438

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A PLACEBO-CONTROLLED, DOSE-RISING STUDY IN HEALTHY MALE VOLUNTEERS TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE ORAL DOSES OF YM905

Aims of Study

Pharmacologic treatment of overactive bladder (OAB) may be limited by the occurrence of side effects. The primary objective of this study was to evaluate the safety and tolerability of single doses of YM905, a novel, bladder-selective antimuscarinic, administered in a dose-escalating manner. Secondary aims were to determine the maximal tolerable dose of YM905, if possible; to assess the pharmacokinetics of single oral doses; and to generate pharmacodynamic data on the comparative antimuscarinic effects of YM905 and oxybutynin.

Methods

Sixty-eight healthy male subjects, aged 18 to 45 years, were screened for inclusion in this double-blind, placebo-controlled, randomized study. Eligible subjects (n=61; aged 19 to 40 years; mean, 23.1) were divided into seven groups, Groups A through G, after informed consent was obtained; no subject received more than one dose of study drug. YM905, (1S,3R)-3-quinuclidinyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monosuccinate, was administered in the following doses: 5, 10, 20, 40, 60, 80, and 100 mg. In each study group, six subjects received YM905, and two subjects received placebo. In Groups A, B, and C, two additional subjects received oxybutynin (5 mg, single dose).

Safety was assessed by determining the nature, frequency, and severity of adverse events (AEs) and by ECG monitoring, hematology and biochemistry tests, urinalysis, monitoring of vital signs, and physical examination. The pharmacokinetics of single doses of YM905 were assessed by evaluating the $AUC_{0\text{-}INF}$, AUC_{last}, C_{max}, t_{max}, and $t_{½}$. Visual nearpoint, salivary flow (both M_3 mediated), and R-R interval variability (M_2 mediated) were evaluated as pharmacodynamic parameters to assess antimuscarinic activity.

Results

During the admission period (day 1-3), AEs were reported in 39 of 42 (93%) YM905 subjects, 4 of 6 (67%) oxybutynin subjects, and 8 of 13 (62%) placebo subjects. The most commonly reported AEs were dry mouth (YM905: 18 subjects; placebo: 1), blurred vision (YM905: 14; placebo: 2), headache (YM905: 8; oxybutynin: 2; placebo: 1), and drowsiness (YM905: 6). The frequency, duration, and severity of dry mouth and blurred vision appeared to increase with dose. Drowsiness occurred in only the two highest-dose groups. There was no relation between the incidence of AEs and the extent of exposure to YM905, evaluated in terms of the plasma concentration. No effects on vital signs, laboratory parameters, ECG recordings, or the physical examination were observed. No serious AEs were observed.

YM905 was orally absorbed, with a mean t_{max} ranging from 3.3 to 4.8 hours, independent of dose. The $t_{½}$ was relatively long, ranging from 40.2 to 102.6 hours. However, the 102.6-hour $t_{½}$ in the 80-mg group was caused by two outliers (when data from the 80-mg group were eliminated, $t_{½}$ ranged from 40.2 to 55.4 hours and was dose independent). The C_{max} (6.5 ng/mL to 108.5 ng/mL) and the AUC_{last} (143 to 2613 ng·h/mL) appeared to increase in a dose-linear manner. Because of the relatively short sampling time (48 hours) in relation to the long half-life (approximately 50 hours), a high percentage of the $AUC_{0\text{-}INF}$ (37.5% to 61.9%) had to be extrapolated. These same features were the likely causes of the high intersubject variability in $t_{½}$ and $AUC_{0\text{-}INF}$. Visual nearpoint showed a dose-response relationship for the 60-, 80-, and 100-mg YM905 dose groups, beginning at 2 hours after drug administration. The decrease in salivary flow also showed a dose-response relationship at YM905 doses of 40 mg or higher, beginning 1 hour after drug administration. There was no dose-response relationship for the coefficient of variation (CV) of the R-R interval. There was no marked difference in the mean CV of the R-R interval at 24 hours between the YM905, placebo, and oxybutynin groups.

Conclusions

Given that YM905 was administered in large doses to determine safety and tolerability and that oxybutynin was administered in a subtherapeutic dose (5 mg once daily instead of 5 mg tid), it was expected, and observed, that incidence of AEs related to antimuscarinic activity would be higher with YM905 than

oxybutynin. Similarly, escalating doses of YM905 were anticipated to result in a higher incidence of antimuscarinic AEs, and such a dose-response relationship was observed. However, there was no evidence that incidence of AEs was related to extent of exposure. Although no maximal tolerable dose was definitively identified, the frequency of AEs in the 100-mg group suggests this dose would not be appropriate for multidose treatment. YM905 was orally absorbed, and C_{max} increased in a dose-linear fashion. Its relatively long half-life (approximately 50 hours) suggests a once daily dosing regimen may be possible. Future studies should allow a longer sampling period to obtain more accurate results for $t_{½}$ and $AUC_{0\text{-}INF}$.