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USE OF TOLTERODINE IN CHILDREN WITH NEUROGENIC DETRUSOR OVERACTIVITY: RELATIONSHIP BETWEEN DOSE AND URODYNAMIC RESPONSE

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ABSTRACT

Purpose: Three exploratory studies were conducted to investigate the pharmacokinetics (PK) and safety of tolterodine in children 1 month to 15 years old with neurogenic detrusor overactivity. We urodynamically evaluated the dose and concentration effects of tolterodine to establish safe and effective dosing regimens.

Materials and Methods: Three open-label, dose escalating studies were conducted in children with stable neurological disease and detrusor overactivity. In studies 1 (patient aged 1 month to 4 years) and 2 (5 to 10 years) patients received 0.03, 0.06 and 0.12 mg/kg tolterodine solution day twice daily for 4 weeks each. In study 3 (patient age 11 to 15 years) patients received 2, 4 and 6 mg tolterodine extended-release capsules once daily for 4 weeks each. PK was assessed after 8 weeks, urodynamic assessments were conducted after each 4-week dosing period and 3-day micturition diaries were completed.

Results: Patients in studies 1 (19) and 2 (15) showed some dose related increases in volume to first detrusor contraction and cystometric bladder capacity. In study 3 (11 patients) there were no obvious dose-response relationships. PK results from studies 1 and 2 suggest that there was no apparent effect of age (≤10 y) on these parameters. In study 3 time of maximum observed serum concentration and apparent terminal half-life were delayed, which is consistent with the extended-release formulation. Tolterodine was well tolerated, and there was no apparent relationship between tolterodine dose and adverse events in any study.

Conclusions: These results support the safety of age and body weight adjusted dosing regimens for further clinical evaluation of tolterodine in children with neurogenic detrusor overactivity.

KEY WORDS: child; drug therapy; bladder, neurogenic; muscarinic antagonists

In pediatric patients with neurological disease, uninhibited detrusor contractions and poor bladder compliance may lead to increased intravesical pressure and other significant morbidity affecting the urinary system, including urinary tract infection, urolithiasis, hydroureteronephrosis, vesicoureteral reflux, impairment of renal function and ultimately renal failure. Historically, the muscarinic antagonist oxybutynin has been used as an oral or intravesical agent to treat neurogenic detrusor overactivity (NDO) in pediatric patients.[1,2] However, oxybutynin treatment is associated with significant anticholinergic adverse events and high dropout rates.[3,4] The antimuscarinic tolterodine has proven efficacy and safety in the treatment of overactive bladder in adults, and only 1 other published case series has evaluated its efficacy in children with NDO.[5]

We report the results from 3 open-label dose escalation studies of tolterodine in children with NDO. These exploratory studies were designed to investigate the pharmacokinetics (PK) and safety of tolterodine in children with NDO ranging in age from 1 month to 15 years. The primary objective was to urodynamically evaluate the dose and concentration effects of tolterodine to establish safe and effective dosing regimens for pediatric patients with NDO.

MATERIALS AND METHODS

Three multicenter, open-label, dose escalating studies of similar design were conducted in the United States. Study 1 included children 1 month to 4 years old, study 2 enrolled children 5 to 10 years old and study 3 included patients 11 to 15 years old. In all 3 studies eligible patients had stable neurological disease and urodynamic evidence of NDO, and were on clean intermittent catheterization. All eligible patients were within the normal range for body weight or body mass index (BMI, between 5th and 95th percentiles of the Centers for Disease Control and Prevention Growth and BMI charts for the United States). Key exclusion criteria were urinary tract abnormalities, grade IV or greater vesicoureteral reflux, management with indwelling catheter for more than 6 months or within 4 weeks of study initiation, and clinically significant urinary tract infection (UTI) 4 weeks before enrollment. The study was approved by institutional review boards at all participating centers and informed consent was obtained from all parents/guardians.

After a washout period (6 to 14 days depending on previous treatment status), children in studies 1 and 2 received the following sequential doses of 1 mg/5 ml tolterodine oral solution twice daily for 4 weeks each. Dose escalation proceeded as 0.03 mg/kg (period 1), 0.06 mg/kg (period 2) and 0.12 mg/kg per day (period 3) a day. Patients in study 3 received

Study received institutional review board approval.
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tolterodine extended released (ER) once daily at 2 mg (period 1), 4 mg (period 2) and 6 mg (period 3) doses for 4 weeks each. For each patient dose escalation was approved only after a review of safety data collected after 4 weeks of treatment during the preceding dosage. Patients were seen at screening (day −14 to −6), baseline (day 1), and after 4 (day 28), 8 (day 58) and 12 (day 84) weeks of treatment.

At the 8-week treatment visit for studies 1 and 2 blood samples were drawn before dose and at 0.5, 1, 2, 6 and 8 hours after dose (after 4 weeks of twice daily regimen of 0.06 mg/kg a day). In study 3 blood samples were drawn before dose and at 0.5, 1, 3, 4, 6, 12 and 24 hours after dose (after 4 weeks of regimen of 4 mg/kg a day). All samples were assayed for concentrations of tolterodine and the active metabolite 5-hydroxymethyl tolterodine (DD01) in serum. In all 3 studies the primary end points were the serum PK of the active moiety (sum of unbound tolterodine and DD01). Secondary end points were the PK for tolterodine and DD01. The area under the serum concentration-time curve from dosing to 12 hours (AUC_{0-12}) in studies 1 and 2, to 24 hours (AUC_{0-24}) for study 3 and maximum observed serum concentration (C_{max}) were calculated. AUC, C_{max}, the time of occurrence of C_{max} (t_{max}) and apparent terminal half-life ($t_{1/2,z}$) were calculated for tolterodine and DD01, and oral clearance (CL/F) was calculated for tolterodine only. AUCs were estimated using population PK.

Urodynamic assessment was a secondary end point, and evaluations were conducted after each 4-week treatment period. Urodynamic parameters included volume (ml) to first detrusor contraction (>10 cm H_2O pressure), functional bladder capacity and intravesical volume at 40 cm H_2O pressure. Clinical efficacy was assessed using micturition diary variables, including the number of catheterizations per micturition per 24 hours, number of incontinence episodes per 24 hours and volume voided (ml) per catheterization per micturition. Patients and their families were instructed to complete the diaries for 3 days immediately preceding the next scheduled clinic visit. A catheterization/micturition episode was defined as an interval during which the method of drainage contained 1 or more catheterization or spontaneous void, or when total volume of 10 ml or greater was recorded. Safety and tolerability assessments included serum chemistry and hematology tests, electrocardiograms and adverse event (AE) reporting.

RESULTS

Patient disposition. Although sample sizes were relatively small in all 3 studies, completion rates were 90% or greater. In study 1, 19 patients enrolled and 2 discontinued during period 2 (1 owing to an AE, 1 withdrew consent). In study 2, 15 patients enrolled and all 15 completed the study. In study 3, 11 patients enrolled and 1 patient withdrew consent during period 3. Baseline demographics and clinical characteristics are summarized in table 1.

All patients who received any study drug were included in the safety population, and patients who had blood drawn were included in the PK population. Because these studies were planned as exploratory, all data were analyzed in a descriptive manner, and no formal hypothesis testing was performed. For urodynamic parameters and micturition diary variables, results are presented as median percentage changes from baseline because the data were not normally distributed.

Pharmacokinetics. Pharmacokinetic results are summarized in table 2 for the active moiety, tolterodine and DD01 for all 3 studies during period 2. One patient from study 1 and 2 patients from study 2 were excluded from the PK analysis owing to a dosing error on the PK day.

Urodynamic variables. In general, the small sample sizes and considerable interpatient variability are reflected in the wide 95% confidence intervals for the pharmacodynamic results. For volume to first detrusor contraction (>10 cm H_2O pressure) median values doubled from baseline to period 2 in studies 1 and 2 but the increases were not dose related. In study 3 there were dose related increases in volume from baseline to period 1 (26%) and period 2 (48%), and the 6 mg dose was associated with a decrease in volume (fig. 1).

In study 1 escalating doses of tolterodine were not associated with changes in cystometric bladder capacity. In study 2 the 0.06 mg/kg dose was associated with the smallest median percentage increases, and a dose response was observed between the 0.03 and 0.12 mg/kg doses. In study 3 the 2 mg tolterodine ER dose was associated with the largest increase, and the 4 and 6 mg doses were associated with small, comparable increases (fig. 2).

Finally, in study 1 escalating doses of tolterodine were not associated with increases in maximum intravesical volume (at 40 cm H_2O pressure). In study 2 the 0.06 and 0.12 mg/kg tolterodine doses were associated with marked and comparable median percentage increases in volume. In study 3 the 2 mg tolterodine ER dose was associated with a dramatic increase in volume but there was no effect with the 4 or 6 mg doses (fig. 3).

Micturition diary variables. In studies 1 and 2 escalating tolterodine doses were associated with greater improvements in the number of incontinence episodes per 24 hours. In study

TABLE 1. *Baseline demographic and clinical characteristics*

Characteristic	Study 1	Study 2	Study 3
No. pts	19	15	11
No. boys (%)	10 (53)	7 (47)	5 (46)
Mean ± SD age (yrs)	2 ± 1.7	8 ± 1.7	13 ± 1.4
No. white (%)	16 (84)	11 (73)	8 (73)
Median kg wt (range)	11.6 (5.4–19.3)	23.7 (15.7–46.7)	55.3 (25.9–75.7)
No. medical history (%):*			
Meningomyelocele	18 (95)	9 (60)	8 (73)
Congenital spinal cord anomaly	5 (26)	6 (40)	2 (18)
Paraplegia	3 (16)	4 (27)	3 (27)
Spinal cord injury	1 (5)	2 (13)	2 (18)
Spinal claudication	1 (5)	0 (0)	1 (9)
Traumatic brain injury	0 (0)	1 (7)	0 (0)
Mean ± SD catheterizations/micturitions/24 hrs	4.8 ± 1.4	4.7 ± 1.4	5.4 ± 1.9
Mean ± SD incontinence episodes/24 hrs	5.2 ± 1.9	4.3 ± 1.0	2.4 ± 1.8
Mean ± SD ml vol/catheterization/micturition	34.9 ± 16.1	88.8 ± 45.9	131.9 ± 48.8
Mean mg tolterodine dose (range):			
Period 1	0.34 (0.16–0.65)	0.81 (0.49–1.4)	0.04 (0.03–0.07)†
Period 2	0.71 (0.38–1.31)	1.66 (0.95–2.95)	0.08 (0.05–0.14)†
Period 3	1.48 (0.80–2.64)	3.41 (1.92–6.00)	0.12 (0.08–0.20)†

* Patients may appear in more than 1 category.
† Mean dose for study 3 is mg/kg per day.