

PAT1-inhibitors reduce oral absorption rate of vigabatrin in rats

Pharmacokinetic model supports the role of proton-coupled amino acid transporter (PAT1) in vigabatrin absorption

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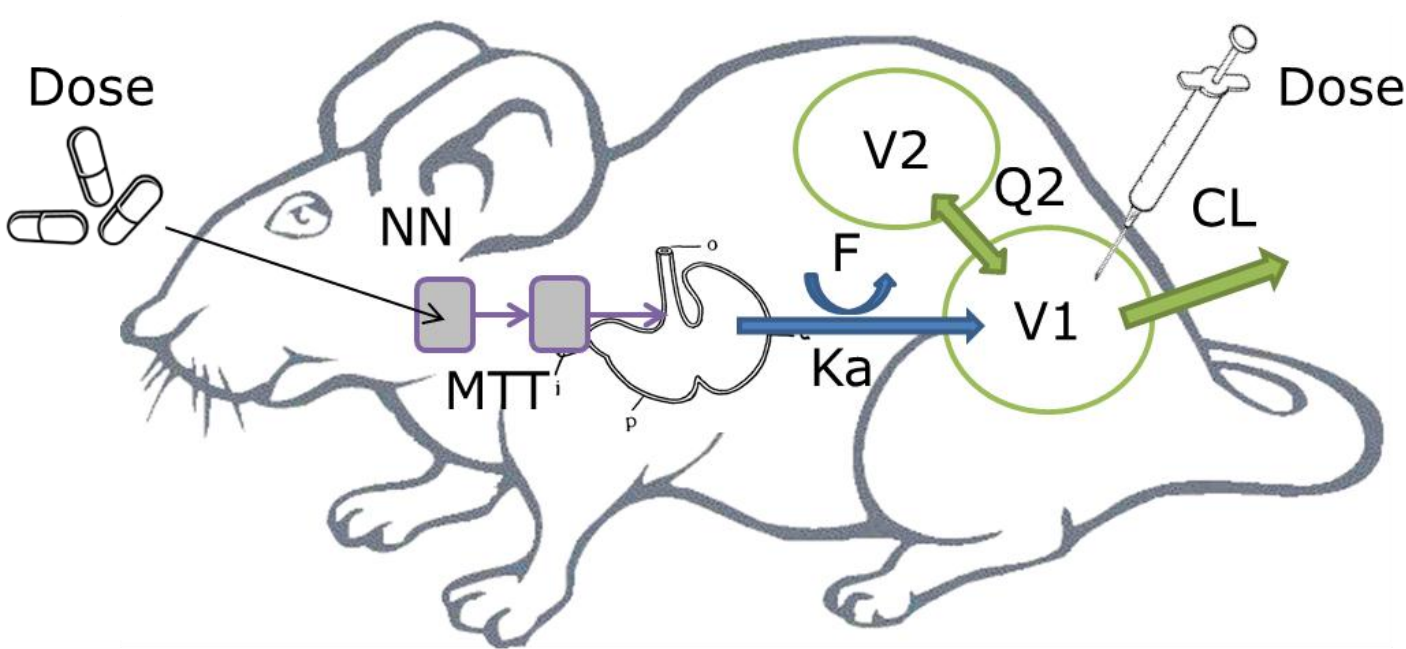
Introduction

Vigabatrin is an anti-epileptic drug substance primarily used to treat infantile spasms. Vigabatrin is known to be rapidly absorbed from the intestine, despite very hydrophilic properties¹. Recent *in vitro* studies (not published) have suggested that the proton-coupled amino acid transporter (PAT1) is a transporter of vigabatrin in intestinal epithelia.

Aim

To investigate the involvement of PAT1 in intestinal vigabatrin absorption *in vivo*.

A two-compartment disposition model with first order absorption and a transit compartment delay model² was developed in NONMEM 7



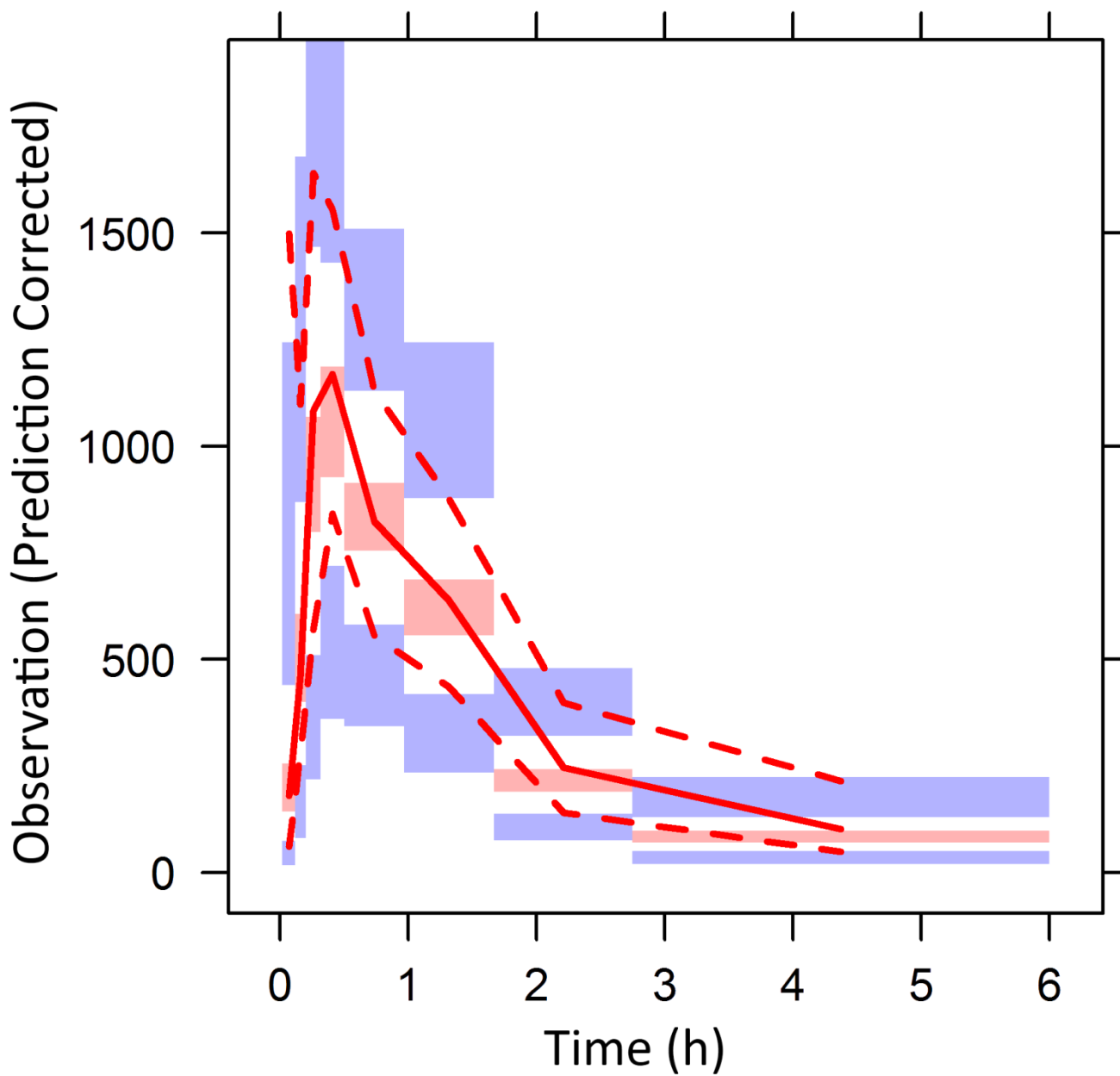
Structural model parameters
CL/ Q2 : Systemic/ intercompartmental clearance
V1/ V2: Central/peripheral compartment volume
Ka: First order absorption rate constant
F: Oral bioavailability
NN: Number of transit compartments
MTT: Mean transit time in transit compartments

Vigabatrin absorption pharmacokinetic model

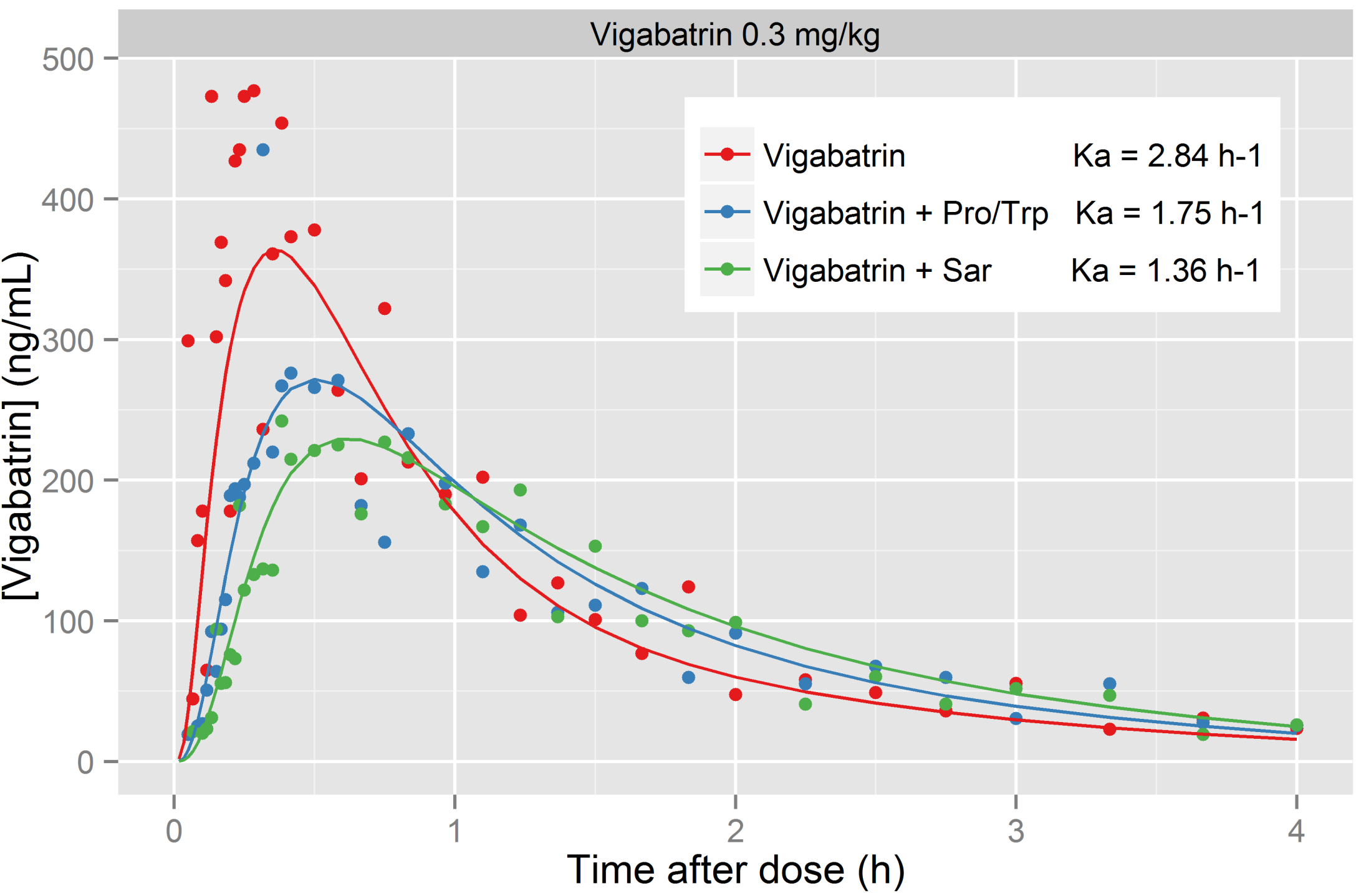
PK parameters values related to vigabatrin absorption			
Parameter	Mean (%RSE)	IIV (%RSE)	Covariate effects
Ka (h ⁻¹)	2.84 (19.9)	-	At dose 0.3mg/kg: ↓ Inhibitor Pro/Trp ↓ Inhibitor Sar
MTT (h)	0.078 (13.1)	42.7 (16.5)	↑ Inhibitor Pro/Trp ↑ Inhibitor Sar ↓ Dose: 0.3mg/kg
NN	1.34 (20.0)	-	-
F	0.60 (5.5)	-	-

IIV = Intraindividual variability expressed as coefficient of variation (%CV). All structural model and random effects parameters not presented had RSE < 22%.

Prediction corrected VPC³ for oral doses of vigabatrin to evaluate model fit. Red lines are mean and 95% confidence interval of original data. Red and blue areas are 95% confidence intervals of model mean and prediction intervals.

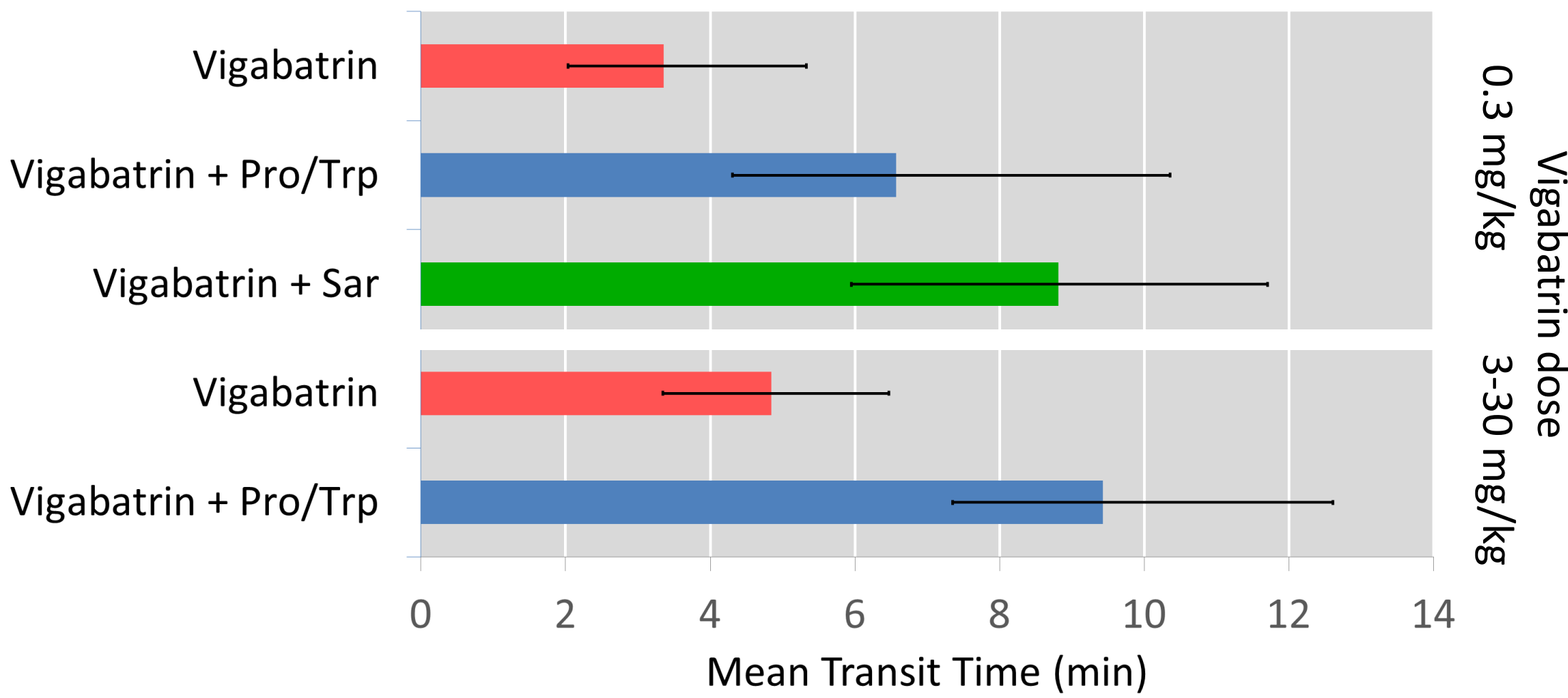


Absorption rate is reduced by PAT1-inhibitors



Simulated population pharmacokinetic profiles for an average weight rat at vigabatrin doses of 0.3mg/kg. Significant reductions in Ka were described by discrete covariates for PAT1 inhibitors Pro/Trp (RSE=30%) and Sar (RSE=16%) at vigabatrin dose = 0.3mg/kg .

Absorption delay is prolonged by PAT1-inhibitors



Mean transit time (MTT) and 95% confidence interval after oral vigabatrin administration. Discrete covariates described significant reduction of MTT at vigabatrin dose 0.3mg/kg versus higher doses (RSE=19%) and increase in MTT with PAT1 inhibitors Pro/Trp (RSE=16%) and Sar (RSE=24%). Population mean and confidence intervals were calculated from 200 bootstraps performed in PsN.

Oral bioavailability is not altered by PAT1-inhibitors

F = 60 % (RSE=5.5%)

No significant intra-individual variability, weight covariates or dose effects were found on bioavailability in the final model. No discrete covariates described significant effects on bioavailability with co-administration of PAT1 inhibitors Pro/Trp or Sar.

Methods

Absorption was investigated in 78 Sprague Dawley rats after administration of vigabatrin, orally (0.3, 3.0 or 30mg/kg) or intravenously (1.0 mg/kg). Inhibition of PAT1 was investigated by co-administering proline/tryptophan (Pro/Trp) or sarcosine (Sar). Pharmacokinetic modelling was performed in NONMEM 7 with PsN, Pirana, Xpose and ggplot2 libraries for R.

References

[1] Perucca, E. Therapeutic drug monitoring 27.6 (2005): 714-717
[2] Savic, R.M., et al. J Pharmacokinet Pharmacodyn (2007). 34(5): p. 711-26
[3] Bergstrand, M., et al. The AAPS journal 13.2 (2011): 143-151

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Conclusion

- Inhibitors of PAT1 reduce the absorption rate of vigabatrin
- Inhibitors of PAT1 prolong the absorption delay of vigabatrin
- Inhibitors of PAT1 do not alter the bioavailability of vigabatrin

It is concluded that PAT1 is involved in intestinal absorption of vigabatrin *in vivo*