



Mathematical modeling of gastric emptying: a joint model for losartan and its active metabolite EXP-3174

II-68

Eleni Karatza, Vangelis Karalis

Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Greece

Objectives

Pharmacokinetics of Losartan potassium (a BCS class III drug) seem to be significantly affected by gastric emptying, resulting in a plasma concentration – time profile showing multiple peaks (1). The objective of the present study was to develop a joint pharmacokinetic model, describing gastric emptying and the so-derived multiple peak profile of losartan (LOS) and its active metabolite (EXP-3174).

Methods

LOS and EXP-3174 plasma concentration (C) – time (t) data were obtained from a single dose, 2x2 bioequivalence study comparing two immediate release oral products (Losartan 50mg/Verisfield UK Ltd vs. Cozaar®/Merck, study code 415/2003) in 35 men and women (4 dropouts). Concentrations of EXP-3174 were converted to LOS equivalents for simultaneous parent and metabolite fitting using a molecular weight of 436.9 g/mole for the active metabolite and 422.9 g/mole for the parent drug. Dose administered was also converted in LOS equivalents using a molecular weight of 461.01 g/mole for losartan potassium. Non-linear mixed-effect modeling was applied and a variety of pharmacokinetic models were examined. In order to mathematically describe the delayed and highly variable appearance of LOS and EXP-3174 in plasma, resulting in oscillations of the concentration (Figure 1), several approaches were explored including the use of: gastrointestinal pseudo-compartments, time-dependent gastric emptying, first order rate constant ‘releasing’ drug at specific time-intervals, delay differential equations, and sinusoidal functions mimicking periodic gastric emptying. Models tested were evaluated based on their physiological relevance as well as goodness-of-fit criteria and plots. Several error models were evaluated. Occasion, treatment, weight, high, sex, and age were evaluated as potential covariates. Possible covariance between parameters was also assessed. Standard errors were computed through stochastic approximation algorithm to calculate the Fisher Information Matrix, while the log likelihood estimation was performed using the importance sampling Monte Carlo method. The entire computational work was performed in Monolix 2018R1.

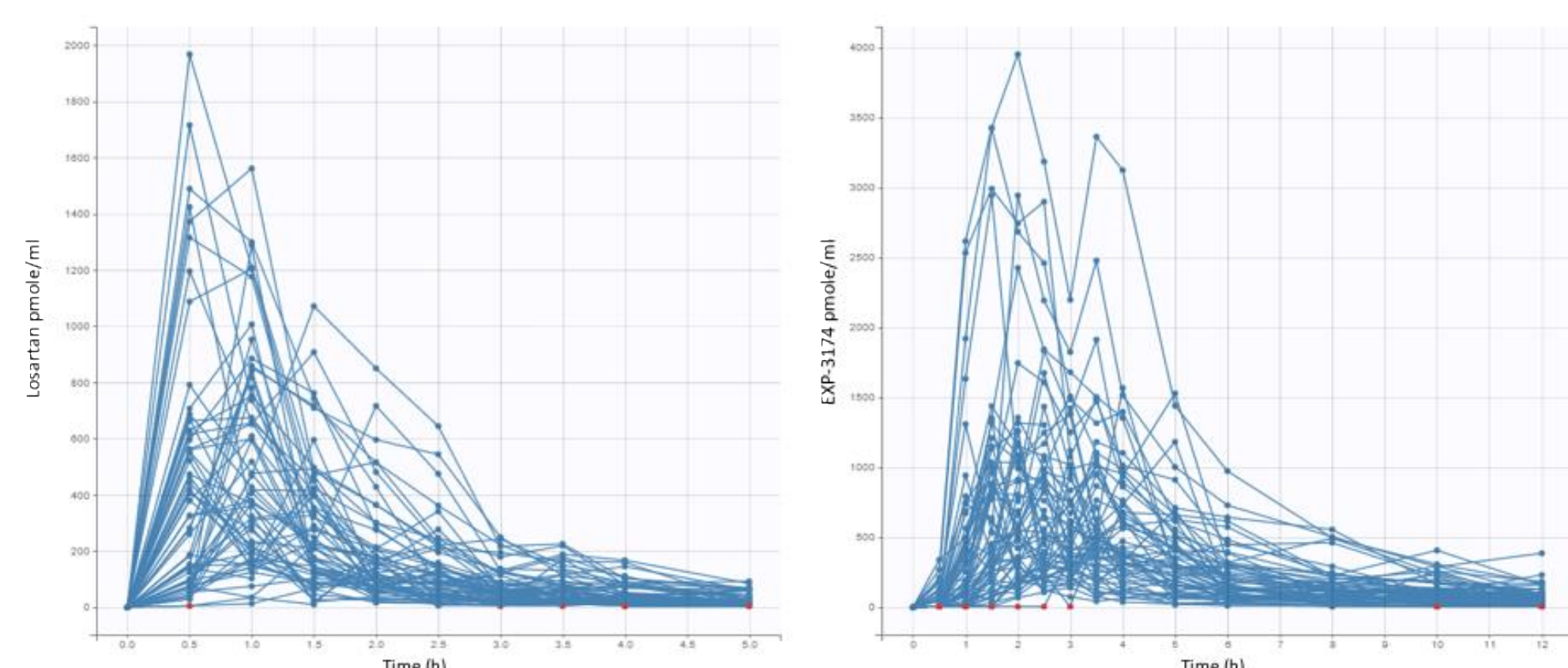


Figure 1. Spaghetti plots of Losartan and EXP-3174 (active metabolite) plasma concentrations.

Results

The disposition of LOS was best described by a two-compartment model preceded by another compartment representing a pre-absorption gastrointestinal compartment. For EXP-3174, a one-compartment model led to the optimum performance. Delay differential equations were found to be the most appropriate approach to mathematically describe the oscillations (2) observed in the plasma concentration of LOS and EXP-3174. Indeed, both the absorption rate of LOS and its metabolite formation rate were successfully expressed by first order constants integrated in a system of delay differential equations. However, due to computational constraints and model’s instability, a sinusoidal equation describing periodic gastric emptying, driving absorption was finally selected (Figure 2).

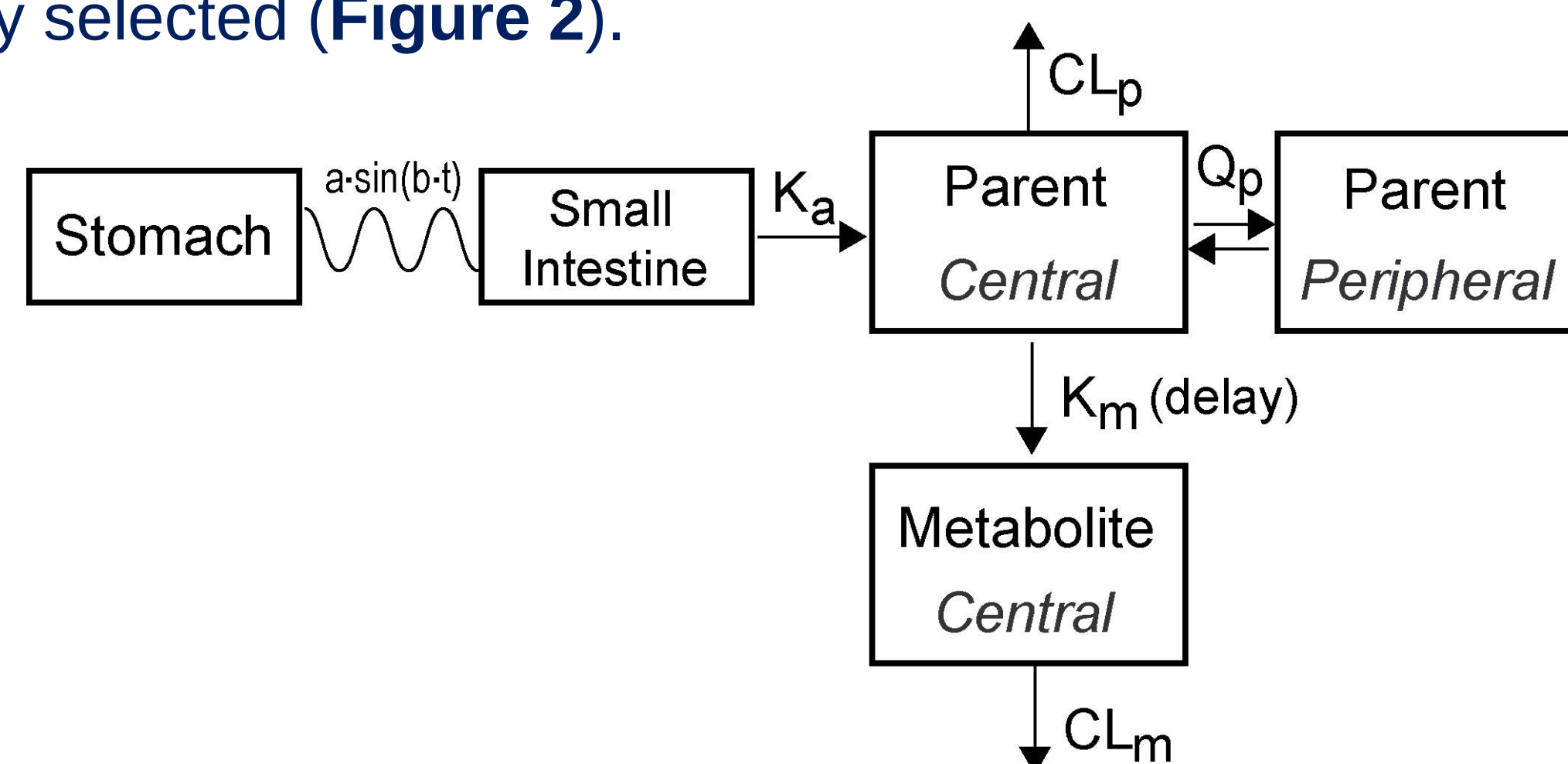


Figure 2. Schematic representation of the finally selected best structural model.

The pharmacokinetic parameters derived for losartan and its active metabolite, as well as goodness of fit criteria are presented in Table 1. It should be noted that the amplitude ($a=4.24 \text{ h}^{-1}$) and the period of gastric emptying ($2\pi/b=2\pi/2.9\approx 2.16$) were calculated, resulting in $Kg=4.24*\sin(2.9*t) \text{ h}^{-1}$ function to describe gastric emptying kinetics. When $\sin(2.9*t)$ reached negative values, Kg was considered 0, i.e. indicating a closed pyloric valve.

Residual variability was best estimated using a proportional error model for both compounds. Statistically significant co-variance was identified between the apparent clearance from the central compartment and the inter-compartmental clearance of the parent drug. No statistically significant covariates were found.

Table 1. Model parameters and goodness of fit criteria.

Population parameters (fixed effects)				Standard deviation of Random effects				Goodness of fit criteria	
Parameter		S.E.	R.S.E.(%)	Omega		S.E.	R.S.E.(%)	-2LL	7350.39
a (amplitude) (h ⁻¹)	4.24	0.69	16.3	a (amplitude) (h ⁻¹)	0.465	0.204	43.9	AIC	7400.39
b (period)	2.9	1.23	42.6	b (period)	1.29	0.49	38.1	BIC	7453.57
ka (h ⁻¹)	2.13	0.455	21.3	ka (h ⁻¹)	0.137	0.0724	52.7		
Vp1/F (L)	10.1	2.5	25.3	Vp1/F (L)	0.245	0.188	76.8		
Vp2/F (L)	183	80	43.4	Vp2/F (L)	1.33	0.395	29.6		
Q/F (L/h)	72.6	15	20.9	Q/F (L/h)	0.704	0.208	29.6		
CL/F (L/h)	114	14	12.1	CL/F (L/h)	0.615	0.0948	15.4		
Km (h ⁻¹)	0.400	0.0278	6.94	Km (h ⁻¹)	0.216	0.0957	44.3		
Tau (h)	0.284	0.0408	14.4	Tau (h)	0.621	0.126	20.3		
Vm/F (L)	2.36	0.229	9.69	Vm/F (L)	0.423	0.0744	17.6		
CLm/F (L/h)	1.18	0.14	11.7	CLm/F (L/h)	0.28	0.0921	32.9		

Proportional Error Model Parameters				Covariance			
parameter		S.E.	R.S.E.(%)	Correlations		S.E.	R.S.E.(%)
b parent	0.55	0.0234	4.26	Q/F-CL/F	0.819	0.109	13.3
b metabolite	0.525	0.0199	3.8				

The accuracy and predictive performance of the model was also examined by Visual Predictive Check (VPC) diagrams, Observed vs. Predicted scatter plots and individual fittings as presented in Figure 3, 4, and 5.

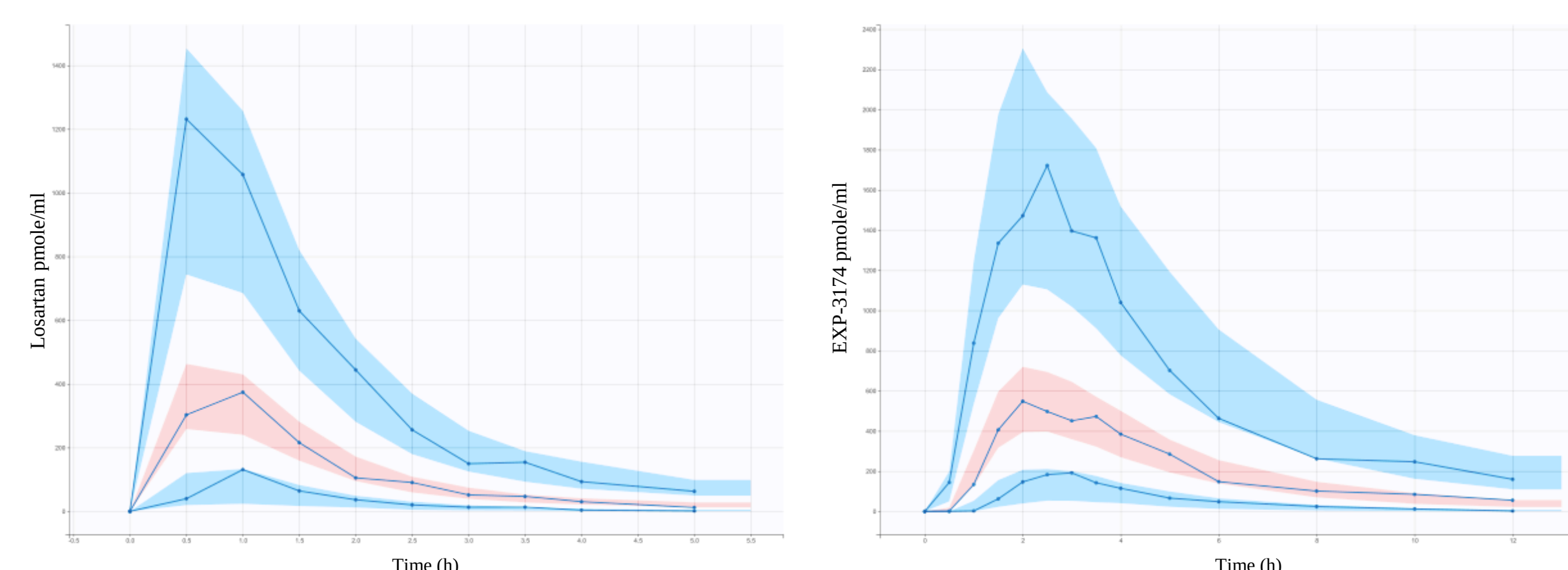


Figure 3. VPC plots of Losartan and EXP-3174 (active metabolite) plasma concentrations.

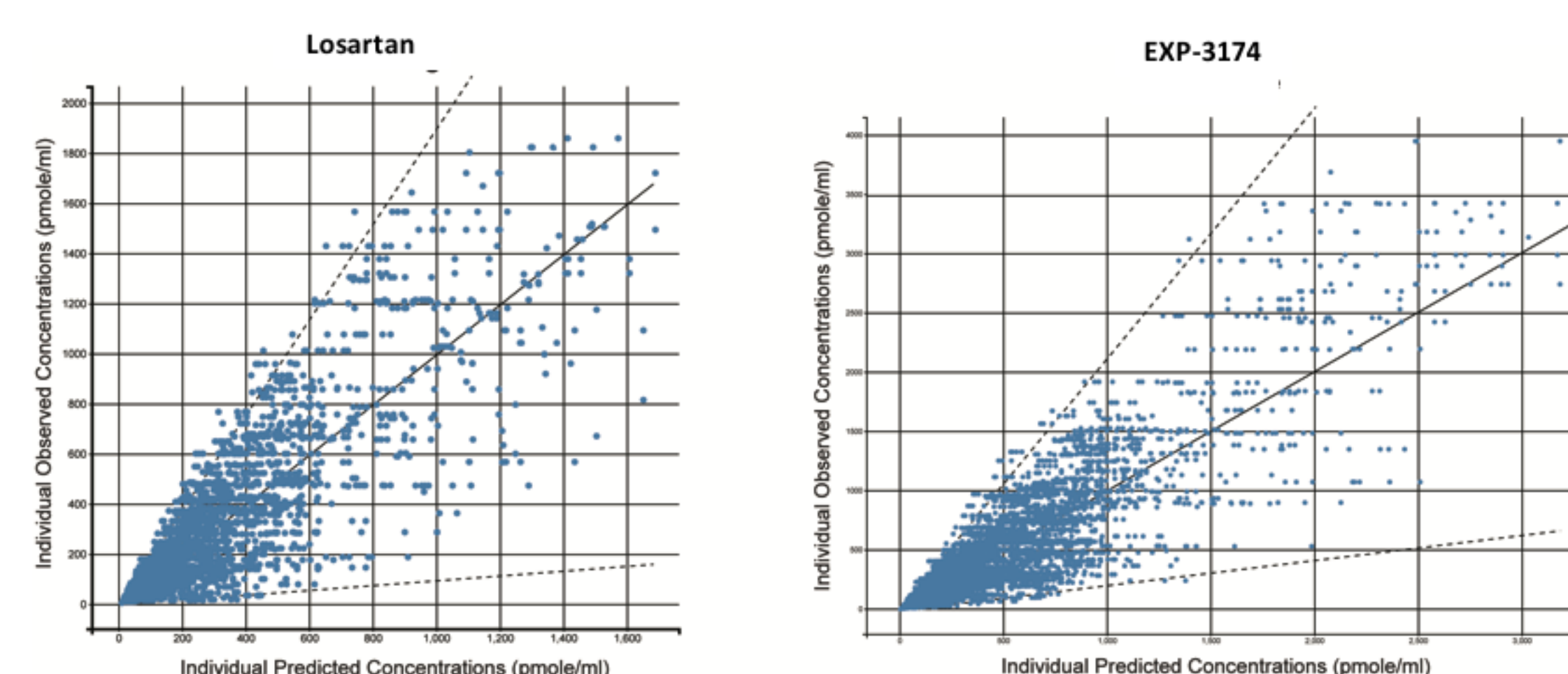


Figure 4. Observed vs. predicted plots of Losartan and EXP-3174 (active metabolite) plasma concentrations.

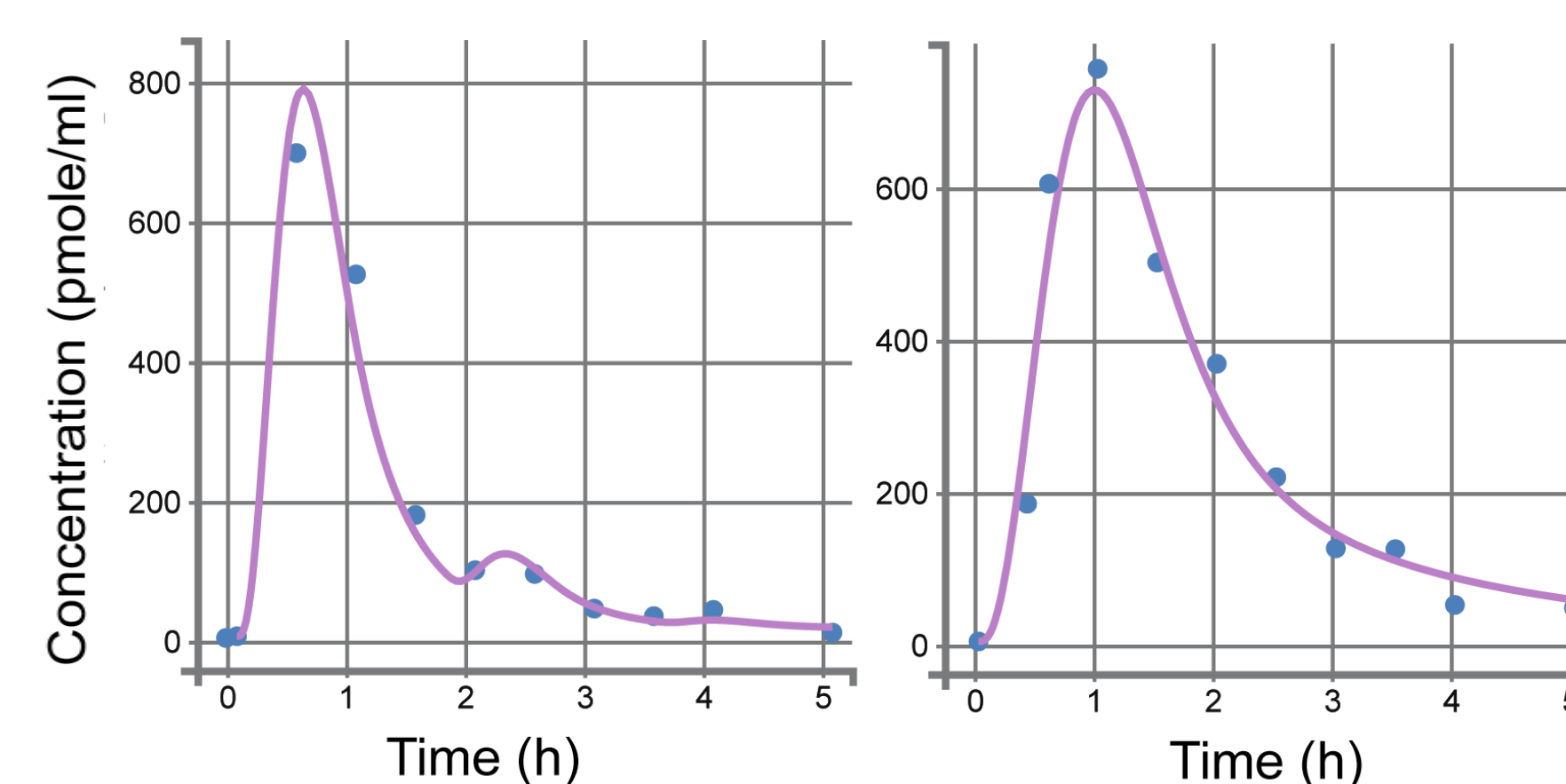


Figure 5. Individual model fittings for losartan's C-t profiles of two indicative volunteers.

Conclusions

The most appropriate joint pharmacokinetic model for LOS and EXP-3174 plasma C-t data consisted of a two-compartment model for LOS and a one-compartment model for EXP-3174, using a simple sinusoidal equation to describe periodic gastric emptying and delay differential equations for metabolite formation rate.

Acknowledgments

The authors wish to thank Verisfield UK Ltd for providing the C-t data.

References

1. Oberle RL, Amidon GL. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. *J Pharmacokinet Biopharm.* 1987;15(5):529-44.
2. Raphaël Kuate, Marc Lavielle, Eric Blaudez, Kaelig Chatel, Jerome Marquet, et al.. A delay differential equation solver for MONOLIX & MLXPLORE. [Research Report] RR-8489, INRIA. 2014, pp.19.