Modelling and Simulation of ketoconazole inhibition when co-administration time is not sufficient: role of CYP3A function recovery

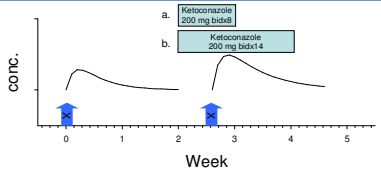
Nucci G, Poggesi I, and Gomeni R

Clinical Pharmacology/Modeling&Simulation, GlaxoSmithKline, Verona, Italy

Introduction

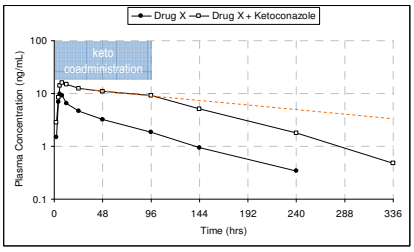
In this study ketoconazole (keto), a potent CYP3A inhibitor, was co-administered with GSK drug X (X) to assess the effect of keto inhibition on X pharmacokinetics as well as the relevance of CYP3A (3A) on X metabolism.

Fig. 1. Design of study and amendment



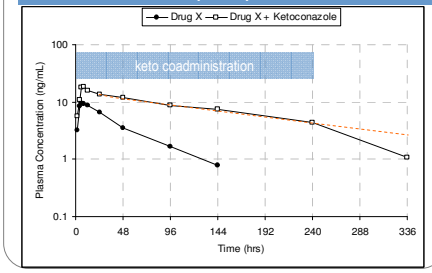
The initial design was fairly standard (Fig.1, a: group 1). The PK of X was followed for 2 weeks post-dose, as the typical terminal half life of X is 40 to 60h. An interim PK check was conducted to understand the magnitude of interaction (Fig. 2), which suggested that extending the co-administration of keto was required for the assessment of the full magnitude of interaction.

Fig. 2. Mean plasma concentrations of drug X alone and with ketoconazole at interim (n=7).



The study was therefore amended, so that the maximum recommended 14-day duration of keto treatment was exploited (Fig. 1, b: group 2). Again, the assessment of the full inhibition was not possible with standard methods, as the slope of the decline of X plasma concentration-time curves returned back to the non-inhibited values after stopping keto (Figure 3), leading to the paradoxical observation of higher AUClast ratios than AUC(0-∞) ratios.

Fig. 3. Mean plasma concentrations of drug X alone and with ketoconazole in group 2 (n=14).



Objective

The objective of this study was to model keto-X interaction data to estimate the full extent of metabolic inhibition. This would allow assessing the fraction of X metabolized by 3A and, in turn, the prediction of the effect of other 3A inhibitors on X pharmacokinetics.

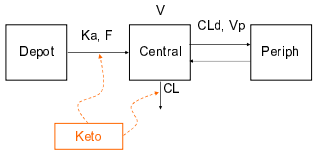
Experimental Data

36 healthy subjects have been administered at least one dose of X in this study (693 total data samples) with 33 completing the inhibition phase (group 1 or 2). The last quantifiable data samples were typically 144 h post-dose in the non-inhibited state and 336 h post-dose when keto was co-administered.

Methods

A two-compartment model with first-order absorption and lag-time was used (as it provided good description of X PK in previous studies). It was first fitted to the non-inhibited state data using NONMEM VI with the FOCE-INTERACTION estimation method. The inhibition phase was then introduced using time of keto co-administration as covariate. Different keto inhibition structures were employed and the best one (based on GOF considerations) was retained (Fig. 4).

Fig. 4. Model structure for the keto interaction with drug X. Note that only the fraction absorbed (F) and clearance (CL) were made dependent from inhibition



Results

Keto was found to decrease both CL and first pass of X (modeled as an increase in relative bioavailability).

As expected from the physiology, subjects with higher baseline CL had also higher inhibition (*i.e.* a correlation was included between the non-inhibited CL and the extent of inhibition). The time course of the recovery from the inhibited state was introduced as an exponential function of time after stopping keto treatment (see Fig. 5). Different time courses were attempted for separately describing the recovery of 3A activity on F and CL, however without success. The final model provided very reasonable fitting of the inhibited and non-inhibited phases after keto co-administration with different durations (Fig. 6)

Fig. 5. Estimated Time Course and Recovery of the Oral Clearance of X with and without keto co-administration

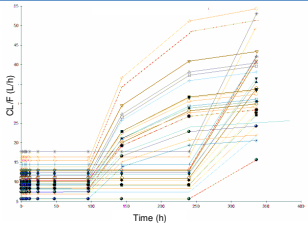
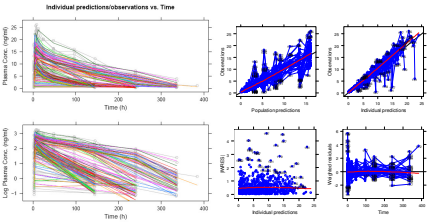
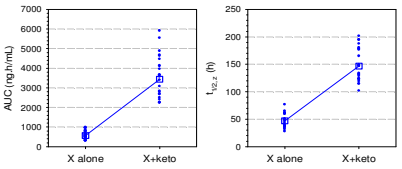


Fig. 6. Individual predictions and observations (left) and basic Goodness of Fit Plots for the Final Model (right)



The model results were in excellent agreement with the noncompartmental analysis but allowed to predict (*via* simulation) the full extent of inhibition (Fig. 7) and, in turn, the % of 3A involvement in X metabolism (Ohno *et al.* Clin Pharmacokinet 2007).

Fig. 7. Individual and mean simulated AUC(0-∞) and t½ for drug X alone and with keto with full inhibition (n=24)



The model also allowed us to estimate the systemic half-live of 3A (~44 h), which is in reasonable agreement with the range of 3A turnover rates reported in the literature.

Conclusions

- Duration of inhibitor co-administration matters for compounds with long half-life, in order to get a precise estimate of the full inhibitory effect. When this is not possible using standard methods, population PK modeling can help.
- In this example, the inhibition model provided good fit of the observed data and enabled to assess individual and population interaction results. The predictions of full inhibition obtained here were in good agreement with those obtained using SIMCYP.
- Using simulations, it was possible to evaluate the full extent of 3A involvement in X metabolism. This allowed to anticipate the extent of interaction with other inhibitors.