigues C¹, Chhun S², Chiron C¹, Dulac O¹, Rey E¹, Pons G¹, Jullien V^{1,3}
¹INSERM U1129, ²INSERM U1151, ³Service de Pharmacologie, HEGP

Introduction

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

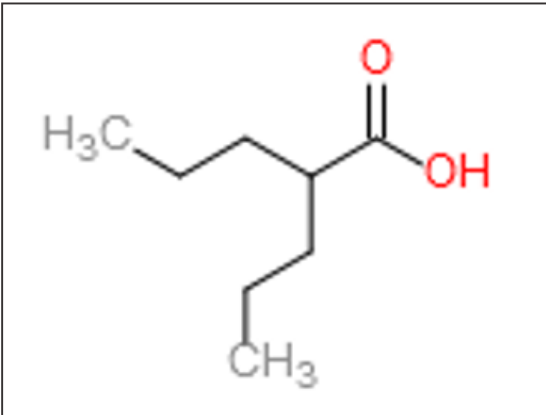


Figure 1. Valproic acid

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

- To develop a population pharmacokinetic model for this SR-granule formulation in epileptic children taking into account the saturable protein binding properties of VPA
- 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
- Saturation of protein binding
 - Physiological protein-binding model [6]
 - B_{max} and K_d fixed to published values [7] (130 and 7.8 mg/L, respectively)
 - Unbound CL and V estimated
- Flip-flop parametrization [8]:
 - K_a constrained to be higher than K_e
 - $K_a = K_e + C$
 - 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 [9]

Final model:

$$\begin{aligned}k_a &= 0.274 \text{ h}^{-1} \\CL_u/F &= 6.24 \times (BW/70)^{0.75} \text{ L/h} \\V_u/F &= 130 \times (BW/70) \text{ L} \\C_t &= C_u + \frac{B_{\text{max}} \times C_u}{K_d + C_u} \\f_u &= \frac{C_u}{C_t} \\CL_t &= f_u \times CL_u \\V_t &= f_u \times V_u\end{aligned}$$

Model Evaluation

- No bias observed (Figure 2)

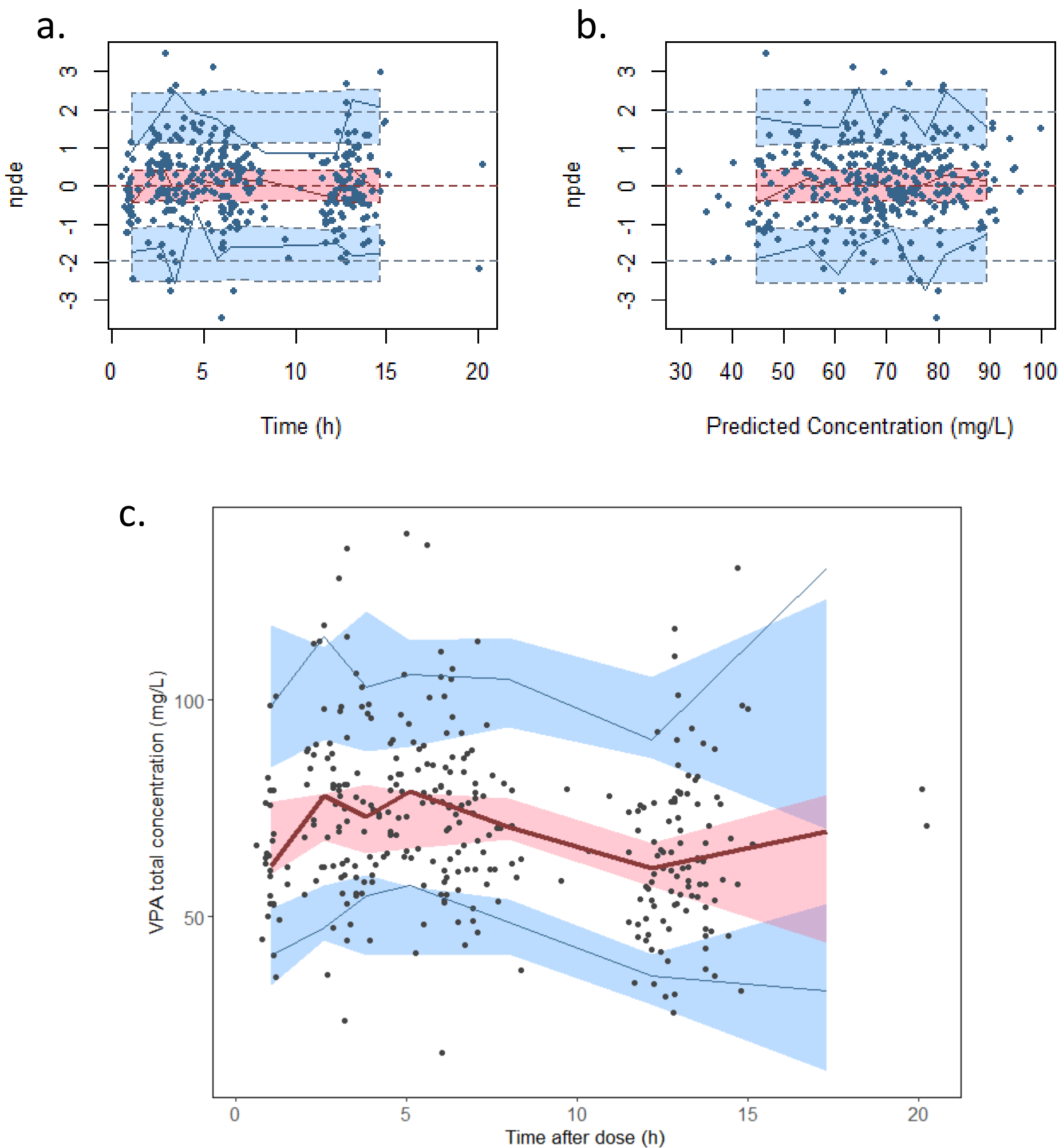


Figure 2. a. NPDE versus time after dose; b. NPDE versus population predictions; c. Prediction and variability corrected visual predictive checks obtained with the final model. Black dots represent the observed concentrations

Results (continuation)

Determination of unbound target C_{trough}

- 4.2 – 14.8 mg/L

Dose evaluation

- The highest probability to obtain a C_{trough} within the target range for 10-kg children was obtained with a 40 mg/kg daily dose, whereas daily doses of 30 and 20 mg/kg were found appropriate for 20 to 30- and ≥ 40 -kg children respectively (Figure 3)
- For these same doses, the exposure to unbound VPA could differ by 40% (Figure 4) $\rightarrow f_u$ increased with increasing doses but also with BW

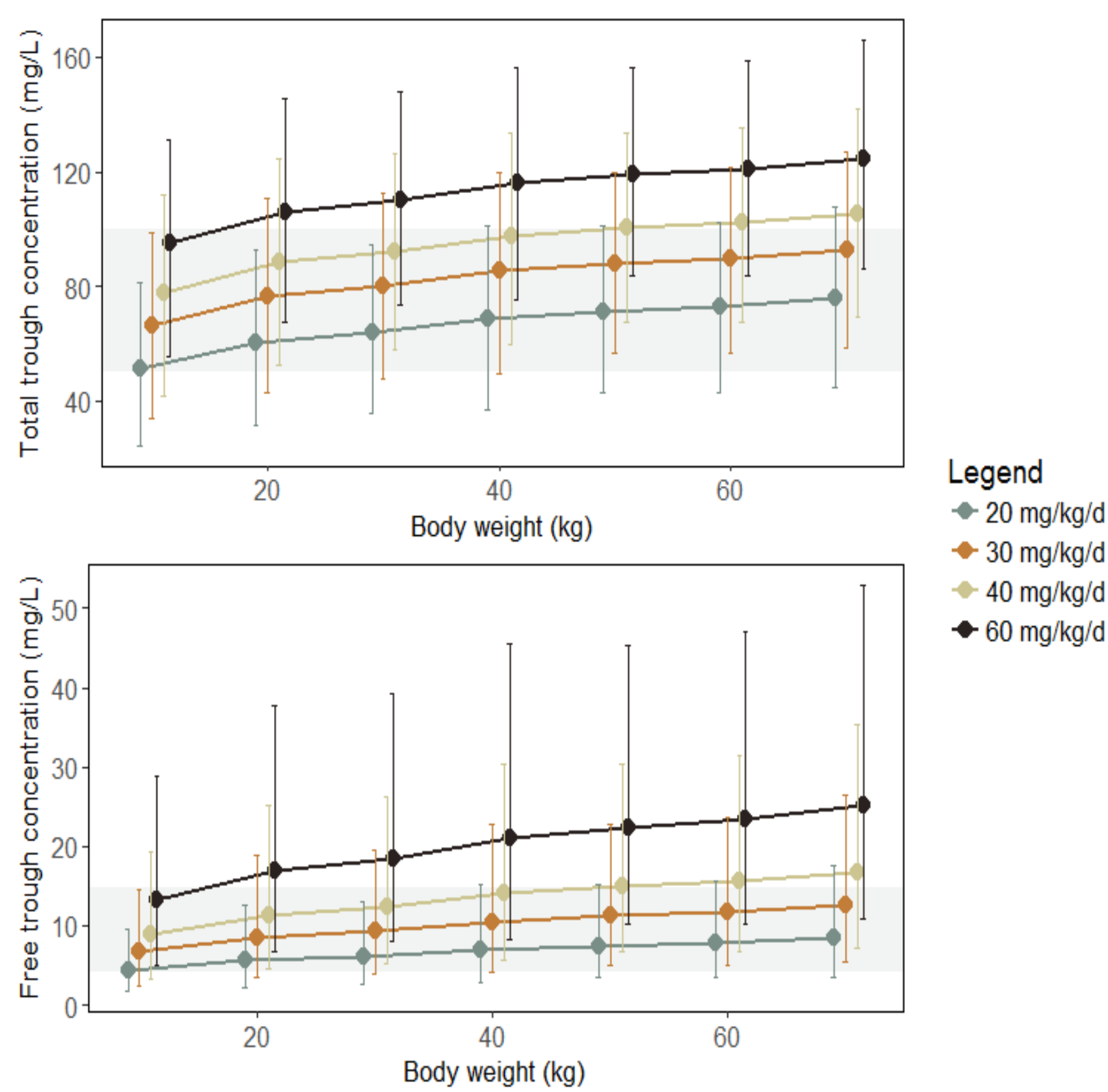


Figure 3. Median and 95% confidence intervals of VPA trough concentrations predicted by the final model with respect to dose and body weight. Semitransparent green field represents the target therapeutic range (50-100 mg/L)

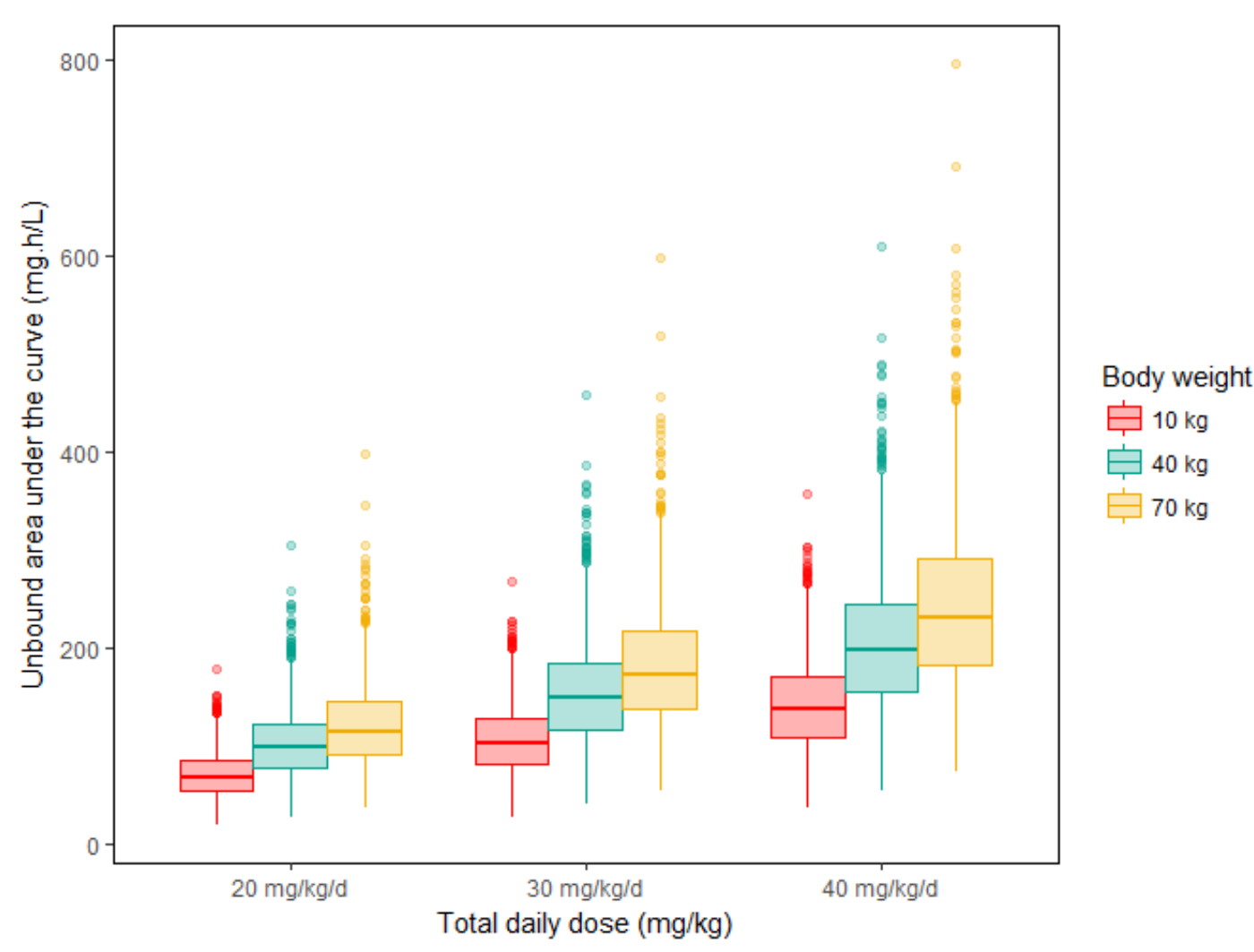


Figure 4. Unbound exposition with respect to total daily dose and body weight

Discussion & Conclusion

- The first population model of the SR granule formulation of VPA was developed, evidencing flip-flop occurrence
- This model took into account the nonlinear relationship between dose and clearance secondary to the saturable protein binding
- Dose recommendations are adequate except for children < 20 kg who may need a dose of 40mg/kg

Paper

Rodrigues, C., Chhun, S., Chiron, C. et al. Eur J Clin Pharmacol (2018) 74: 793.
<https://doi.org/10.1007/s00228-018-2444-2>



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Contact

Christelle Rodrigues
INSERM UMR 1129
Email: christelle.rodrigues@inserm.fr

Vincent Jullien
INSERM UMR 1129
Service de Pharmacologie, HEGP
Email: vincent.jullien@aphp.fr

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