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Smith N. [1], van Zijtveld J. [2], Swart P. J. [2]
1. Yamanouchi USA, 2. Yamanouchi Europe B.V.

CO-ADMINISTRATION OF KETOCONAZOLE, A POTENT CYP3A4 INHIBITOR, DOES NOT AFFECT SAFETY OR TOLERABILITY OF YM905

Aims of Study

YM905 is a novel, bladder-selective antimuscarinic being developed for the treatment of overactive bladder (OAB). The metabolism of YM905 involves hepatic cytochrome P450 (CYP) 3A4; this raises the possibility that its pharmacokinetics might be altered by other drugs that either induce or inhibit this enzyme. The objective of this study was to evaluate the effects of multiple doses of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of single, oral 10-mg doses of YM905 in healthy volunteers and to study the effects, if any, on YM905's safety and tolerability.

Methods

The study employed an open, two-period design and included 17 subjects (9 men and 8 women; aged 18 to 50 years, mean, 30 years; mean weight, 72.3 kg). In the first phase, subjects received a single 10-mg oral dose of YM905 after an overnight fast. After a 14-day washout period, subjects began 21 days of treatment with once daily oral ketoconazole (200 mg). A single, oral dose of 10 mg YM905 was administered on the seventh day of ketoconazole dosing. Blood samples for determination of plasma YM905 concentrations were taken just before and up to 14 days after each YM905 dose. Blood samples were also taken on days 5 through 9 of ketoconazole dosing to determine when steady state was achieved. The following pharmacokinetic parameters were determined for YM905: maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the time versus plasma concentration curve from time zero until that of the last measurable plasma concentration and infinity (AUC_{last} and $AUC_{0\text{-}INF}$), and elimination half-life ($t_{½}$). Analysis of variance and calculation of 90% confidence intervals (CIs) were used to compare pharmacokinetic results before and during ketoconazole administration. Values for C_{max}, AUC_{last}, $AUC_{0\text{-}INF}$, and $t_{½}$ were log transformed prior to analysis. It was determined that there would be no significant effect of ketoconazole on the pharmacokinetics of YM905 if the 90% CIs for the log-transformed C_{max}, AUC_{last}, and $AUC_{0\text{-}INF}$ all fell within the prespecified equivalence interval of 0.80 to 1.25. Safety was evaluated by reporting of adverse events, physical examinations, clinical laboratory analysis, recording of vital signs, and ECGs, with the objective of comparing the safety and tolerability of YM905 in the presence of ketoconazole.

Results

Sixteen of the 17 subjects enrolled completed all phases of the study. One subject withdrew prior to the second YM905 dose for treatment of a urinary tract infection.

Pharmacokinetic results indicate that steady-state for ketoconazole was reached by the time the YM905 dose was given, and co-administration of ketoconazole caused a statistically significant interaction on the pharmacokinetics of YM905 (see Table 1). Multiple-dose administration of 200 mg/day ketoconazole significantly increased C_{max} by about 40% and both AUC_{last} and $AUC_{0\text{-}INF}$ by approximately 100%. Co-administration of ketoconazole also produced an approximately 55% increase in $t_{½}$, but did not change t_{max}. The effects of ketoconazole on the pharmacokinetics of YM905 are probably due to inhibition of first-pass metabolism by CYP3A4.

Table 1. Pharmacokinetic parameters for single 10-mg oral doses of YM905 with and without co-administration of ketoconazole.

Parameter*	YM905 alone	YM905 + Ketoconazole	Ratio of means	90% CI
ln C_{max} (ng/mL)	14.1	20.0	1.43	1.29-1.57
ln AUC_{last} (ng·h/mL)	662	1360	2.05	1.84-2.29
ln $AUC_{0\text{-}INF}$ (ng·h/mL)	716	1447	2.02	1.83-2.23
ln $t_{½}$ (hours)	48.0	75.1	1.56	1.46-1.68
t_{max} (hours)	6.0	6.0	-	-

* Least squares mean from analysis of variance, ln = log transformed

YM905 was well tolerated when administered alone or with ketoconazole. Adverse events occurred in 53% (9 of 17) of subjects during treatment with YM905 alone and in 56% (9 of 16) of subjects during treatment with

YM905 plus ketoconazole. In addition, 41% (7 of 17) of subjects reported side effects during treatment with ketoconazole alone. Headache was the most frequently reported side effect during treatment with either YM905 or ketoconazole alone (18% and 12%, respectively), and dry mouth was the most frequent side effect when YM905 and ketoconazole were administered together (19%).

Conclusions

Co-administration of ketoconazole increases the plasma levels of YM905 twofold by inhibiting first-pass metabolism mediated by CYP3A4. The increased plasma levels of YM905 resulting from this drug interaction are well tolerated by healthy adults, as indicated by no substantial increase in adverse events and no significant effects on vital signs, ECGs, clinical laboratory values, or physical examinations. The pharmacokinetic interaction, while statistically significant, may prove not to be clinically significant.