Investigation of the impact of population parameters describing gastric emptying on bioequivalence metrics

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Introduction

Losartan is known to be a BCS class I compound. Gastric emptying was shown to significantly affect the disposition of losartan (LOS) and its active metabolite (EXP-3174). Two population models were developed describing LOS and EXP-3174 distribution accounting also for gastric emptying either by implementing Delay Differential Equations (DDE) and/or using a sinusoidal equation [1,2]. This phenomenon has been noted to significantly affect the bioequivalence outcome of other BCS class I and III compounds [3].

Objectives

This study aimed to validate the two models developed and in the second place to investigate which among their parameters mostly affect bioequivalence (BE) metrics, namely Cmax and AUC.

Methods

LOS and EXP-3174 plasma concentration profiles were obtained from a single dose, 2x2 bioequivalence study in 31 men and women, receiving 100mg (2x50mg) losartan potassium in the form of immediate release tablets. Following a population pharmacokinetic analysis using Monolix ® 2018R1 the disposition of LOS and metabolite EXP-3174 were described by a joint two compartment-one compartment model with delayed first order metabolite formation. Plasma oscillations noted in certain losartan C-t profiles were attributed to gastric emptying that was best modeled either by first order gastric emptying followed by delayed first order absorption constant (Delay-model) or by a sinusoidal equation describing gastric emptying followed by first order absorption (Sinus-model) [2] (**Figure 1**).

Matlab® DDE solver (dde23) was used to solve the delay differential equations obtained from each model using population parameter estimates found in each case. The C-t profiles obtained in each case were compared to the empirical C-t profiles using Wilcoxon paired rank test.

Principal component analysis (PCA) was performed with the individual parameter estimates obtained from each model separately and the respective bioequivalence metrics (Cmax, AUC and Tmax) of each volunteer using R. Package factoextra was implemented for the PCA analysis [4]

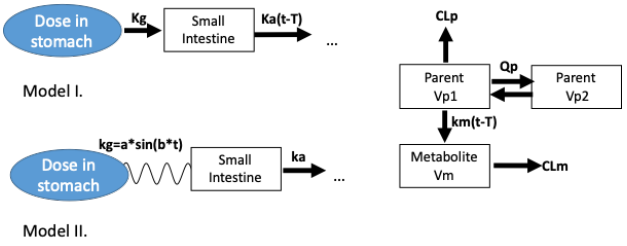

Figure 1. Schematic representation of the structural models developed.

Results

Through Matlab® DDE solver (dde23) the two models were arithmetically solved and predicted profiles were generated using parameter estimates found from each population pharmacokinetic analysis. Predicted concentrations obtained using each model were similar to the observed concentrations in both cases. Indeed, there was no statistically significant difference of the mean empirical C-t profile and solution of the Delay-model (p=0.2744) or solution of the Sinus- model (p=0.5966) using the population estimates. This finding was also evident through the superposition of the three C-t profiles obtained (**Figure 2**).

Two separate PCA analyses were performed including bioequivalence metrics and individual parameter estimates of the Delay-Model and the Sinus-Model (B). In both cases five principal components (PC) were identified explaining 82% of cumulative variability using individual parameter estimates of the Delay-model and 80% of cumulative variability using individual parameter estimates of the Sinus-model.

Results from PCA using individual model parameters derived from the analysis with the Delay-model (**Figure 3A**) showed through loadings of the first principal component that constant time delay (0.4543) was significantly correlated with Cmax (-0.8959) and AUC (-0.8151). Additionally, through loadings of the third principal component gastric emptying rate constant (0.7961) and delayed first order absorption constant (0.8235) were significantly correlated with Tmax (-0.8213).

Results from PCA using individual model parameters derived from the analysis with Sinus-model (**Figure 3B**) showed through loadings of the first principal component that amplitude of gastric emptying (-0.4630) and 2π/period of gastric emptying (-0.4286) were significantly correlated with AUC (-0.9018) and Cmax(-0.8279). In addition, through loadings of the third principal component amplitude of gastric emptying (-0.8365), 2π/period of gastric emptying (-0.4004) and first order absorption rate constant (0.8507) were significantly correlated with Cmax (0.4999) and Tmax(-0.6963).

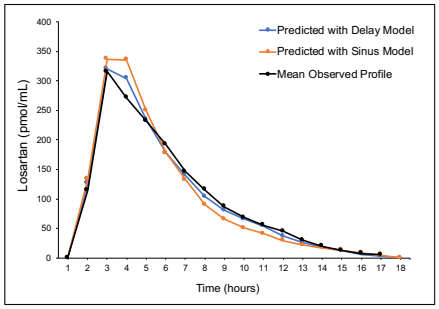

Figure 2. C-t profiles empirical (black), predicted by solving Model 1 (blue) and Model 2 (orange)

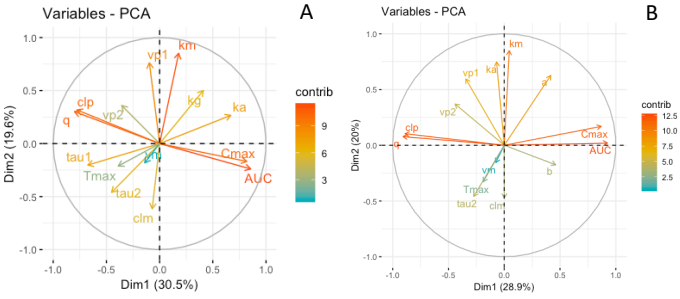

Figure 3. PCA Analysis including bioequivalence metrics and individual parameter estimates of Delay-Model (A) and of Sinus- Model (B)

Conclusions

These findings indicate that gastric emptying may be modeled efficiently using both approaches proposed herein. A significant effect of parameters describing gastric emptying on bioequivalence metrics was noted suggesting that this phenomenon may affect the outcome of a bioequivalence study using BCS class I compounds.

References

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[4] Alboukadel Kassambara and Fabian Mundt (2017). factoextra: Extract and Visualize the Results of Multivariate Data Analyses. R package version 1.0.5. https://CRAN.R-project.org/package=factoextra