Population PK and PK/PD Analyses of an Enzyme Inhibitor in Healthy Volunteers

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Objective

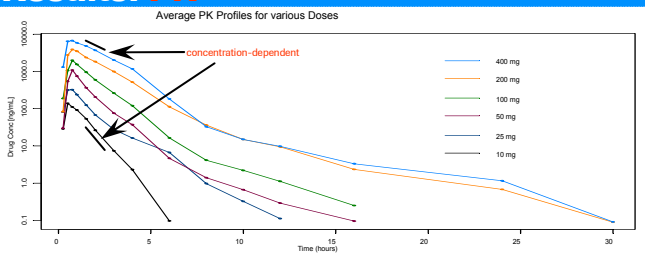
To analyze phase I study information in healthy volunteers and to develop structural PK and PK/PD models in preparation for analyzing Phase II study information in patients.

Material and Methods

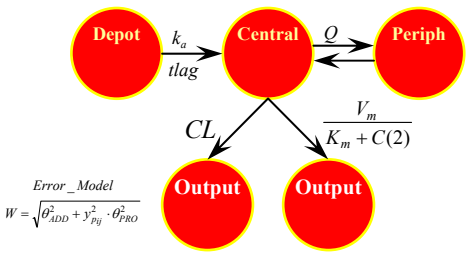
Single doses of 10, 25, 50, 100, 200, and 400 mg were administered to 48 healthy volunteers. Data consisted of 16 plasma enzyme inhibitor (drug) concentration and enzyme activity measurements from dosing till 30 hours.

A NONMEM population analysis to describe the drug's PK commenced with a simple model and progressed by adding complexity. A NONMEM population analysis to describe the PK/PD relationship compared effect-compartment, indirect physiological response, and slow-binding models (Äbelö, et al.).

Results: PK

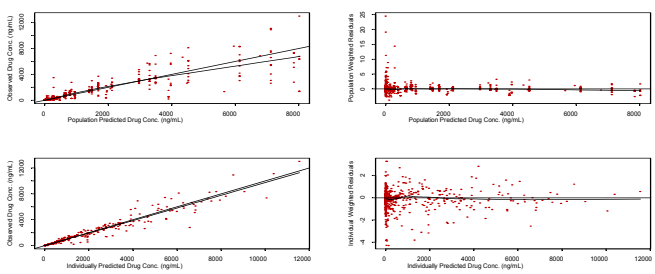


=>The concentration-dependent rate of elimination suggested that Michaelis-Menten elimination should be investigated.

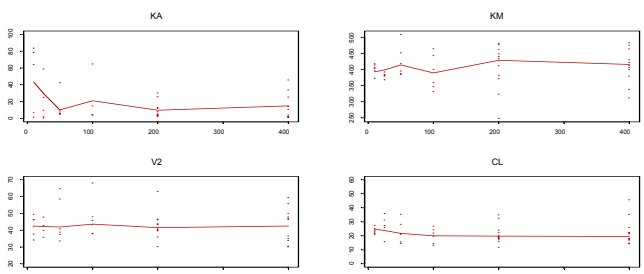


A two-compartment model with first order absorption and a combination of first order and Michaelis-Menten elimination adequately described the PK of the drug. The First Order Conditional Estimation (FOCE) method of NONMEM was used. The standard deviation of the proportional component of the error model was 23% and the additive component was 2.7-fold greater than the limit of quantification. The PK parameters were well-estimated (s.e for k_a ~22%, CL ~5%, V_m ~17%, and K_m ~17%) and no bias was observed when either the population or individual weighted residual error was depicted versus predicted concentration or time. The estimated population values for k_a, CL, V_m, and K_m were 14.4 [h^{-1}], 22.8 [L/h], 16.6 [mg/h], and 407 [µg/L], respectively. Complete metabolic saturation would decrease clearance to nearly one third its maximum value. IIV for k_a, V_2, CL, and K_M were 153%, 25%, 33%, and 21%, respectively.

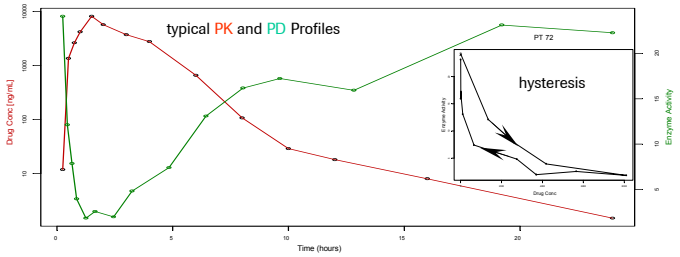
Goodness of Fit: Obs. Conc. & Weighted Residuals versus Pred. Conc.



Goodness of Fit: PK Parameter Dose Independency

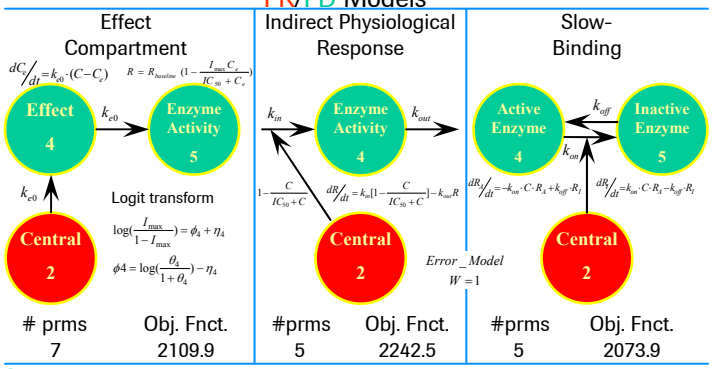


Results: PK/PD



=>The observed hysteresis suggested that models other than direct models should be investigated.

PK/PD Models



Since the baseline enzyme activity was observed to vary greatly, pre-dose enzyme activity (BSL) was a covariate for each volunteer (Sheiner), i.e.,

Effect Compartment:

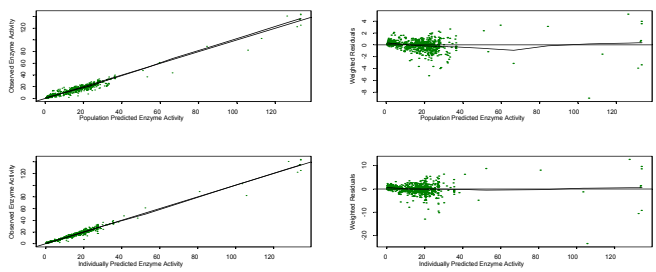
```
$ERROR
BASE=BSL+THETA(1)*ETA(1)
IPRED=BASE*(1-EFF)
Y=IPRED + THETA(1)*ERR(1)
 $OMEGA 1 FIX
 $SIGMA 1 FIX
```

Indirect Response and Slow Binding:

```
$ERROR
BASE=BSL + THETA(1)*ETA(1)
IPRED = BASE + F
Y = IPRED + THETA(1)*ERR(1)
$OMEGA 1 FIX
$SIGMA 1 FIX
```

The slow-binding model, i.e., a slow dissociation of the drug from the enzyme, best described the PK/PD of the drug. The FOCE method of NONMEM was used. No bias was observed and all parameters were well estimated (s.e. < 10%). The standard deviation of the enzyme activity and the rate constants for enzyme deactivation and subsequent activation were estimated to be 2.6 [pmol/ng/min], 0.060*C [h^{-1}] (C [µg/L] is the inhibitor concentration), and 0.793 [h^{-1}], respectively. As an example, the binding rate is predicted to be greater than the dissociation rate for drug concentrations above ~12 mg/L and an order of magnitude greater for drug concentrations above ~120 mg/L.

Goodness of Fit: Obs. Act. & Weighted Residuals versus Pred. Act. for Slow Binding Model



Discussion and Conclusion

A PK model having both linear and Michaelis-Menten elimination components is consistent with the existing knowledge of the drug, i.e., there is a high likelihood to saturate a metabolic pathway. In the future, the Michaelis-Menten parameters and the metabolism velocity will be investigated by using metabolite data. Furthermore, the preliminary structural PK and PK/PD models developed from healthy volunteer information will be enhanced when patient information becomes available.

References

1) Angela Äbelö, Johan Gabrielsson, Björn Holstein, Ulf G. Eriksson, Johan Holmberg, Mats O. Karlsson; Pharmacodynamic modelling of reversible gastric acid pump inhibition in dog and man; European Journal of Pharmaceutical Sciences 14 (2001) 339-346

2) Lewis Sheiner; NONMEM Tips #16 - April 2, 2003 - Modeling a "baseline" component and an additive "drug" component