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ABSOLUTE BIOAVAILABILITY OF YM905 IN HEALTHY MALE VOLUNTEERS: A SINGLE-DOSE, RANDOMIZED, TWO-PERIOD CROSSOVER STUDY

Aims of Study

Anticholinergic drugs are commonly used to treat patients with overactive bladder (OAB). YM905 is a bladder-selective antimuscarinic being developed for the treatment of patients with OAB. Its tissue selectivity has the potential to minimize anticholinergic side effects while providing effective relief of OAB symptoms. The objective of this study was to determine the absolute bioavailability of YM905 in healthy male volunteers.

Methods

The study employed an open, randomized, two-period crossover design and included 12 healthy male subjects (10 Caucasians and 2 Asians; aged 20 to 45 years, mean, 31.7; body weight 62 to 91 kg). Subjects were randomized to receive either a single, 10-mg oral dose of YM905 or an intravenous (IV) infusion containing 5 mg of YM905. After a 14-day washout period, subjects were crossed over to the alternate treatment. Blood samples for determination of plasma YM905 concentrations were collected before and for up to 192 hours after each YM905 administration. Urine samples were collected over the same interval. Plasma concentrations of YM905 and urinary concentrations of YM905 were determined using validated methods. Noncompartmental methods for both oral and IV YM905 administration were used to determine maximum plasma concentration (C_{max}), area under the time versus plasma concentration curve from time zero until infinity ($AUC_{0\text{-}INF}$), and elimination half life ($t_{½}$). Clearance (CL), volume of distribution (V_z), and volume of distribution at steady state (V_{ss}) were also determined after IV administration of YM905. Bioavailability (F) of YM905 was defined as the ratio of log-transformed values $AUC_{0\text{-}INF}$ for oral administration and $AUC_{0\text{-}INF}$ for IV administration. Urinary data were used to determine renal clearance (CL_R) for YM905.

Safety was evaluated by reporting of adverse events, physical examinations, clinical laboratory analysis, recording of vital signs, and ECGs.

Results

All 12 subjects who received YM905 were included in the safety analysis; nine subjects were included in the pharmacokinetic analysis (3 subjects had to be excluded from the analysis because of illness, serious adverse event—which was highly unlikely to be related to study drug—and withdrawal of consent). Pharmacokinetic results for oral and IV YM905 are summarized in Table 1. Comparison of the ratios of log-transformed $AUC_{0\text{-}INF}$ values for oral and IV administration of YM905 resulted in an absolute bioavailability of 88%.

Table 1. Pharmacokinetic parameters for oral and IV YM905.

Parameter (arithmetic mean)	Oral YM905 (10 mg)	IV YM905 (5 mg)
C_{max} (ng/mL)	15.2	19.0
$AUC_{0\text{-}INF}$ (ng·h/mL)	793	386
$t_{½}$ (hours)	53.1	52.4
CL (L/h)	-	9.39
V_z (L)	-	671
V_{ss} (L)	-	599
CL_R (L/h)	0.763	0.670
Bioavailability (%)	88.0%	

Ten of the 12 (83%) subjects reported a total of 33 adverse events. The most common treatment-emergent adverse events (TEAEs) were headache (13 reports), somnolence (5 reports), and phlebitis (3 reports). All but three of the TEAEs were mild or moderate in severity. Three adverse events (in two patients) were considered severe: phlebitis in one subject and personality disorder and depression in another subject (these three events are not considered related to YM905). There were no clinically significant effects of YM905 administration on vital signs, laboratory parameters, or ECGs.

Conclusions

Oral administration of YM905 (10 mg) demonstrates a high absolute bioavailability of 88% in healthy male subjects. YM905 is extensively distributed, has a low clearance, and has a long elimination half-life, suggesting a long exposure. These factors suggest that YM905 is an excellent candidate for once-daily administration.