

PKPD bridging and extrapolation of the efficacy of gabapentin and tramadol in paediatric chronic pain.

Paul Healy¹, Luka Verrest², Oscar Della Pasqua^{1,3}

¹ Clinical Pharmacology & Therapeutics Group, School of Pharmacy, University College London, London, UK.

² Department of Pharmacy and Pharmacology, Antoni van Leeuwenhoek Hospital, Amsterdam.

³ Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Uxbridge, UK.



Introduction

- Paediatric neuropathic chronic pain has been considered rare although in recent years the diagnosis of this syndrome seems to be increasing. Often, drugs used for pain in adults are administered off-label in children ^[1] at doses derived empirically from adult doses.
- The GAPP consortium^[2] was set up to establish the dose rationale and assess the efficacy and safety of gabapentin in patients aged between 3 months and ≤18 years, diagnosed with chronic pain, as compared to tramadol.
- Our investigation was aimed at defining the appropriate doses of gabapentin and tramadol to be used in this population and identifying opportunities to optimise exposure to a new formulation of gabapentin by scaling disposition characteristics from adults to children.
- Doses and dosing regimens currently used in clinical practice (10 mg/kg for gabapentin and 1-8 mg/kg for tramadol) were considered as a starting point for the proposed model-based analysis.

Methods

- Nonlinear mixed effects modelling was used to scale the PK of gabapentin and tramadol assuming comparable exposure-response relationships between 1) adults and children, and 2) between acute and chronic pain conditions.
- Data analysis included extrapolation of drug disposition parameters from adults to children using allometric scaling principles and PK data from the published literature ^[4].
- Clinical trial simulations using a one-compartment model for gabapentin ^[1] and a two-compartment model for tramadol ^[3] were performed to evaluate paediatric exposure to a range of dosing regimens based on body weight as the main covariate factor.
- In addition, simulation scenarios were used to optimise titration and sampling procedures.

Dose Rationale for Gabapentin and Tramadol

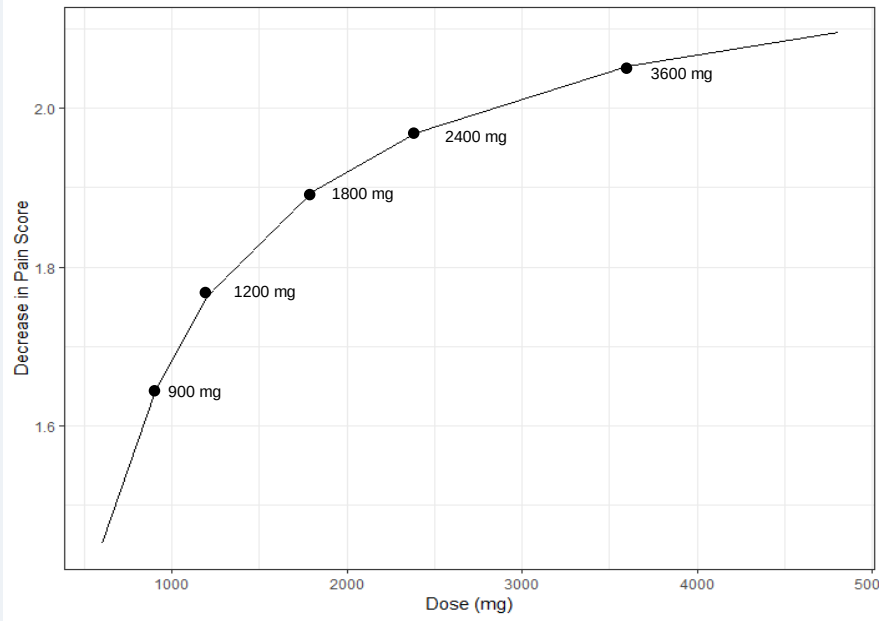


Figure 1. Dose-response curve derived from a dose-finding study with gabapentin in adult patients with neuropathic pain ^[5].

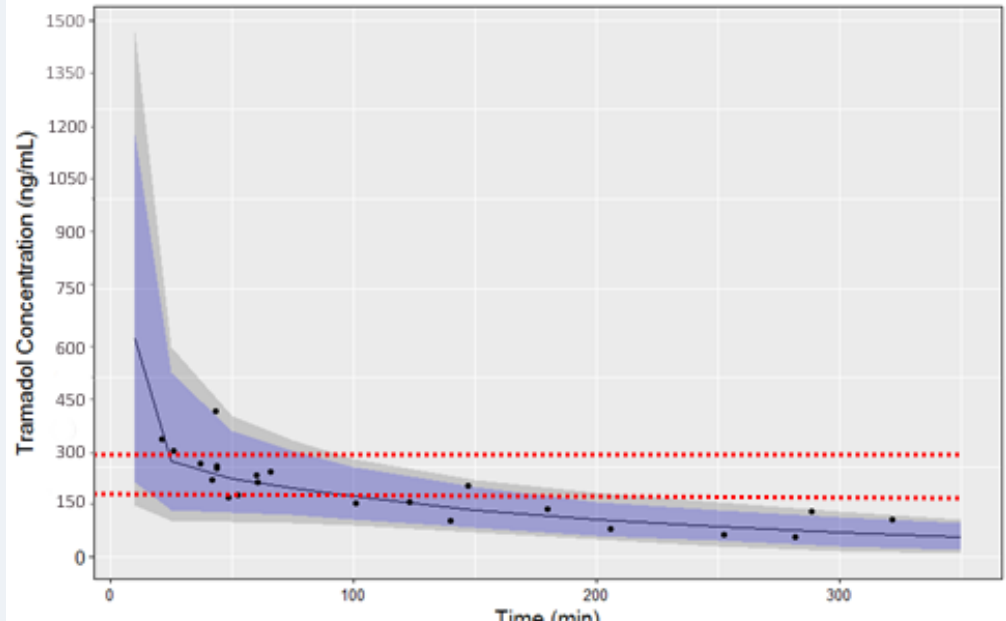


Figure 2. Plasma concentration vs time profile ^[2] in patients receiving a 1 mg/kg infusion of tramadol. Dashed red lines at 200 and 300 ng/mL. Purple shaded area represents 90% confidence interval and the grey shaded area represents the 95% confidence interval. Black line is the mean concentration.

- Figure 1 shows data from a gabapentin dose-finding trial in adults ^[5] diagnosed with postherpetic neuralgia, where pain score was measured using an 11-point Likert scale (0 = no pain to 10 = worst possible pain).
- For tramadol (Figure 2), no dose finding study was identified to support its dose rationale. Instead, efficacious levels were derived from clinical trial data ^[2] in acute pain, where analgesia was correlated with plasma levels between 200-300 ng/mL. These levels are associated with minimal concerns for safety, as they fall within the range endorsed for adults (100 to 800 ng/mL) by the International Association of Forensic Toxicologists. Tramadol toxicity has been identified between 1000 and 2000 ng/mL.

Pharmacokinetic (PK) Models

Table 1 shows the pharmacokinetic parameter estimates used to simulate systemic exposure to gabapentin (left) and tramadol (right) in paediatric patients.

Parameter (Units)	Population estimate (95% CI)
CL=θ1*CRCL (L/h)	0.116 (0.110–0.122)
V=(θ2+θ3*WT)*2.05 (L)	3.26 (–0.68–7.20)
	1.34 (1.13–1.55)
Ka (min ⁻¹)	1.24 (1.01–1.47)
Tlag (h)	0.181 (0.106–0.256)
Inter-individual variability	
CL	0.088
Vd	0.094
Ka	0.185
Tlag	0.626
Residual variability	
Additive (µg/mL)	1.32
Proportional	0.064

Parameter (Units)	Population Estimate (CI 95%)
V = θ1+ θ2*(WT/19.64) (L)	3.12 (0.4-7)
	4.89 (1.75-11)
Clf (L/h)	0.51 (0.21-1.2)
Cle = θ4*WT/19.64) (L/h)	14.7 (12.6-16.2)
K ₁₂ (L/h)	8.4 (5.1-12.6)
K ₂₁ (L/h)	1.76 (1.5-2.7)
Ka (min ⁻¹)	0.834
F [x 100 (%)] (fraction)	0.68
Inter-individual variability	
V	0.168
Clf	0.144
Cle	0.078
K ₁₂	0.281
Residual variability	
Additive error (ng/mL)	43.01 (10-59)

Table 1. Population PK model parameter estimates. CL = Clearance; V = Central Volume of Distribution; Ka = First order absorption rate constant; Tlag=Lag time. Clf = Apparent formation clearance of the metabolite, M1; Cle = Clearance of tramadol; K₁₂ & K₂₁ = transfer rate constants; F = Oral bioavailability; WT = body weight; θ = population parameter. Parameter estimates are listed together with their 95% confidence intervals in parentheses.

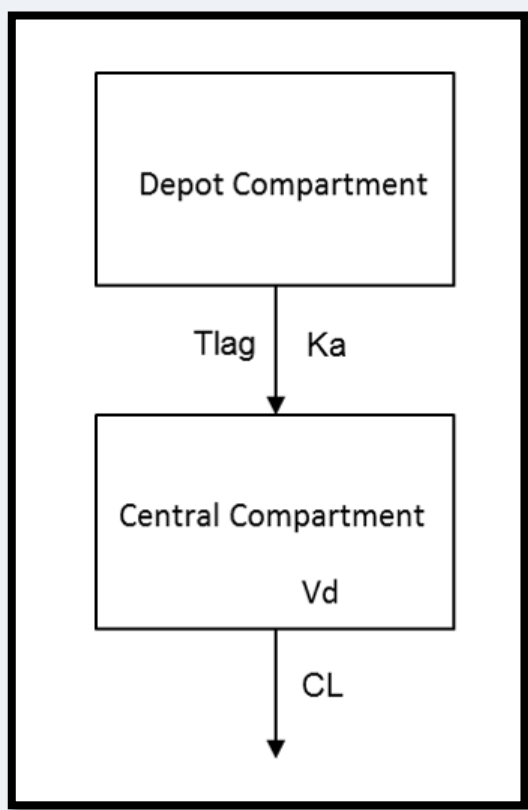


Figure 3. Diagram of the final population PK model describing the disposition of gabapentin.

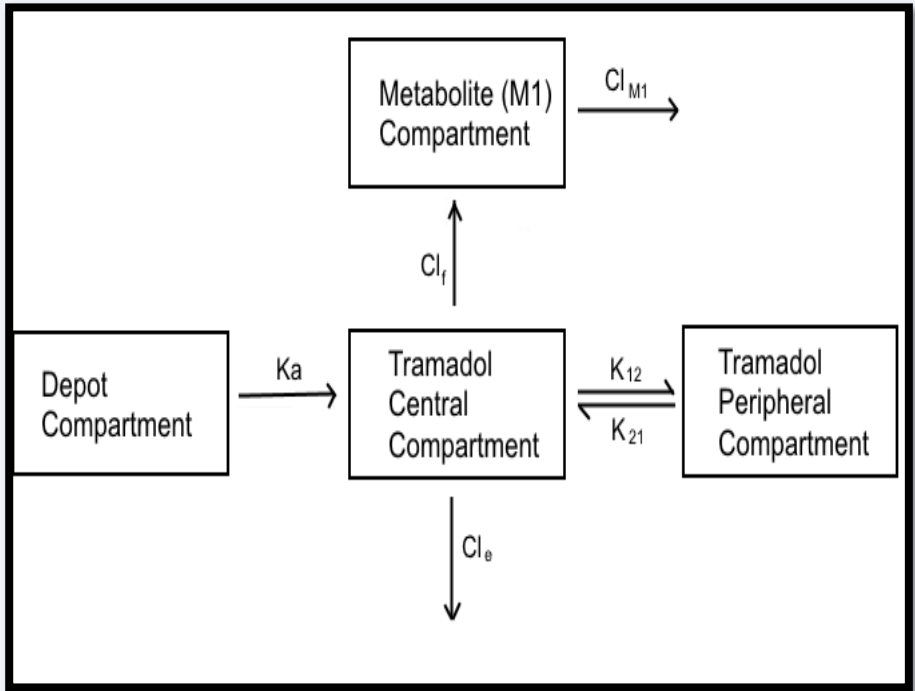


Figure 4. Diagram of the final population PK model describing the disposition of tramadol.

Simulated Exposure during Titration and Maintenance Phases

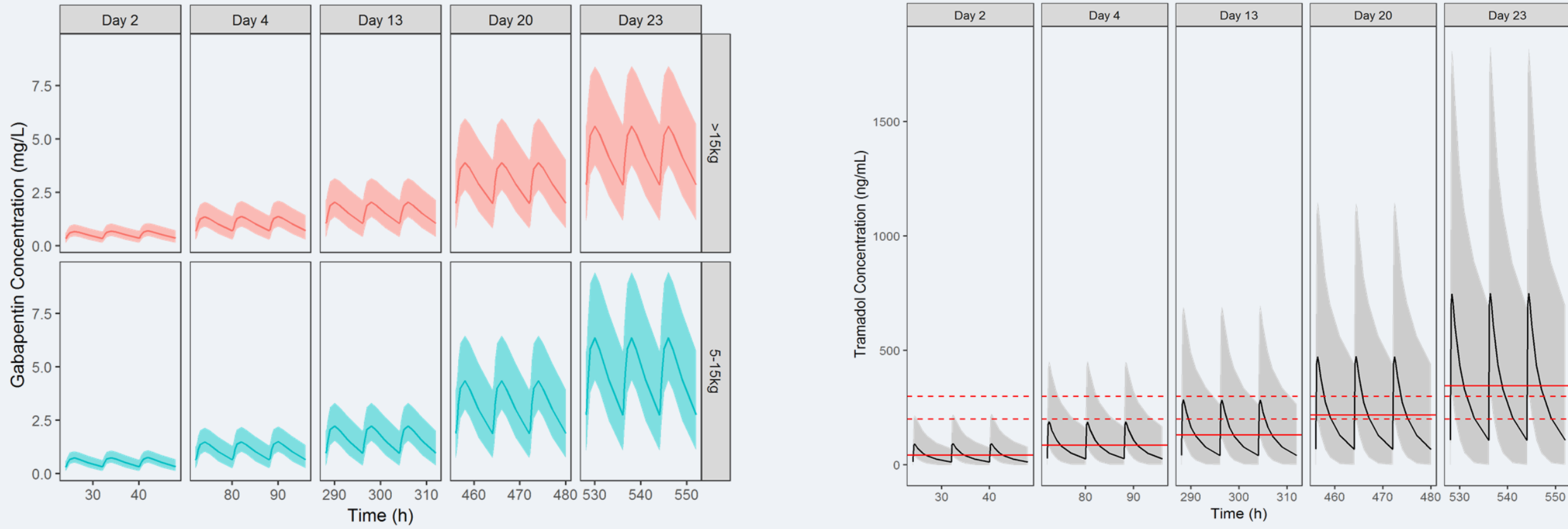


Figure 5. Simulated concentration versus time profiles of gabapentin (left) and tramadol (right) during titration and maintenance phase (day 23 onwards) steps. Gabapentin PK profiles are split into weight bands. Red dotted lines display putative efficacious concentration window for tramadol.

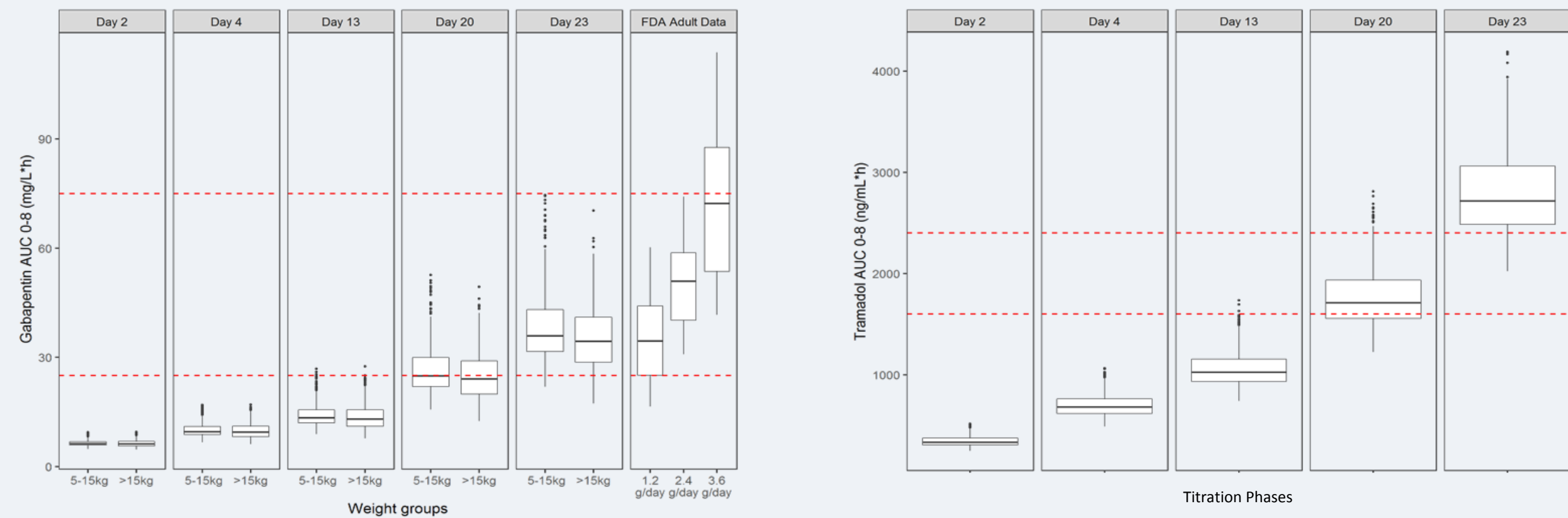


Figure 6. Whisker-box plots describing the simulated systemic exposure (AUC) of gabapentin (left) and tramadol (right) on the last day of each titration step. Red dotted lines display putative efficacious exposure range. Simulated patient population included a total of 800 patients across the target age groups.

Secondary PK Parameters – Simulated Scenarios

Table 2. Summary of secondary PK parameters for gabapentin (left) and tramadol (right) during titration and maintenance phases. Values shown are the median and range (between parentheses).

Gabapentin						Tramadol				
Weight Group	Day	Dose	Cmax (mg/L)	Css (mg/L)	AUC ₀₋₈ (mg/L/h)	Day	Dose	Cmax (ng/mL)	Css (ng/mL)	AUC 0-8 (ng/mL/h)
>15 kg	2	5	2.8	0.79	6.3	2	1	158.7	43.9	351.1
			(1.9 – 4.0)	(0.42 - 1.3)	(3.4 - 10.4)			(82.4-312.6)	(16.3-105.8)	(130.3-846.1)
5-15 kg	2	7	2.8	0.80	6.4	4	2	320.1	88.4	707.5
			(2.0 – 4.0)	(0.43 – 1.3)	(3.5 -10.4)			(165-639.9)	(32.5-220.7)	(259.7-1766)
>15 kg	4	10	3.5	1.2	9.7	13	3	480.6	132.3	1058
			(2.4 -5.0)	(0.65 -2.2)	(5.2 – 17.6)			(248.4-968.1)	(48.7-336.4)	(648.2-2691.5)
5-15 kg	4	14	3.5	1.2	9.9	20	5	802.6	221	1767.8
			(2.4 – 5.2)	(0.68 – 2.2)	(5.5 -17.5)			(412.9-1617.7)	(81-561.3)	(933.7-4490.3)
>15 kg	13	15	4.1	1.7	13.4	23	8	1273	350.2	2801.4
			(2.8 – 6.3)	(0.88 -3.2)	(7.1 – 25.5)			(655.4-2540.2)	(129.0-883.5)	(1032.4-7068)
5-15 kg	13	21	4.1	1.7	13.7					
			(2.9 – 6.4)	(0.94 -3.2)	(7.6 – 25.5)					
>15 kg	20	30	6.2	3.0	24.5					
			(4.0 -10.1)	(1.6 – 5.9)	(12.9 – 47.0)					
5-15 kg	20	42	6.6	3.2	25.6					
			(4.4 – 10.7)	(1.8 – 6.1)	(14.0 – 49.0)					
>15 kg	23	45	8.3	4.4	35.0					
			(5.2 -13.8)	(2.3 – 8.3)	(18.5 – 66.1)					
5-15 kg	23	63	9.1	4.7	37.2					
			(5.8 – 15.3)	(2.6 – 8.9)	(20.4 – 71.2)					

- Simulations showed that efficacious steady-state exposure (AUC₀₋₈) of 32.8 µg*h/mL and steady-state concentrations of 200-300 ng/mL can be achieved during maintenance phase of treatment with gabapentin and tramadol, respectively.

- These levels are preceded by titration steps, with doses ranging from 7-63 mg/kg in patients between 5-15 kg and 5-45 mg/kg in patients >15kg. For tramadol, the target exposure was associated with a maximum daily intake of 8 mg/kg can be achieved by the similar titration steps, with doses ranging of 1-8 mg/kg t.i.d. both given over a 3-week titration period.

Conclusions

- In contrast to evidence generation based on empirical protocols, this study illustrates how quantitative clinical pharmacology principles can be used during the design phase of a study to ensure a scientifically robust dose rationale, as compared to simply titrating to effect.
- Moreover, use of clinical trial simulations has provided an opportunity to identify suitable titration steps for subsequent characterisation of the pharmacokinetic-pharmacodynamic relationships for gabapentin and tramadol in the target paediatric population.

References

- Ouellet D et al. (2001) Population pharmacokinetics of gabapentin in infants and children. *Epilepsy Res.* 47:229–41.
- Kaguelidou F et al. (2018) Non-inferiority double-blind randomised controlled trial comparing gabapentin versus tramadol for the treatment of chronic neuropathic or mixed pain in children and adolescents: the GABA-1 trial—a study protocol. *BMJ Open* 9: e023296.
- Garrido MJ et al. (2006). Population Pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharm Res.* 23(9): 2014–2023.
- Payne KA et al. (2002) Pharmacokinetics of oral tramadol drops for postoperative pain relief in children aged 4 to 7 Years - A pilot study. *Anesth Prog.* 49(4): 109–112.
- Rice AS et al. (2001) Postherpetic neuralgia study group. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain.* 94(2):215-24.



This investigation is part of the European GAPP consortium funded by the European Union Seventh Framework Program, under Grant Agreement No 602041. The recommendations from the current analysis were implemented into the GABA-1 study protocol (<https://clinicaltrials.gov/ct2/show/NCT02722603?cond=gabapentin+pain&age=0&rank=3>)