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TROSPIUM CHLORIDE IMPROVES SYMPTOMS OF OVERACTIVE BLADDER WITHIN ONE WEEK

Aims of Study

Trospium chloride (TCl), a quaternary amine, is an antimuscarinic agent and a leading treatment for overactive bladder (OAB) in Europe for over 20 yrs and is currently being studied in the US to treat OAB. Drug therapy for OAB has been hindered by delay in symptomatic response to active drug agents. One objective of this US trial was to evaluate the onset of action of TCl in reducing the symptoms of OAB within the first week of treatment as part of a 12 week study.

Methods

This was a multicenter, parallel, randomized, double-blind, placebo-controlled trial. Patients diagnosed with OAB entered a 3-week washout period that included a 7-day baseline bladder diary. Patients must have had $\geq$ 10 voids/day and $\geq$ 1 urge urinary incontinence episodes/day in order to be randomized (TCl 20 mg bid or placebo). Patients were evaluated at 1, 4 and 12 weeks. A 7-day bladder diary was collected during the first week of drug treatment to allow for a daily assessment of onset of activity. Efficacy analyses were done using the intent-to-treat sample with the last observation carried forward (LOCF) data sets. ANOVA models or where appropriate, rank ANOVA were used. In addition, to specifically assess onset of action, a reverse step-wise analysis was used, where the first step is begun with a positive observed case (OC) analysis at the last visit (week 12), and each subsequent analysis steps backward in time until statistical significance favouring TCl over placebo in the OC analysis is lost. This was a conditional analysis, with alpha = 0.05 at each test.

Results

Fifty-one study sites entered 523 patients in the study (261 placebo vs 262 TCl). The mean age was 62 years and 74% were female. The most frequently reported AEs were dry mouth (21.8% for TCl vs. 6.5% for placebo) and constipation (9.5% for TCl vs. 3.8% for placebo). The dropout rate between the two treatment groups was identical.

The mean 24-hour frequency at baseline was 12.7/day for TCl treated patients and 12.9/day for placebo treated patients and for urge urinary incontinence episodes was a mean of 3.9/day for TCl treated patients and 4.3/day for placebo treated patients.

TCl was found to significantly reduce the frequency of voids within 3 days when compared to placebo. Statistical trends were observed at days 4, 5 & 6 and from Day 7 onward a significant reduction in void frequency was observed through week 12 (Day 84).

Table 1: Onset of Action of Trospium Chloride during the First Week of Treatment and at Day 28 & 84 on 24-Hour Frequency (ANOVA, LOCF)

Days	1	2	3	4	5	6	7	28	84
Placebo	-0.48	-0.55	-0.60	-0.75	-1.08	-1.17	-1.04	-1.07	-1.29
TCl	-0.34	-0.71	-1.07	-1.18	-1.54	-1.65	-1.68	-2.20	-2.37
p value	ns	ns	.05	.11	.07	.06	.02	<.0001	<.0001

In addition, TCl was shown to significantly reduce the episodes of urge urinary incontinence within 7 days of beginning treatment.

Table 2: Onset of Action of Trospium Chloride during the First Week of Treatment and at Day 28 & 84 on Urge Urinary Incontinence Episodes/24 hours (rank ANOVA, LOCF)

Days	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*28*	*84*	
Placebo	-0.95	-1.11	-1.24	-1.38	-1.53	-1.52	-1.51	-1.87	-1.98	
TCl	-0.83	-1.15	-1.43	-1.46	-1.66	-1.53	-1.67	-2.02	-2.20	
p value	ns	ns	.06	ns	.06	ns	.05	.003	.01	

Using the reverse step-wise analysis, trospium was shown to produce a significant effect in reducing the urinary frequency and urge urinary incontinence episodes by week 1.

Table 3: Onset of Action of Trospium Chloride Using Reverse Step-wise Analysis (OC-completers)

Week 1	n	Trospium LSMean	Placebo LSMean	p-value
24-hour frequency	217	-1.37	-0.81	p=0.004
Urge Incontinence	217	-1.48	-1.24	p=0.028

Conclusions

Trospium chloride was effective in reducing 24-hour frequency and urge urinary incontinence episodes/day in patients with OAB within one week of beginning treatment. Trospium chloride was well tolerated.