The Impact of Dose-Staggering on the Inhibitory Effect of Ketoconazole on Midazolam Clearance, and Its Prediction Using Physiologicallv-Based Pharmacokinetic Modelling

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Introduction

Most studies that attempt to predict metabolically based drug-drug interactions from *in-vitro* data rely on a simplistic model

$$\frac{AUC\ (inhibited)}{AUC\ (uninhibited)} = 1 + \frac{[I]}{Ki}$$

where [I] is the inhibitor concentration at the enzyme site and Ki is the inhibition constant However, this cannot accommodate differences in *in vivo* study design such as the relative dosing times of the interacting drugs (dose staggering) and [I] is assumed to be time–invariant. Simulations using a mechanistic physiologically based pharmacokinetic (PBPK) model have shown that dose staggering could have a major effect on the magnitude of mDDIs[1]. Since experimental data to assess the impact of dose staggering are scarce[2,3] a clinical study was carried out using midazolam (MDZ) and ketoconazole (KTZ) to investigate the influence of dose staggering and the results were compared to simulations by Simcyp® (V6).

Methods

Six healthy subjects (3 male; age range 21-46 y), gave informed consent to an open, randomised, 6 arm crossover study. The protocol was approved by the ethics committee of the Medical Faculty of Osmangazi University. Each subject received 5mg MDZ (p.o.) with and without a single oral 400 mg dose of KTZ according to the protocols shown in Fig.1 (i.e. KTZ 12 and 2 hours before, concomitantly with, 2 and 4 hours after MDZ). Blood samples were taken up to 12 hours after MDZ administration and plasma MDZ was measured by LC-MS. Concentration time profiles for these dosing schedules were simulated using Simcyp®V6 with 10 trials of 6 subjects. AUC(12h) values for simulated and experimental data were compared.

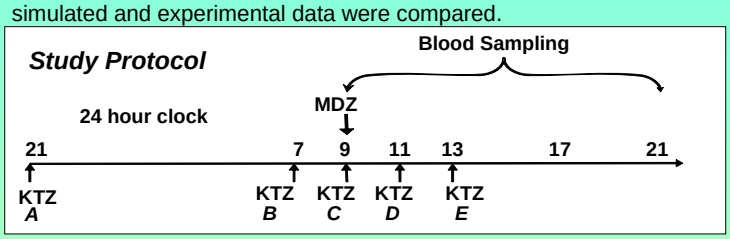

Figure 1. Dosing protocols for the 5 arms of the study involving administration of KTZ (MDZ was given on its own in the 6th arm).

Results

Plasma MDZ concentration-time profiles are shown in Fig. 2 and the effects of inhibition by KTZ on the Cmax and AUC values of MDZ are summarised in Figure 3.

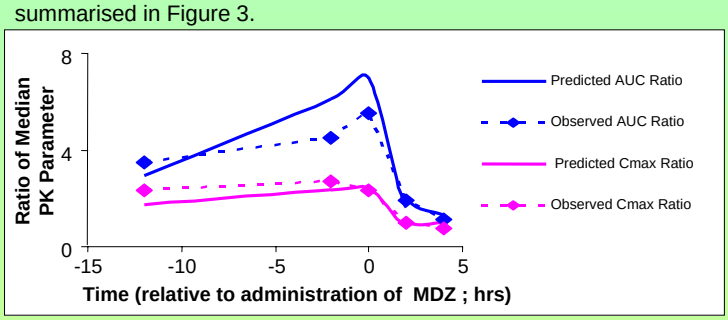

Figure 3: $Cmax_{[after\ inhibition]}/Cmax_{[control]}$ and $AUC_{[after\ inhibition]}/AUC_{[contro]}$ plotted against the time interval between single doses of KTZ and MDZ. A negative interval indicates KTZ administration before MDZ; a positive interval indicates KTZ administration after MDZ.

References

(1) Yang, J., Kjellson,M., Rostami-Hodjegan, A and Tucker, G.T. 2003: Eur. J. Pharm.Sci., 20, 223-32 ; (2) Neuvonen, P. J., Varhe, A., Olkkola, K.T: 1996 Clin. Pharmacol. Ther. 60, 326-331 ; (3) Seidegard, J. 2000 Clin. Pharmacol. Ther. 68, 13-17

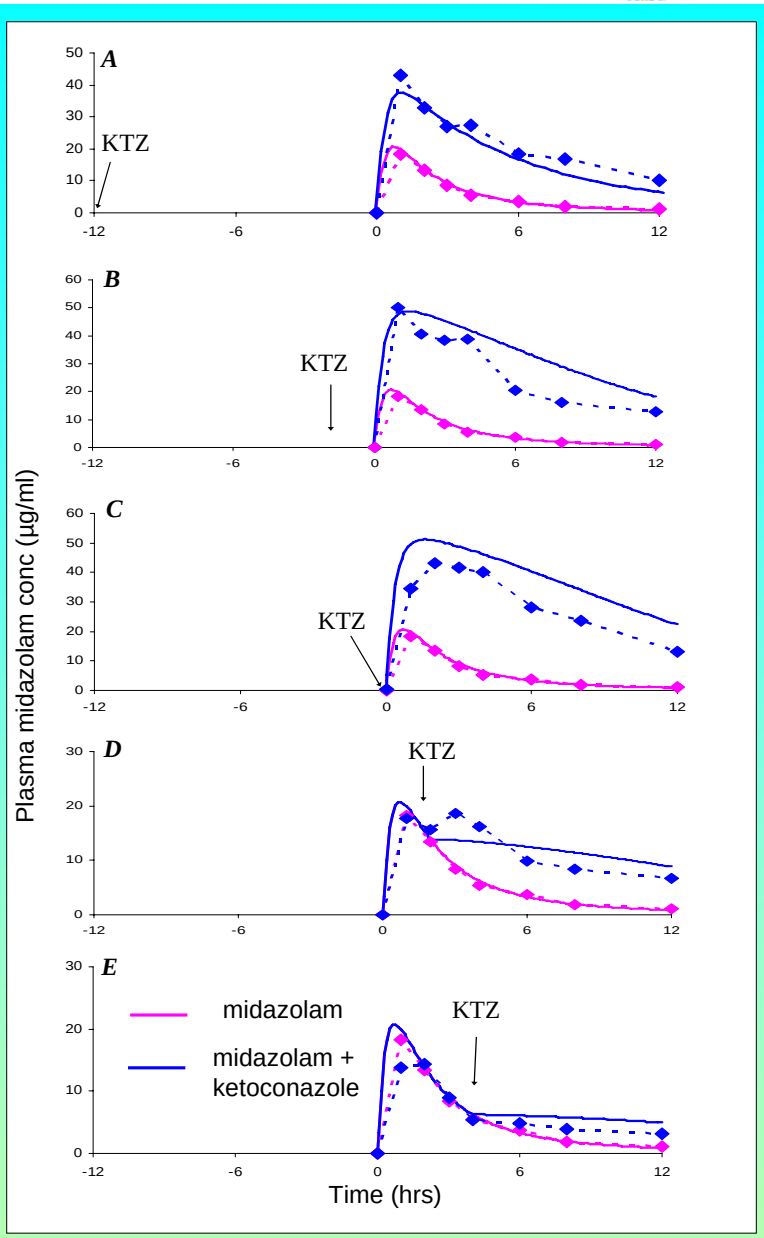

Figure 2: Plasma MDZ concentration-time profile under 5 different MDZ-KTZ dosage staggering protocols (A-E) compared with control (pink line and markers). Solid lines indicate predicted profile (Simcyp® V6) and dotted lines with diamond markers indicate experimental data

Discussion & Conclusion

Administration of KTZ increased AUC of MDZ even when KTZ was given 4 hours after MDZ. The maximum increase in AUC occurred after concomitant administration of the drugs. This was in contrast to the increase in Cmax ratio where the changes were similar for concomitant administration of KTZ and MDZ and administration of KTZ 2 hours before MDZ.

Changes in both AUC and Cmax were substantially lower when KTZ was taken after MDZ, reflecting the lack of inhibition during first pass metabolism of MDZ. Administration of KTZ after MDZ did not affect Cmax but AUC was increased.

The effects of dose staggering on the MDZ/KTZ interaction were predicted by Simcyp®, demonstrating the utility of mechanistic PBPK models for assessing complex study designs.