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Uchida T. [1], Smulders R. A. [2], Abila B. [2], Mulder H. [2]
1. Yamanouchi Pharmaceutical Company, Ltd., 2. Yamanouchi Europe B.V.

PHARMACOKINETICS OF YM905, A NOVEL, BLADDER-SELECTIVE ANTIMUSCARINIC, ARE NOT ADVERSELY AFFECTED BY FOOD

Aims of Study

YM905 is a novel, bladder-selective antimuscarinic with the potential to ameliorate overactive bladder (OAB) with minimal anticholinergic side effects (eg, dry mouth, constipation, somnolence, blurred vision, impaired cognitive function). The objective of this study was to compare the pharmacokinetics of YM905 in the fed and fasted states in healthy volunteers.

Methods

The study employed an open, two-period, crossover design and included 24 white males (28.4 ± 7.0 years of age, body weight 73.7 ± 10.1 kg). Subjects (12 in each group) received 10 mg YM905 in either the fasted state or 5 minutes after ingestion of a standard high-fat meal.[1] After a 14-day washout period, subjects were crossed over to the alternative treatment. Blood samples (6 mL) were taken before and 30 minutes to 144 hours after dosing. The following pharmacokinetic parameters were determined using noncompartmental methods: 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 $AUC_{0\text{-}INF}$), elimination half life ($t_{½}$), and time from dosing until the first measurable drug concentration (t_{lag}). Analysis of variance and calculation of 90% confidence intervals (CIs) were used to compare pharmacokinetic results from the fasted and fed states. Values for C_{max}, AUC_{last}, and $AUC_{0\text{-}INF}$ were log transformed prior to analysis. It was determined that ingestion of food would have no effect on the pharmacokinetics of YM905 if the 90% CIs for C_{max}, AUC_{last}, and $AUC_{0\text{-}INF}$ all fell within the prespecified equivalence interval of 0.80 to 1.25.[1]
Safety was evaluated by reporting of adverse events, physical examinations, clinical laboratory analysis, recording of vital signs, and ECGs.

Results

Twenty-three of the 24 subjects enrolled completed both phases of the study, and results from all 23 completers are included in the pharmacokinetic analysis. One subject withdrew for personal reasons after receiving one 10-mg dose of YM905. Only safety results from this subject are reported.

Ingestion of a standard high-fat meal had no clinically relevant effect on the pharmacokinetics of YM905 (Table 1). The geometric mean ratios for log-transformed C_{max}, AUC_{last}, and $AUC_{0\text{-}INF}$ were all very close to 1.0, and the 90% CIs for each parameter were well within the predefined limits of 0.80 to 1.25. Ingestion of a standard high-fat meal also had little effect on t_{lag}, t_{max}, or $t_{½}$ for YM905.

Table 1. Pharmacokinetic parameters for YM905 in the fasted and fed states.

	Mean values			
Parameter	Fasted state	Fed state	Geometric mean ratio	90% CI
C_{max} (ng/mL)	13.6	14.0	1.033	0.953-1.120
AUC_{last} (ng·h/mL)	652	697	1.068	0.990-1.153
$AUC_{0\text{-}INF}$ (ng·h/mL)	758	789	1.040	0.976-1.109
t_{lag} (hours)	0.46	0.63	-	-
t_{max} (hours)	6.0	5.8	-	-
$t_{½}$ (hours)	50.8	46.8	-	-

Safety results indicated that YM905 was well tolerated when administered in either the fed or fasted state. Overall, 54% of subjects (n=13) experienced adverse events, but only 17% (n=4) had side effects (all mild) that were possibly or probably related to YM905. These included headache, dry mouth, diarrhea, and abnormal dreams. There were no clinically significant changes in ECGs or effects of treatment on vital signs, physical examinations, or laboratory values.

Conclusions

The results of this study demonstrate that the pharmacokinetic profile for single, oral 10-mg doses of YM905 is not affected by ingestion of food. Study results also show that YM905 was safe and well tolerated by this

small cohort of healthy subjects. The lack of effect of food on the pharmacokinetics of YM905 suggests that it may be administered without regard to meals in patients with OAB.

Reference:

[1] Center for Drug Evaluation and Research. Food-effect bioavailability and fed bioequivalence studies: study design, data analysis, and labeling. Draft guidance. Rockville, Md.: US Dept of Health and Human Services; October 2001.