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ASSESSMENT OF TROSPIUM CHLORIDE EFFECT ON ALERTNESS BY THE STANFORD SLEEPINESS SCALE

Hypothesis / aims of study

The anticholinergics as a drug class are associated with CNS adverse events, among them is somnolence or sleepiness. The aim of this study was to determine the effects of trospium chloride (TCl) 20 mg tablets versus placebo (pbo), given twice daily, on daytime sleepiness as measured by the Stanford Sleepiness Scale (SSS)[1].

Study design, materials and methods

This study was a multicenter, parallel, randomized (assigned), double-blind, placebo-controlled trial in patients who met inclusion and exclusion criteria for symptoms of overactive bladder (OAB)[2] and was conducted from June 2003 to January 2004. In addition to assessing TCl effect on the symptoms of OAB, the SSS was used to assess daytime sleepiness and alertness. The effect of treatment on daytime sleepiness was a secondary outcome variable of the OAB trial assessed at baseline and Weeks 1, 4, and 12 using the SSS.

The SSS is a self-rating, validated scale used to quantify acute sleepiness. The patient chooses the number on the SSS associated with the 1 of 7 statements that best describes their level of alertness at the time they complete the scale. At each study visit, the patient also recordsthe time they complete the form and records the date and time of their last dose of study medication. The completion of the SSS was the first task asked of the patients at each visit. No effort was made to control the time of day for collection of the SSS.

Change from baseline in the SSS score for all patients was analyzed between treatment groups. Comparison of change in SSS score between treatment groups for those patients at the estimated Tmax (maximum plasma concentration of TCl levels post dose) for TCl of 3-6 hours was also analyzed. Analyses were done using the intent-to-treat (ITT) with the last observation carried forward (LOCF) data sets. ANOVA models were used. Sample size was determined for the primary OAB outcome variables.[2]

Results

A total of 658 patients (TCl 329 patients, pbo 329 patients) were randomly assigned (random allocation method determined by computer random number generation) on a 1:1 ratio to receive either TCl 20 mg or pbo twice daily. The patient population was predominantly female (TCl 81.2%; pbo 81.8%). The mean age in the TCl group was 61.1 years and 61.0 years in the pbo group. There were no discontinuations due to sleepiness or decreased alertness.

Change in Stanford Sleepiness Scale

	SSS		SSS at Tmax for TCl	
	Placebo n=326	TCl n=327	Placebo n=179	TCl n=182
Baseline score	1.94	1.98	1.82	1.91
Week 1	-0.12	-0.20	-0.20	-0.42
Week 4	-0.14	-0.17	-0.19	-0.20
Week 12	-0.11	-0.16	-0.18	-0.17

No statistical differences between treatment groups were detected.

Interpretation of results

The change in average SSS score and change in average SSS score at estimated Tmax for TCl were minimal and comparable for the TCl and placebo treatment groups at Weeks 1, 4, and 12. The findings of minimal and comparable decreases in average SSS score and average SSS score at estimated Tmax for the trospium chloride and placebo treatment groups provides clinical support for the absence of daytime sleepiness associated with trospium chloride treatment. In addition, the incidence of central nervous system adverse events attributed to TCl was not different than placebo (9.1% vs. 8.5%, respectively). These findings are consistent with animal studies, which demonstrated lack of CNS penetration of radio-labeled TCl and EEG studies.[3]

Concluding message

The absence of CNS effects in clinical trials for OAB may be attributed to the method of spontaneously reported adverse event data collection and the absence of validated measurements. Trospium chloride was found to not produce any daytime sleepiness or affect alertness as measured by the validated SSS. These results are consistent with animal laboratory studies, human experimental and clinical studies, and general clinical use of this compound. The absence of CNS events is attributed to the quaternary amine - hydrophilic nature of the molecule that prevents blood-brain barrier penetration. Future studies with other OAB treatments to evaluate CNS effects in general and at risk subset populations may be warranted.

References

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