Development of a Pharmacokinetic Model for Oseltamivir in Ferrets Using Iterative Two-Stage Analysis

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Objectives

Oseltamivir phosphate is an orally available prodrug (inactive, non-toxic) and is metabolized to its active species, oseltamivir carboxylate (OC). It is an inhibitor of influenza A and B neuraminidase. Ferrets are useful animal models frequently used in studying influenza. We sought to develop a simple PK model to describe the active metabolite PK in the ferret without explicitly including prodrug in the model. A simpler but robust PK model would facilitate future study designs and PK/PD analyses.

Methods

Study 1: Single dose, intensively sampled animals were inoculated with 10^2 $TCID_{50}$ (50% Tissue Culture Infective Dose) of A/Shenzheng/406H/2006 (H5N1) and dosed with 5 or 12.5 mg/kg of oseltamivir free base, while uninfected ferrets were dosed at 5 mg/kg. PK samples were collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hrs after dosing. There were 3 animals in each group, totaling 9 in the study.

Study 2: Multiple dose, sparsely sampled animals were inoculated with either 10^2 TCID50 of A/Shenzheng/406H/2006 (H5N1) or 10^6 $TCID_{50}$ of A/HongKong/433581/2009 (H3N2). Animals were dosed either at 0, 12.5, or 25.0 mg/kg twice daily for 5 days. PK samples were collected at 1, 4, 49, and 52 hours after the first dose. There were 6 animals in each group, totaling 36 in the study.

Pharmacometrics: The candidate PK models were fit to the OC concentrations (X_4/V_c) using iterative 2-stage analysis (ADAPT 5); weighting was by the inverse of the error variance; model discrimination was by Akaike's information criterion.

All the CL and V parameters were conditioned on two fractions: oral bioavailability (F) and fraction of parent changed to metabolite (F_m). We assumed log-normal distribution of all parameters, and linear PK.

Initial estimates for the iterative 2-stage were obtained by fitting the rich PK dataset individually using standard 2-stage approach (ADAPT 5). The median and the variance of the parameters obtained from these analyses were used as initial estimates for the population mean and variance.

A Monte Carlo Simulation was performed with the resulting population model to simulate median and 80% confidence interval at the ferret dose that results in the same median OC $AUC_{0\text{-}12h}$ in humans during steady state (SS) at the approved dose of 75 mg BID, 3220 ng•h/mL (Int J Antimicrob Ag 2010 35:461–467). 100 ferrets were simulated, with the following modifications: CV% for Vc, CLd, and Kt were reduced to 50%, and all covariance terms related to these 3 parameters were fixed to zero. Any other covariance terms with correlation within ± 0.15 were also fixed to zero. The dose used was 3.87 mg/kg of free base po bid for 5 days. A random seed of 1 was used. Simulated SS concentrations were taken on the 6th day during the 11th dose.

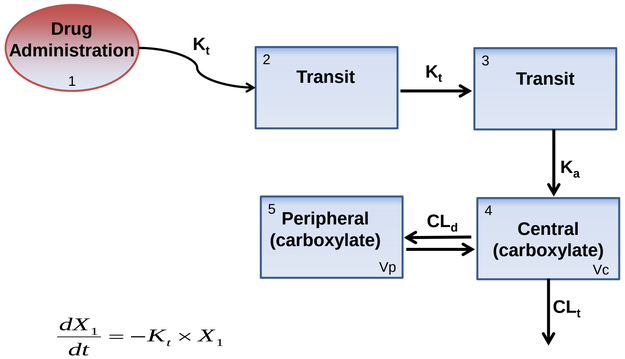
Results

Distribution (CL_d) and elimination (CL_t) clearances were linear. The overall R^2 of the model was 0.93.

The model performed well with no bias. There was an even distribution of residuals throughout the entire range of concentrations and time. The Monte Carlo Simulation showed wide variability in concentration-time profiles.

Structural Model

The final PK model had a drug administration compartment and two transit compartments (transit rate constant K_t) leading to the appearance (K_a) of active metabolite in the plasma (V_c) and the tissue (V_p) compartments.



$$\frac{dX_1}{dt} = -K_t \times X_1$$

$$\frac{dX_2}{dt} = K_t \times X_1 - K_t \times X_2$$

$$\frac{dX_3}{dt} = K_t \times X_2 - K_a \times X_3$$

$$\frac{dX_4}{dt} = K_a \times X_3 - \frac{CL_d \times X_4}{V_c} + \frac{CL_d \times X_5}{V_p} - \frac{CL_t \times X_4}{V_c}$$

$$\frac{dX_5}{dt} = \frac{CL_d \times X_4}{V_c} - \frac{CL_d \times X_5}{V_p}$$

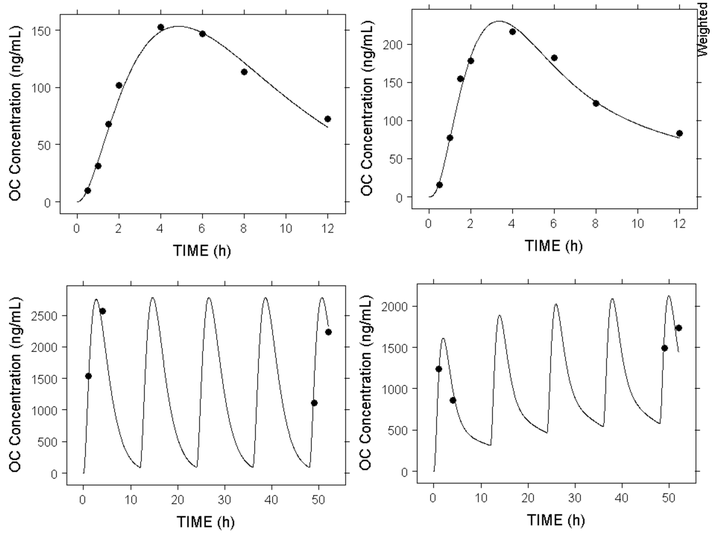
Initial Estimates

	K_t (h^{-1})	K_a (h^{-1})	CL_d (L/h)	CL_t (L/h)	V_c (L)	V_p (L)
Mean	0.403	0.654	0.432	3.25	0.633	4.14
Variance (SD^2)	0.494^2	0.502^2	0.473^2	2.202^2	0.572^2	3.81^2

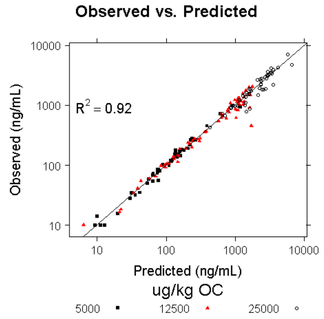
Final Population Parameters

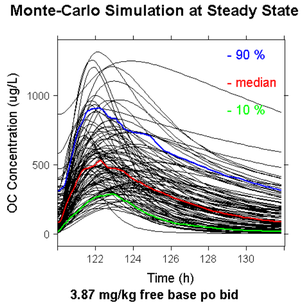
	K_t (h^{-1})	K_a (h^{-1})	CL_d (L/h)	CL_t (L/h)	V_c (L)	V_p (L)
Geometric mean	0.816	0.999	1.80	1.55	0.0674	5.66
median	1.00	1.00	1.00	1.27	0.08	4.13
CV%	60.1	4.23	135	61.9	277	150

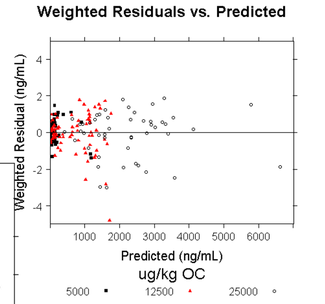
Sample Post-hoc Fits

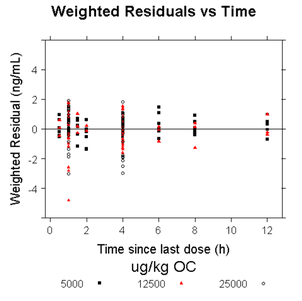


Diagnostic Plots









Conclusion

The PK model proposed fits both rich and sparse PK data well. The inter-individual variance is substantive. This simplified model can be used to perform PK/PD analysis and design optimal sampling strategies for future oseltamivir studies in the ferret.

Acknowledgements

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