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SINGLE- AND MULTIPLE-DOSE PHARMACOKINETICS OF ONCE-DAILY TROSPIUM CHLORIDE 30 MG IN HEALTHY ELDERLY SUBJECTS

Hypothesis / aims of study

Trospium chloride 30 mg is a newly developed once-daily (QD) formulation of trospium that utilizes an extended-release technology based on a combination of time- and pH-dependent bead coating disintegration; this controlled-release mechanism has been designed to provide therapeutic plasma levels of trospium over a 24-hour period. Trospium twice daily (BID) has demonstrated efficacy and a favorable tolerability profile in the treatment of overactive bladder syndrome (OAB [1]) defined as urgency with or without urge incontinence, usually with frequency and nocturia. In addition, the trospium chloride compound is not metabolized via the cytochrome P450 enzyme system. It can be confidently prescribed alongside the majority of commonly used medications without concern for adverse metabolic drug–drug interactions [2]. This study evaluated the steady-state and single-dose pharmacokinetics of trospium chloride 30 mg QD in elderly subjects following 10-days of dosing and over a 24-h dosing period, respectively.

Study design, materials and methods

Nonsmoking, healthy men and women aged 65–80 years with a weight within ±30% of the ideal for their height and frame were eligible for inclusion in this study. All enrolled subjects were administered trospium chloride 30 mg capsules QD following a minimum of a 10-h fast and at least 1 h prior to breakfast for 10 days. Predose blood samples for analysis of trough plasma concentrations were collected on Days 2, 8, and 9. In addition, predose blood samples for pharmacokinetic analysis were collected at 0 h on Days 1 and 10. Postdose samples were collected at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 18 h on Days 1 and 10 and additionally at 24, 48, and 72 h on Day 10. Primary endpoints were characterization of the single-dose pharmacokinetics of trospium 30 mg QD over a 24-h period, in addition to the steady-state pharmacokinetics of trospium 30 mg QD following 10-days of dosing. Safety and tolerability of trospium 30 mg QD were assessed via adverse-event (AE) monitoring, clinical laboratory evaluations, physical examinations, vital signs, and 12-lead electrocardiograms.

Results

Overall, 11 subjects (2 men [18.2%] and 9 women [81.8%]) with a mean age of 67.5 years (SD ±3.2 years) were enrolled in the study. Trospium was detectable in the plasma 1 h after administration of a single trospium 30 mg QD capsule and remained quantifiable at 24 h (figure). Following a single dose of trospium 30 mg QD, trospium was absorbed with a median time to reach maximum concentration (T_{max}) of 5.0 h; this increased to 5.5 h after multiple doses. Trospium 30 mg QD reached steady state on Day 9 of the study; steady-state pharmacokinetics following 10 days' dosing are given in the table below. Overall, 3 subjects reported AEs that were thought to be possibly related to study treatment. No deaths or serious AEs were reported.

Figure Mean plasma pharmacokinetic profile of trospium on Day 1 in elderly subjects following a single oral administration of trospium 30 mg QD

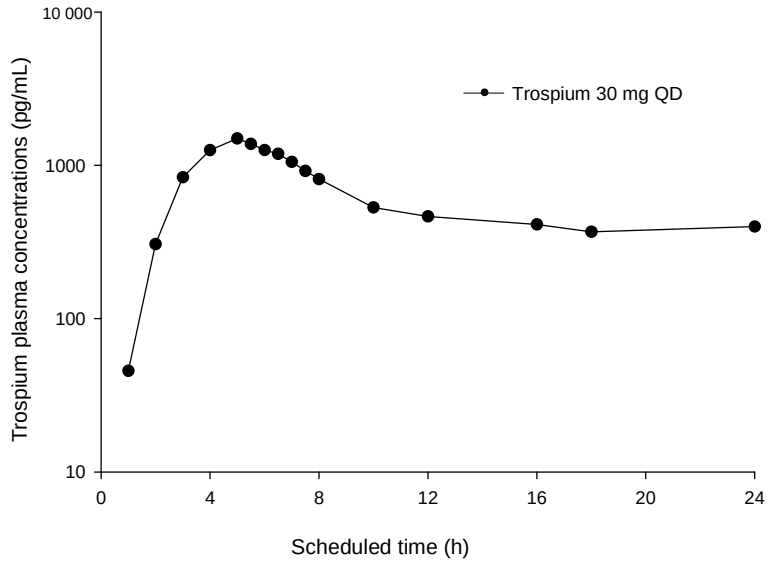

Table Mean (standard deviation) steady-state pharmacokinetic parameters of trospium 30 mg QD after 10 days' dosing

$AUC_{(0-\infty)}$ (pg·h/mL)	**$AUC_{(0-Tlast)}$ (pg·h/mL)**	**$AUC_{(0-24h)}$ (pg·h/mL)**	**C_{max} (pg/mL)**	**Median T_{max} (h)**	**$t_{1/2}$ (h)**	**HVD (h)**
40 980 (20 279)	35 910 (16 608)	19 070 (9292)	1456 (790)	5.50	31.01 (10.72)	14.57 (10.38)

$AUC_{(0-\infty)}$, area under the concentration–time curve from time zero (predose) extrapolated to infinity; $AUC_{(0-Tlast)}$, area under the concentration–time curve from time zero (predose) to the time of the last measurable concentration; $AUC_{(0-}$

$_{24h)}$, area under the concentration–time curve from zero (predose) to 24 h; C_{max}, maximum concentration obtained; T_{max}, time of maximum concentration; $t_{1/2}$, the apparent terminal half life; HVD, half-value duration.

Interpretation of results

Trospium 30 mg QD had a T_{max} of 5.5 h and a $t_{1/2}$ of approximately 31 h allowing delivery of trospium throughout the day. Trospium BID has a similar T_{max} to that of trospium QD (approximately 5 h); however, its $t_{1/2}$ is much shorter at approximately 18 h necessitating a twice-daily regimen [3]. Trospium 30 mg QD was well tolerated when administered as a single daily dose in healthy subjects aged 65–80 years.

Concluding message

Trospium QD provided sustained systemic drug exposure over the entire administration interval allowing convenient once daily dosing. This favorable pharmacokinetic profile combined with acceptable tolerability and the low potential for drug–drug interactions makes trospium QD potentially suitable for a wide range of patients with OAB.

References

1. Urology (2006) 67: 275–280.
2. Pharmacol Toxicol (1999) 85: 299–304.
3. Sanctura® (trospium chloride) Prescribing Information, 2006. Available at: http://www.sanctura.com/pdf/sanctura_pi.pdf. Last accessed on March 29, 2007

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CLINICAL TRIAL REGISTRATION: This clinical trial has not yet been registered in a public clinical trials registry.

HUMAN SUBJECTS: This study was approved by the The IRB was: Arkansas Research Medical Testing, LLC, Human Volunteers Research Committee and followed the Declaration of Helsinki Informed consent was obtained from the patients.