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TOLTERODINE TREATMENT FOR CHILDREN WITH SYMPTOMS OF URINARY URGE INCONTINENCE SUGGESTIVE OF DETRUSOR OVERACTIVITY: RESULTS FROM 2 RANDOMIZED, PLACEBO CONTROLLED TRIALS

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ABSTRACT

Purpose: We report the results of the first 2 large randomized controlled trials designed to evaluate the efficacy and safety of tolterodine extended release in children 5 to 10 years old with symptoms of urinary urge incontinence suggestive of detrusor overactivity.

Materials and Methods: Two double-blind, placebo controlled trials were conducted sequentially. Children 5 to 10 years old with incontinence suggestive of detrusor overactivity (1 or more diurnal incontinence episodes per 24 hours) were randomized to tolterodine (2 mg daily) or placebo for 12 weeks. The primary end point was the change from baseline to week 12 in the number of incontinence episodes per week. Changes from baseline in the number of voids per 24 hours and volume of urine per void were also evaluated. Exploratory analyses were conducted to determine whether particular subsets of patients showed differential responses to treatment.

Results: A total of 224 and 487 children (mean age 8 years) were randomized to placebo and tolterodine, respectively. Differences in the number of incontinence episodes per week, voids per 24 hours, and volume of urine per void between tolterodine and placebo did not reach statistical significance. This finding may be explained by a high placebo response and under dosage of tolterodine among children with greater body weight. Tolterodine was well tolerated.

Conclusions: Analysis of the primary efficacy outcome did not reveal a statistically significant effect of treatment. However, secondary analyses demonstrated that tolterodine was well tolerated among 5 to 10-year-old children with diurnal incontinence. Exploratory analyses also showed that children weighing 35 kg or less with detrusor overactivity characterized by incontinence and/or frequent voiding benefited most from tolterodine treatment, suggesting that a weight adjusted dosing regimen may be required for optimal response among older and heavier children.

KEY WORDS: child, drug therapy, urinary incontinence, muscarinic antagonists

Among children daytime urinary urge incontinence is a relatively common condition.[1] Antimuscarinic therapy is a widely used treatment for pediatric incontinence.[2–9] We report results from the first 2 large randomized controlled trials of tolterodine for incontinence suggestive of detrusor overactivity in children.

MATERIALS AND METHODS

Two sequential, double-blind, placebo controlled trials were conducted. After a 1 to 2-week washout/run-in period pediatric patients were centrally randomized at a 2:1 ratio to receive tolterodine extended release (2 mg daily) or placebo for 12 weeks based on a previous pharmacokinetic study.[3]

Eligible children were 5 to 10 years old with symptoms of urge incontinence suggestive of detrusor overactivity (1 diurnal incontinence episode or more per 24 hours for 5 or more days out of 7). In the second study children were also required to have 6 or more voids per 24 hours at baseline. Pretreatment assessments were performed using uroflowmetry and ultrasound for post-void residual (PVR) volume. Key exclusion criteria were treatment for detrusor overactivity within 14 days of randomization, monosymptomatic nocturnal enuresis and giggle incontinence. Patients were also excluded if they had urinary tract infection (UTI), a history of urinary retention or a neuropathic bladder. Those with PVR volume that was 20% or more of functional bladder capacity were also excluded. Informed consent was obtained from all parents or guardians.

In both studies efficacy was assessed using 7-day voiding diaries. Patients made 4 clinic visits and were asked to maintain a diary (with the help of parents and teacher) for 7 days preceding the randomization visit and during weeks 4 and 12 of treatment. No timed voiding instructions were given. The primary end point was the change in the number of diurnal incontinence episodes per week. Secondary end points included changes in number of voids per 24 hours and volume of urine per void. Parental assessment of treatment benefit was also evaluated. In study 1 parents were asked if the child had benefited from treatment. In study 2 parents completed a treatment satisfaction questionnaire that assessed activity

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limitations, emotions, quality of life and symptoms (4 items), ease of use and compliance (4 items), and overall satisfaction with treatment, including parental willingness to continue and/or recommend treatment (3 items).

In study 1 randomized patients who received 1 or more doses of study medication comprised the intent to treat population. Analysis of variance was used for continuous variables, and missing data were imputed using the last observation carried forward from baseline. Multiple regression analyses were performed using the change in incontinence episodes per week as the response variable and terms for treatment, baseline values, sex, age, weight and body mass index as predictors. Exploratory subgroup analyses were conducted based on these results. In study 2 all randomized patients were evaluated for efficacy, and randomized patients who received 1 or more doses of study medication were evaluated for safety. Analysis of covariance was used with incontinence episodes per week as a covariate, and treatment, country and treatment by country interaction as cofactors. Patient subgroups were identified a priori using demographic characteristics (age, sex, weight) for exploratory analyses.

Safety assessments included the recording of adverse events, withdrawals, PVR volume, electrocardiograms and laboratory tests. Blood samples were drawn at week 12 and assayed for concentrations of tolterodine and its active metabolite (DD01) in serum. Exposure to the active moiety (sum of unbound serum concentrations of tolterodine and DD01) was highly predictive of efficacy. The area under the concentration vs time curve from 0 to 24 hours (AUC_{0-24}) was estimated using population pharmacokinetics. Breakpoints in active moiety exposure were identified to define the exposure threshold above which there was a statistically significant effect on response. Regression analyses were used to investigate whether exposure and/or selected baseline characteristics were significant independent predictors of response. Covariates included exposure, baseline incontinence episodes per week and demographics (sex, weight, ethnicity, country). All statistical tests were 2-sided (α level = 0.05).

RESULTS

Demographics. In study 1, 107 patients were randomized to placebo and 235 to tolterodine, and 88% completed the study. In study 2, 117 patients were randomized to placebo and 252 to tolterodine, and 93% completed the study (table 1). Treatment groups were comparable with respect to demographic and clinical characteristics (table 2). In study 1 mean plus or minus SD treatment duration was 82 ± 17 days in the tolterodine group and 77 ± 23 days in the placebo group, with 90% of tolterodine and 85% of placebo recipients taking 75% or more of the study drug. In study 2 mean plus or minus SD treatment duration was 85 ± 9 days in the tolterodine group and 83 ± 14 days in the placebo group, with 92% of all patients taking 75% or more of the study drug.

TABLE 1. *Patient flow for studies 1 and 2*

	No. Study 1*	No. Study 2†
Pts enrolled:	342	369
Placebo	107	117
Tolterodine	235	252
Withdrawn from placebo group:	17	8
Adverse event	5	2
Lack of efficacy	0	3
Lost to followup	3	0
Protocol violation	1	2
Withdrew consent	8	1
Withdrawals from tolterodine group:	23	17
Adverse event	11	4
Lack of efficacy	0	2
Lost to followup	3	7
Protocol violation	4	3
Withdrew consent	5	1
Completed studies:		
Placebo	90	109
Tolterodine	212	234

* All participants took 1 or more doses of assigned agent.

† All participants took 1 or more doses of assigned agent except for 1 child in placebo group.

Efficacy. In study 1 there were statistically significant within group improvements in the number of incontinence episodes per week, voids per 24 hours and volume of urine per void. However, between group differences did not reach statistical significance (table 3). Multiple regression modeling revealed that the number of baseline incontinence episodes per week was a significant predictor of the change in incontinence episodes per week ($p < 0.0001$). Among tolterodine patients the magnitude of this change increased as baseline incontinence episodes per week increased. Baseline voids per 24 hours amplified this effect. Similar relationships were not observed among placebo patients. The highest placebo response was observed in patients with fewer than 6 voids per 24 hours and more than 15 incontinence episodes per week at baseline (fig. 1).

In both groups patients with 6 or more voids per 24 hours at baseline accounted for more than 50% of the study population. Among these patients treatment with tolterodine vs placebo resulted in a significant decrease in incontinence episodes per week ($p < 0.01$) and a significant increase in volume of urine per void ($p < 0.02$, fig. 2). No significant between group differences were observed for the change in voids per 24 hours among patients with 6 or more voids per 24 hours. There were no significant between group differences for any outcome among patients with fewer than 6 voids per 24 hours at baseline.

Patients enrolled in study 2 were required to have 6 or more voids per 24 hours at baseline. By week 12 patients in both groups demonstrated greater declines in incontinence episodes per week (placebo −8.8, tolterodine −10.0) compared with those from study 1 (−3.8 and −5.3, respectively, table 3). The between group difference (−0.9) did not reach statistical significance. There were no significant treatment effects on the number of voids per 24 hours. However, there was a significant effect on volume of urine per void (table 3). Multiple regression of the primary end point showed significant effects when patients were stratified by weight. Among patients weighing 35 kg or less the decrease from baseline in incontinence episodes per week was significantly greater among tolterodine (−10.4 ± 12.0, 219 patients) than placebo recipients (−8.6 ± 10.8, 99 patients, $p < 0.05$).

Treatment benefit. In study 1 there was a significant treatment effect based on parental assessment of treatment benefit. Among parents of children who received tolterodine 62% reported a benefit of treatment. Among parents of children who received placebo 47% perceived a benefit ($p < 0.01$). In study 2 tolterodine was associated with significant improvements in symptoms and quality of life ($p < 0.05$) but not with changes in activity limitation or emotions compared with placebo. Parents of children taking tolterodine were highly satisfied with treatment outcomes compared to parents of children taking placebo ($p = 0.005$).

Safety and tolerability. Tolterodine was safe and well tolerated. No serious safety concerns were identified. In study 1 the most commonly reported adverse event in both groups was headache (tolterodine 10% vs placebo 14%). In study 2 the most common adverse event was UTI (9%) in the tolterodine group and abdominal pain (8%) in the placebo group (table 4). Dry mouth and constipation occurred infrequently. Across both studies 6 tolterodine recipients (1%) and 2 placebo recipients (1%) had serious adverse events. No serious adverse event in the tolterodine group was considered treatment related. No instances of acute urinary retention were