The Impact of Ketoconazole (KTZ) Dosage Regimen on Midazolam Clearance and Its Prediction Using PBPK Modelling

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Objectives

- Primarily to carry out clinical studies using model substrate (midazolam ; MDZ) and inhibitor (ketoconazole ; KTZ) drugs to provide experimental data on the impact of inhibitor dosage regimen (dose staggering and dose) on metabolic drug -drug interactions (mDDI).
- Subsequently to assess the utility of a mechanistic PBPK (physiologically based pharmacokinetic) model, implemented within Simcyp V6.11, in predicting mDDI involving complex experimental design of clinical studies.

Methods

Dose-staggering between KTZ and MDZ administration - Six healthy subjects (3 male; age range 21-46 y), gave informed consent to participate in an open, randomized, 6 arm crossover study. The protocol was approved by the ethics committee of the Medical Faculty of Osmangazi University. Each subject received 5 mg MDZ (p.o.) with and without a single oral 400 mg dose of KTZ 12 and 2 hours before, concomitantly with, 2 and 4 hours after MDZ.

Varying the dose of KTZ - Nine healthy subjects were recruited as described above (7 male age range 24-54y) into a 4 arm crossover study. Each subject received 5 mg MDZ (p.o.) with or without concomitant administration of a single oral dose of KTZ (100,200 or 400 mg).

Sampling - Blood samples were taken up to 12 hours after MDZ administration and plasma MDZ and KTZ were measured by LC-MS. AUC(12h) values were calculated using the linear trapezoidal rule.

Simulations - Concentration time profiles for different dosing schedules were simulated using Simcyp® (V6.11) for 10 replicate trials of each scenario. The ratios of AUC(12h) after and before inhibition were compared for simulated and experimental data.

Results

Observed and predicted plasma MDZ concentration-time profiles for the dose staggering study are shown in Fig. 1. The effects of KTZ dose staggering on the AUC and Cmax values of MDZ are shown as the ratios of the values in the presence of KTZ to that of control (Fig. 2). The effects of KTZ dose on the same ratios are shown in Fig.3.

Conclusions

Administration of KTZ increased the AUC of MDZ even when KTZ was given 4 hours after MDZ. The maximum increase in AUC occurred after concomitant administration of the drugs. However, this was in contrast to observations with the Cmax ratio where the changes were similar for concomitant and prior administration of KTZ. There was no substantial change in Cmax when KTZ was administered 2-4 hours after MDZ, thus confirming the lack of inhibition during first pass metabolism of MDZ by KTZ.

The increase in AUC and Cmax ratios of MDZ with increasing KTZ dose was less than proportionate, despite a proportionate increase in KTZ AUC between 100 and 200 mg doses and a more than proportionate change of KTZ AUC between the 200 and 400 mg doses (data not shown)

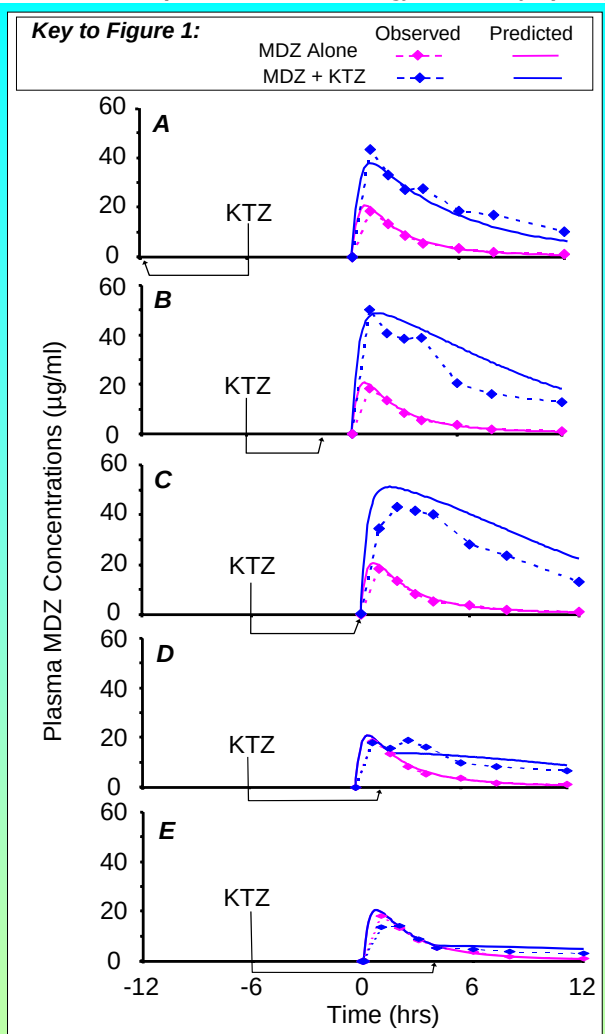

Fig 1- Plasma MDZ concentration-time profile after inhibition by KTZ, using 5 different dosage staggering protocols (A-E), are compared with control (pink line and markers). Predicted profiles (from average of 10 simulated trials) were generated by Simcyp® V6.11 using the MDZ and KTZ library files in the program and the trial designs from each protocol.

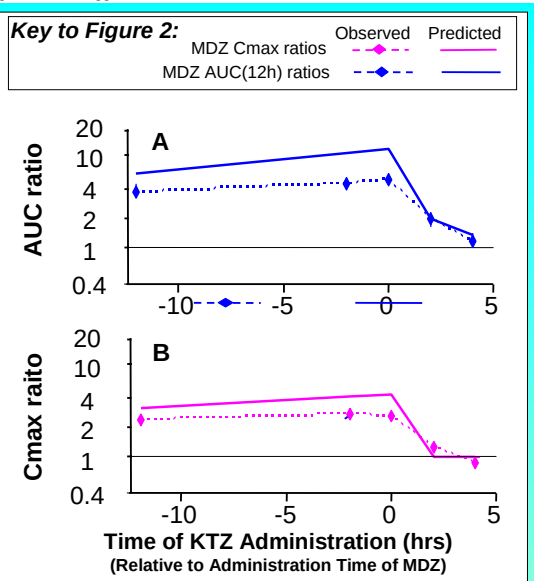

Fig 2 – Observed and predicted ratios of MDZ AUC (Part A) and Cmax (part B) after and before inhibition by KTZ at each time interval between single doses of KTZ and MDZ

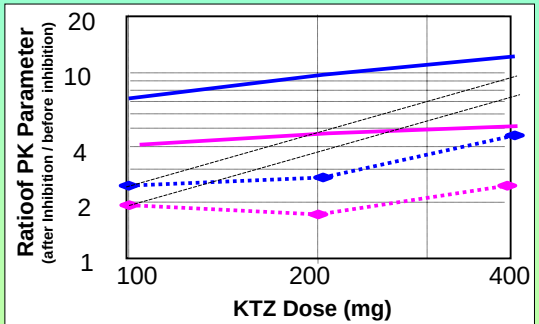

Fig. 3 - Observed and predicted ratios of MDZ AUC and Cmax after and before inhibition by KTZ at each dose of KTZ. The key is the same as in Fig. 2. Dashed lines represent the expected change in each ratio assuming that there is a proportional relationship between the KTZ dose and measured MDZ kinetic parameter of interest.

The patterns in the effects of dose staggering on the MDZ/KTZ interaction simulated using Simcyp® reflect those obtained in the *in vivo* study, thus demonstrating the utility of mechanistic PBPK models for assessing complex study designs. Simulated trials showed variations in the outcome of DDI studies between trials (data not shown). Further studies are required to assess the impact of inter-individual variability (e.g. variation in gut first pass metabolism) on the outcome of studies and its role in determining study power.