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MULTIPLE DOSING WITH YM905, A NOVEL, BLADDER-SELECTIVE ANTIMUSCARINIC, IN HEALTHY MEN: SAFETY, TOLERABILITY, AND PHARMACOKINETICS

Aims of Study

The primary objective of this study is to evaluate the safety and tolerability of increasing oral doses of YM905, a novel, bladder-selective antimuscarinic, administered for 21 consecutive days to healthy male volunteers. Secondary aims were to identify the maximal tolerable dose after multiple doses, to evaluate pharmacodynamics, and to assess pharmacokinetics after single and multiple doses.

Methods

Healthy male subjects aged 18 to 45 years were screened for this double-blind, placebo-controlled, randomized study. Eligible subjects (n=40; aged 20 to 35 years; mean, 27) were assigned to one of four dosing groups: 5, 10, 20, or 30 mg. In each group, eight subjects received YM905, and two received placebo. On day 1, subjects received single doses of YM905 followed by a 3-day, drug-free interval to allow for blood sampling to determine $AUC_{0\text{-}INF}$. YM905 or placebo was then administered once daily for 21 days, so safety and tolerability could be assessed at steady state. Blood samples were obtained up to 96 hours after the last dose. The visual nearpoint and salivary flow were assessed as pharmacodynamic parameters of antimuscarinic activity. R-R interval variability was assessed as a safety parameter. Pharmacokinetics of YM905 after a single dose and after multiple doses was assessed by determining AUC_{last}, $AUC_{0\rightarrow INF}$, $AUC_{0\text{-}24h}$, C_{max}, t_{max}, and $t_{½}$. Urine samples were collected before dosing and up to 96 hours after the first dose to measure drug excretion.

Results

During the consecutive dosing period, adverse events (AEs) were reported by 28 of 32 (88%) YM905 subjects and 7 of 8 (88%) placebo subjects. Most (93%) AEs were mild. All eight subjects who received 30 mg of YM905 withdrew because of AEs: two because of dysuria and six because of the total number of AEs experienced. A ninth subject withdrew for reasons unrelated to the study drug. The most common AEs were dry mouth, blurred vision, and headache. The frequency, duration, and severity of dry mouth and blurred vision appeared to increase with dose. CNS-like side effects were reported in the 30-mg group. There were no consistent changes in vital signs, ECG parameters, or laboratory findings during the study.

Mean visual nearpoint before each daily dose throughout the study period showed no change over time in the 5- or 10-mg groups in YM905 or placebo subjects but increased over time in YM905-treated subjects in the 20- and 30-mg groups. Mean change in visual nearpoint at 4 hours after each daily dose was higher after consecutive treatment in the 10-, 20-, and 30-mg groups compared with pooled placebo results. Although a dose-response relationship was suggested, standard deviation also increased with increases in dose. As no subjects in the 30-mg group completed the study, maximal effect on visual nearpoint may not have been achieved. Mean values for salivary flow before each daily dose decreased over time in all groups in both YM905 and placebo subjects. No dose-response relationship was observed for salivary flow. There was no consistent or clinically meaningful change in R-R interval in any dose groups.

YM905 was eliminated gradually, with a mean $t_{½}$ of about 50 hours. Therefore, steady state was not achieved until 10 days of consecutive dosing, with moderate to high interindividual variation. The $t_{½}$ appeared to be independent of dose and was similar after first and last doses. Mean t_{max} was similar after first and last doses, indicating that pharmacokinetics showed no substantial change after multiple dosing. C_{max} (range: 7.29 to 37.83 ng/mL) and $AUC_{0\text{-}INF}$ (range: 411 to 1839 ng·h/mL) measured after first doses appeared to increase linearly with increases in dose in the 5-, 10-, and 20-mg groups. Increases in the 30-mg group were less than would be expected, possibly because of intersubject variability. Comparison of AUC_{last} and $AUC_{0\text{-}INF}$ showed that about 25% of absorbed drug remained to be eliminated after 96 hours. Only a small amount of drug (3.17% to 5.71%) was excreted in urine.

Conclusions

These findings indicate that YM905 is safe and that 20 mg is the maximal tolerable dose. Pharmacokinetic data indicate that C_{max} and $AUC_{0\text{-}INF}$ increase linearly with dose increases, while $t_{½}$ and t_{max} appear to be dose independent. Future studies should allow treatment periods of at least 2 weeks to ensure attainment of steady state, and bioequivalence studies should allow sampling periods of at least 6 days to avoid having to extrapolate more than 15% of $AUC_{0\text{-}INF}$ values.