

COMPARISON OF DIFFERENT MODELS TO DESCRIBE SIMULTANEOUSLY THE KINETICS OF PARENT DRUG AND METABOLITES AFTER ORAL ADMINISTRATION



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INTRODUCTION

When fitting simultaneously plasma levels of parent drug and metabolite obtained after an oral administration of the drug, generally model A is used. Model B is less frequent and model C, which includes the liver compartment has been used in very few occasions. The motivation to explore those three models came from the results from a multiple oral dose clinical trial where clear model misspecifications were found when models A and B were fitted to the data (see figure 1A). However the trends in the residual plots were almost vanished when model C was applied (figure 1B).

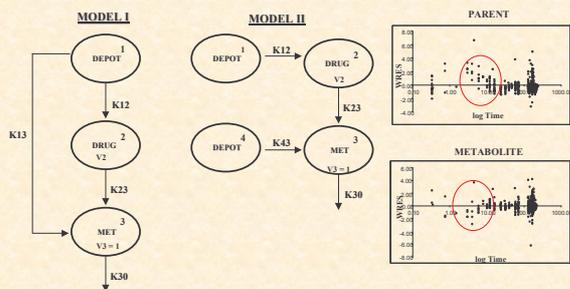


Figure 1A. Schematic representation of models A and B together with the distribution of WRES over time for parent and metabolite obtained for model A.

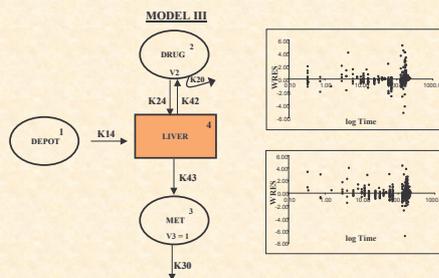


Figure 1B. Schematic representation of model C together with the distribution of WRES over time for parent and metabolite obtained for model C.

PURPOSE

To explore by means of computer simulations situations where the liver compartment model can provide better fits, which trends appearing in the goodness of fit plots suggest the inclusion of liver compartment, and interpretation of the model parameter estimates

METHODS

Simulations for a single individual were performed. Only a single administration scenario was considered. Data were simulated based on the liver compartment model and analysed with the three models. Data were simulated with the estimates obtained for the structural model parameters in the analysis of the real data with the following modifications (the rest of parameters remaining the same):
Condition 1 (C1): 50% increase in the ratio $K43/K30$, with two possibilities increasing $K34$ (C1a) or decreasing $K30$ (C1b),
Condition 2 (C2): 50% decrease in the ratio $K43/K30$, with two possibilities decreasing $K34$ (C2a) or increasing $K30$ (C2b).
Condition 3 (C3): 50% increase in the ratio $K42/K24$, with two possibilities increasing $K42$ (C3a) or decreasing $K24$ (C3b).
Condition 4 (C4): 50% decrease in the ratio $K42/K24$, with two possibilities decreasing $K42$ (C4a) or increasing $K24$ (C4b).
Condition 5 (C5): 50% increasing 50% $K14$.
Condition 6 (C6): 50% decreasing 50% $K14$.

Simulated and model predicted concentration vs time profiles were plotted and superimposed to facilitate visual inspection. The following residual measurement RSS was calculated as follows: $RSS = [(simulated - predicted)/simulated] \times 100$. The distribution of RSS between different conditions and time after administration was also explored.

RESULTS

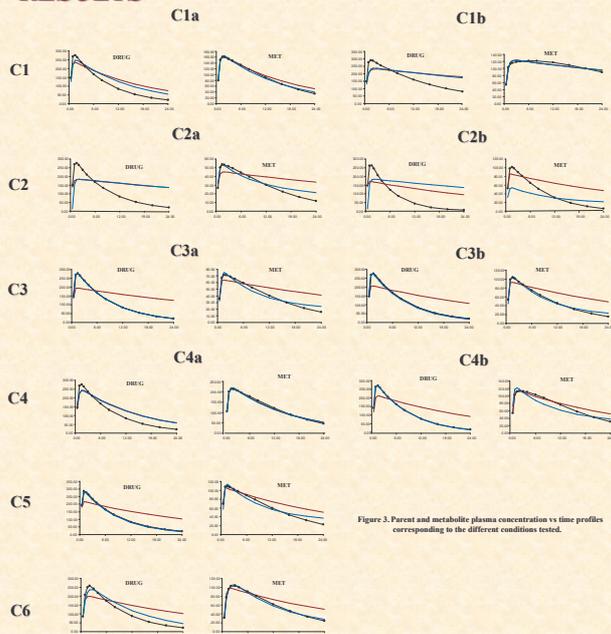


Figure 3. Parent and metabolite plasma concentration vs time profiles corresponding to the different conditions tested.

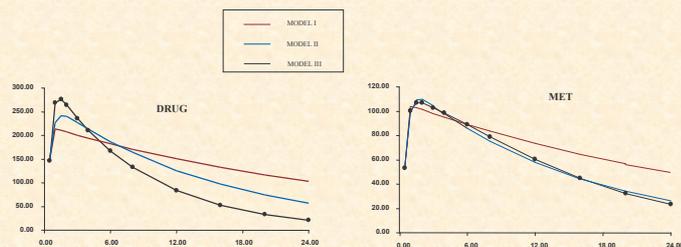


Figure 2. Parent and metabolite plasma concentration vs time profiles corresponding to a single dose and the typical model parameters for models A-C obtained in the clinical study.

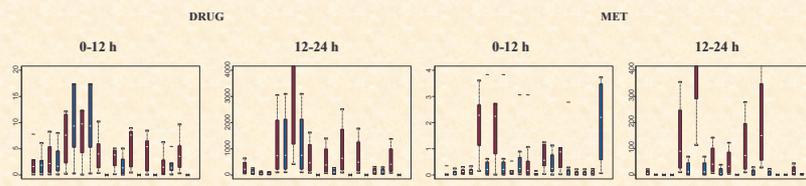


Figure 4. Boxplots of RSS vs the different conditions tested.

CONCLUSIONS

Model A performed very poorly in all the cases studied. For the case of model B there are situations where the model performed satisfactorily such as C3-C6, however model performance in C1-C2 was also very poor for model B, which means that the ratio between the rate of formation and rate of elimination might be the major determinants for distinguish between model B and model C.