

EFFICACY AND SAFETY OF OXYBUTYNYN IN CHILDREN WITH DETRUSOR HYPERREFLEXIA SECONDARY TO NEUROGENIC BLADDER DYSFUNCTION

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ABSTRACT

Purpose: We evaluated the efficacy and safety of oxybutynin in children with detrusor hyperreflexia due to neurological conditions.

Materials and Methods: *Study 1*—A prospective, open label trial of 3 formulations of oxybutynin (tablets, syrup and extended release tablets) was conducted for 24 weeks in children 6 to 15 years old with detrusor hyperreflexia who used oxybutynin and clean intermittent catheterization. The effect of treatment on average urine volume per catheterization and on secondary urodynamic outcomes was evaluated. *Study 2*—The efficacy and safety of oxybutynin syrup were evaluated urodynamically in an open label study of children 1 to 5 years old with detrusor hyperreflexia who used oxybutynin and clean intermittent catheterization.

Results: *Study 1*—Mean urine volume per catheterization (\pm SEM) increased by 25.5 ± 5.9 ml ($p < 0.001$). Maximal cystometric capacity increased by 75.4 ± 9.8 ml ($p < 0.001$). Mean detrusor and intravesical pressures were significantly decreased by -9.2 ± 2.3 ($p \leq 0.001$) and -7.5 ± 2.5 cm H₂O ($p < 0.004$), respectively, at week 24. Of 61 children with uninhibited detrusor contractions 15 cm H₂O or greater at baseline 34 did not have them at week 24 ($p < 0.001$). Improvements in bladder function were consistent across all oxybutynin formulations. *Study 2*—Mean maximal cystometric capacity increased significantly by 71.5 ± 21.99 ml ($p = 0.005$). At study end only 12.5% of patients had uninhibited detrusor contractions 15 cm H₂O or greater compared with 68.8% at baseline ($p = 0.004$). Oxybutynin was well tolerated in both studies. There were no serious treatment related adverse events.

Conclusions: All 3 formulations of oxybutynin are safe and effective in children with neurogenic bladder dysfunction.

KEY WORDS: bladder, neurogenic; cholinergic antagonists; safety

Urological abnormalities in children with neurogenic bladder and detrusor sphincter dyssynergia include detrusor overactivity (detrusor hyperreflexia), uninhibited bladder contractions, increased detrusor pressure, decreased bladder capacity and incontinence.^{1–3} The goals of conservative therapy in these patients are to protect the upper urinary tract and renal function from progressive damage, and to improve quality of life by increasing urinary continence.² Clean intermittent catheterization (CIC) alone or combined with anticholinergic therapy is considered the standard to treat urinary incontinence in these children.² Most commonly oxybutynin chloride is used to manage these

conditions. Substantial evidence confirms the efficacy and safety of oxybutynin in children with neurogenic bladder conditions.^{1,2,4–6} However, few studies have directly studied different formulations of oxybutynin in a pediatric population. Data from prospective clinical research trials are sparse, as are data on oxybutynin use in young children with neurogenic detrusor hyperreflexia. We report the results of 2 multicenter studies. The first study was designed to examine the efficacy and safety of oxybutynin tablets, syrup and extended release tablets in children 6 to 15 years old. The second study explored the use of oxybutynin therapy at least 2 weeks in duration in children 1 to 5 years old.

METHODS AND MATERIALS

Study 1—Study design. This multicenter, open label clinical trial was conducted from February to April 2002 at 24 sites (23 centers in the United States and 1 center in The Netherlands). Eligible children were 6 to 15 years old with a documented diagnosis of detrusor hyperreflexia due to neurogenic conditions, and were using a total daily dose of 10 or 15 mg oral oxybutynin chloride with CIC. Oxybutynin was administered as extended release tablets, tablets or syrup for 24 weeks. The extended release formulation of oxybutynin chloride uses OROS technology (Alza Corp., Palo Alto, California), which involves a semipermeable rate controlling

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Study protocols were approved by institutional review board or ethics committee of each participating center, and parent(s) or guardian(s) gave written consent for study participation. If deemed appropriate, children in study 1 gave consent by signing an assent form. Studies were conducted and monitored according to Good Clinical Practice guidelines.

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membrane surrounding an osmotically active push compartment and a drug core.^{7,8} All children discontinued the current medication for detrusor hyperreflexia with a minimum washout period of 3 days before baseline evaluations. Overall, 116 children were enrolled and treated.

Assessments. The efficacy of treatment was assessed using clinical parameters (voiding diary and catheterization schedules) and urodynamic parameters including maximal cystometric capacity (MCC), detrusor and intravesical pressures at maximum capacity, volume at first involuntary detrusor contraction, assessment of urinary leakage accidents between catheterizations and absence of uninhibited detrusor contractions 15 cm H₂O or greater. Urine volume per catheterization was assessed as the average volume per catheterization during the course of the day, and the volume of the first catheterization after morning awakening. Patients/caretakers documented the number of catheterizations and the volume per catheterization to the nearest 10 ml during a 2-day period at baseline and during treatment weeks 4, 12 and 24. Urodynamic assessments were performed at baseline and at weeks 12 and 24 according to standard procedures. Urodynamic studies were conducted 1 to 2 hours after dosing with oxybutynin tablets and syrup, and at 3 to 4 hours after dosing with oxybutynin extended release tablets.

Safety evaluations, including a review of urodynamic, cardiovascular and laboratory variables, were performed at the time of the initial screening, baseline and end of treatment clinic visits. Tolerability was monitored with special emphasis on the gastrointestinal tract and expected adverse events of anticholinergic agents (eg, constipation, dry mouth).

Study 2—Study design. Study 2 was a smaller exploratory study of oxybutynin syrup in children 1 to 5 years old with known myelomeningocele and detrusor hyperreflexia with detrusor-sphincter dyssynergia due to neurogenic conditions. This was an open label, multicenter study conducted at 4 sites between April and October 2001. All patients were taking a stable dosage of oral or intravesicular oxybutynin chloride and discontinued the current medications within a 3 to 7-day washout period before baseline evaluations. Patients who had been receiving intravesicular oxybutynin were started on an appropriate oral oxybutynin dosage, as determined by the study investigator, 1 week before the washout period. Of 19 children screened 16 were enrolled and all completed the study.

Immediately after the washout period baseline urodynamic evaluations were performed, and thereafter study medication was started. Patients were started on oxybutynin syrup at the levels of the pre-washout oral dosages and regimens. Dose adjustments were made at the discretion of the investigator. However, patients were required to maintain a stable dosage and regimen for at least 2 weeks before end of study assessments.

Assessments. Urodynamic evaluations were performed immediately after the washout period, before administration of the study medication and within 1 to 2 hours after the final dose of study medication. Blood samples for pharmacokinetic analysis were collected as in study 1.

Efficacy outcome variables were MCC, detrusor and intravesical pressures at maximal cystometric capacity, and the absence of uninhibited detrusor contractions 15 cm H₂O or greater as described for study 1. Safety measurements were the same as those for study 1.

Urodynamic study procedures. In both studies baseline urodynamic tests were performed after at least a 3-day washout period. In study 1 the bladder was filled with room temperature saline at a maximal filling rate of 10 to 50 ml per minute, which was adjusted based on patient age and expected bladder capacity. In study 2 the filling rate ranged from 5 to 15 ml per minute, with the majority of patients (11 of 16, 68.8%) at less than 10 ml per minute. For each patient the same filling rate was used during all evaluations. The patients were in the same position (for example, supine,

sitting or standing) for all urodynamic studies. A rectal catheter was placed for measurement of intra-abdominal pressure. The bladder was filled until voiding/leakage began or detrusor pressure increased to 40 cm H₂O over baseline. MCC and maximum detrusor and intravesical pressures at maximal cystometric capacity were recorded, and any uninhibited contractions 15 cm H₂O or greater were noted.

Statistical analyses. Paired t tests were applied in study 1 to test the significance of changes in the urine volume per catheterization from baseline to week 24, and in both studies to test the significance of changes in urodynamic variables from baseline to end point (week 24 for study 1 and end of treatment for study 2). Changes in the proportion of patients with uninhibited detrusor contractions 15 cm H₂O or greater from baseline to week 24 (study 1) or baseline to end of treatment (study 2) were tested for statistical significance using the McNemar test.

RESULTS

Study 1—Patient characteristics. Of 131 children screened 116 with detrusor hyperreflexia due to neurogenic conditions met inclusion criteria and were enrolled in the study. A total of 111 patients completed 24 weeks of treatment. Among enrolled patients 48.3% were male and the majority (63.8%) were white. Mean (\pm SEM) age of the children was 9.6 \pm 0.25 years. Mean height and weight were 128.2 \pm 1.61 cm and 34.5 \pm 1.39 kg, respectively.

A total of 61 patients received oxybutynin extended release tablets, 30 received oxybutynin syrup and 28 received oxybutynin tablets. These numbers total more than 116 because 3 patients switched formulations during the trial. The administered doses of oxybutynin extended release tablets were 5 mg, 10 mg, 15 mg and 20 mg per day. The total daily doses of the syrup were 5 to 30 mg, and of tablets 7.5 to 15 mg, in twice daily, 3 times daily or 4 times daily divided doses (table 1). Total daily oxybutynin dose on a mg/kg basis was 0.20 to less than 0.40 mg/kg (46%) or 0.40 to less than 0.60 mg/kg (35%) in the majority of patients.

Efficacy. The primary efficacy variable, change in mean volume of urine collected per catheterization from baseline to week 24, was 25.5 \pm 5.86 ml, which represented a significant difference (paired t test, $p < 0.001$, table 2). The catheterized volume after morning waking also increased by 33.0 \pm 8.29 ml ($p < 0.001$). The percentage of catheterizations without an intermittent leaking accident increased 21.5% from baseline to week 24 ($p < 0.001$).

Improvement was also noted in urodynamic parameters (table 2). The change from baseline in MCC of 75.4 \pm 9.75 ml represented a significant increase ($p < 0.001$). The change from baseline to week 24 in mean detrusor pressure at maximum cystometric capacity (-9.2 ± 2.30 cm H₂O) was significant ($p = 0.001$), as was that in intravesical pressure (-7.5 ± 2.52 cm H₂O, $p < 0.004$). At week 24, 30 of 105 patients

TABLE 1. Distribution of patients in study 1 by age, formulation and total daily dose of oxybutynin at week 12

| Pt Age (yrs)/Formulation | Total Daily Dose (mg) | | |
|--------------------------|-----------------------|----------|---------------|
| | 5-9.99 | 10-14.99 | 15 or Greater |
| Younger than 10:* | | | |
| Syrup | 4 | 8 | 12 |
| Tablets | 4 | 4 | 4 |
| Extended release tablets | 4 | 17 | 14 |
| 10-15:† | | | |
| Syrup | 0 | 2 | 2 |
| Tablets | 1 | 4 | 8 |
| Extended release tablets | 1 | 13 | 10 |

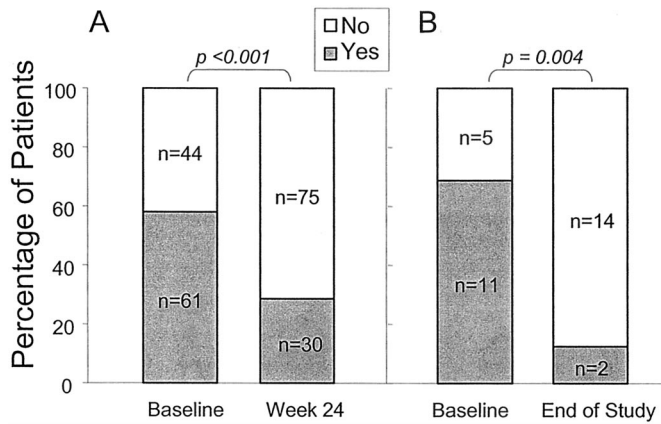
* One patient who switched from syrup to extended release tablets is excluded from results.

† Three patients not taking study medication at 12-week assessment (due to discontinuation or interruption of treatment) are excluded from results.

TABLE 2. Efficacy evaluations at baseline and end point for study 1

| Variable | Baseline (± SEM) | Wk 24 (± SEM) | Change From Baseline (± SEM)* | p Value (paired t test) |
|---------------------------------------------|------------------|---------------|-------------------------------|-------------------------|
| Urine volume per catheterization (ml) | 112.4 (6.57) | 138.2 (6.05) | 25.5 (5.86) | <0.001 |
| Max cystometric capacity (ml) | 196.9 (11.61) | 260.5 (11.97) | 75.4 (9.75) | <0.001 |
| Detrusor pressure (cm H ₂ O) | 42.9 (2.97) | 33.7 (2.59) | -9.2 (2.30) | 0.001 |
| Intravesical pressure (cm H ₂ O) | 55.1 (3.49) | 47.3 (3.04) | -7.5 (2.52) | <0.004 |

* Value at efficacy end point minus value at baseline.



A, percentage of patients in study 1 with uninhibited detrusor contractions 15 cm H₂O or greater at baseline and at week 24 (p < 0.001 for McNemar test of proportion of patients with uninhibited detrusor contractions at baseline vs week 24). B, percentage of patients in study 2 with uninhibited detrusor contractions 15 cm H₂O or greater at baseline and end of treatment (p = 0.004 for McNemar test of proportion of patients with uninhibited detrusor contractions at baseline vs end of treatment).

(28.6%) had uninhibited contractions at 15 cm H₂O or greater. Of the 66 patients with uninhibited contractions at baseline 61 had a followup measurement at week 24, and of these 34 (55.7%) had no uninhibited contractions at week 24 (p < 0.001 for McNemar test of proportion of patients with uninhibited detrusor contractions at baseline versus week 24, see figure). For the patients who continued to experience uninhibited detrusor contractions at week 24 bladder capacity at which contractions occurred increased by 56.6 ± 12.9 ml. This study was not designed to compare efficacy between oxybutynin formulations, but no meaningful differences were observed between groups.

Safety and tolerability. Overall, the study medications were well tolerated. Adverse events (AEs) that occurred with a frequency of 5% or greater are shown in table 3. AEs

TABLE 3. Adverse events with oxybutynin at 5% or greater frequency in study 1

| Adverse Event | Syrup (No./%) | Tablets (No./%) | Extended Release Tablets (No./%) | Totals (No./%) |
|-----------------------------------|---------------|-----------------|----------------------------------|----------------|
| Urinary tract infection | 17/56.7 | 8/28.6 | 32/52.5 | 57/49.1 |
| Headache | 3/10.0 | 4/14.3 | 4/6.6 | 10/8.6 |
| Surgical procedure | 2/6.7 | 1/3.6 | 7/11.5 | 10/8.6 |
| Constipation | 1/3.3 | 2/7.1 | 6/9.8 | 9/7.8 |
| Upper respiratory tract infection | 4/13.3 | 2/7.1 | 3/4.9 | 9/7.8 |
| Pain | 2/6.7 | 1/3.6 | 5/8.2 | 8/6.9 |
| Diarrhea | 0 | 2/7.1 | 6/9.8 | 8/6.9 |
| Otitis media | 3/10.0 | 2/7.1 | 3/4.9 | 8/6.9 |
| Pharyngitis | 2/6.7 | 3/10.7 | 2/3.3 | 7/6.0 |
| Rhinitis | 1/3.3 | 2/7.1 | 3/4.9 | 6/5.2 |

One patient who initiated study treatment with oxybutynin syrup changed to oxybutynin extended release tablets during study, and 2 patients who started treatment with oxybutynin extended release tablets changed to oxybutynin immediate release tablets and then back to oxybutynin extended release tablets.

most frequently reported in this study and commonly seen in this patient population were urinary tract infections and surgical procedures considered unrelated to anticholinergic treatment. Constipation was the most frequently reported treatment related AE. However, many patients with spina bifida receive a colonic washout regimen to resolve neurogenic/neuropathic disturbances of stool evacuation. No patients terminated the study prematurely for safety reasons. There were no deaths, and no serious AEs were considered treatment related. All 3 oxybutynin formulations were well tolerated (table 3). No clinically significant changes in results of serum chemistry or hematology tests or in urinalysis from baseline to end of study were noted.

Study 2—Patient characteristics. All of the 16 children (11 boys and 5 girls) enrolled completed the study. Mean age at enrollment was 3.1 ± 0.30 years, height was 92.1 ± 3.92 cm and weight was 15.6 ± 0.68 kg. Of the children 12 (75%) were white, 3 were Hispanic and 1 was black. Duration of treatment ranged from 13 to 28 days. Daily dose of oxybutynin ranged from 3.6 to 9.0 mg (table 4).

Efficacy. The results of the urodynamic evaluations are shown in table 5. Mean MCC increased significantly by 71.5 ± 21.99 ml (p = 0.005). Mean change in detrusor pressure at maximal cystometric capacity from baseline to the end of treatment was not statistically or clinically significant (0.6 ± 4.79), nor was the change in intravesical pressure (0.9 ± 5.81). Of the 16 patients 11 (68.8%) had uninhibited detrusor contractions 15 cm H₂O or greater at baseline (part B of figure). Mean volume at which these contractions were elicited was 46.0 ± 21.45 ml. At the end of the study only 2 of 16 patients (12.5%) exhibited uninhibited detrusor contractions 15 cm H₂O or greater (part B of figure). Of the 11 patients with uninhibited contractions present at baseline 9 (81.8%) did not have them at the end of treatment (p = 0.004, part B of figure). The other 2 patients were able to hold a greater volume of urine before the onset of uninhibited contractions at the end of treatment compared to baseline.

Safety and tolerability. Overall, oxybutynin syrup was well tolerated. The most commonly reported AE was urinary tract infection (table 6). The severity of all reported AEs was mild or moderate. No deaths, serious AEs or other significant treatment related AEs occurred.

DISCUSSION

To our knowledge study 1 is the first multicenter study to evaluate different formulations of oxybutynin in the treatment of children with detrusor hyperreflexia due to spina

TABLE 4. Distribution of patients in study 2 by age and total daily dose of oxybutynin syrup

| Pt Age (yrs) | Total Daily Dose (mg) | |
|--------------|-----------------------|---------|
| | Less Than 5 | 5–14.99 |
| 1 | 1 | 0 |
| 2 | 1 | 4 |
| 3 | 1 | 3 |
| 4 | 0 | 4 |
| 5 | 0 | 2 |
| Totals | 3 | 13 |

TABLE 5. Values for efficacy variables in study 2 at baseline and end of treatment

| Variable | Baseline | End of Treatment | Change From Baseline* | p Value (paired t test) |
|---------------------------------------------|-------------|------------------|-----------------------|----------------------------|
| Max cystometric capacity (ml) | 104 (20.14) | 175 (20.80) | 71.5 (21.99) | 0.005 |
| Detrusor pressure (cm H ₂ O) | 26.7 (4.80) | 29.3 (4.18) | 0.6 (4.79) | Not significant |
| Intravesical pressure (cm H ₂ O) | 32.9 (6.11) | 35.5 (4.80) | 0.9 (5.81) | Not significant |

* Value at efficacy end point minus value at baseline.

CONCLUSIONS

This investigation demonstrates the efficacy and safety of oxybutynin chloride in the treatment of neurogenic bladder dysfunction in children 6 to 15 years old, and suggests rough equivalence of the 3 formulations examined. The results also support the use of oxybutynin syrup combined with CIC for decreasing bladder contractions and improving bladder capacity in children 1 to 5 years old.

APPENDIX: PRINCIPAL INVESTIGATORS AND STUDY SITES

Richard Adams, MD, Texas Scottish Rite Hospital for Children, Dallas, TX; Jacob V Aranda, MD, Children's Hospital of Michigan, Detroit, MI; Paul Austin, MD, Washington University School of Medicine, St Louis Children's Hospital, St Louis, MO; Douglas Blowey, MD, Children's Mercy Hospital, Kansas City, MO; Anthony Caldamone, MD, University Urological Associates, Providence, RI; Antonio Chaviano, MD, Rush University Medical Center, Chicago, IL; William Clark, MD, Alaska Clinical Research Center, Anchorage, AK; TPVM deJong, Utrecht, The Netherlands; Michael DiSandro, MD, University of Minnesota, Minneapolis, MN; Steven Docimo, MD, Children's Hospital of Pittsburgh, Pittsburgh, PA; Israel Franco, MD, Pediatric Urology Associates, Hawthorne, NY; Richard Grady, MD, Children's Hospital and Regional Medical Center, Seattle, WA; Mark Horowitz, MD, Downstate Medical Center, Brooklyn, NY; William Hulbert, MD, University of Rochester School of Medicine and Dentistry, Rochester, NY; Venkata R Jayanthi, MD, Children's Hospital, Columbus, OH; Barry A Kogan, MD, Albany Medical College, Albany, NY; Martin Koyle, MD, The Children's Hospital, Denver, CO; Andrew Kirsch, MD, Georgia Urology PA, Atlanta, GA; John Lavelle, MD, University of North Carolina at Chapel Hill, Chapel Hill, NC; Paul A Merguerian, MD, Valley Children's Hospital, Madera, CA; Hrair-George Mesrobian, MD, Children's Hospital of Wisconsin, Milwaukee, WI; Kirk Pinto, MD, Urology Associates of North Texas, Fort Worth, TX; Claude Reitelman, MD, Michigan Institute of Urology, PC, St Clair Shores, MI; Richard Rink, MD, Riley Hospital for Children, Indianapolis, IN; Curtis Sheldon, MD, Children's Hospital Medical Center, Cincinnati, OH; Craig Smith, MD, Urological Associates, Peoria, IL; Joel Thompson, MD, Primary Children's Medical Center, Salt Lake City, UT; John Weiner, MD, Duke University Medical Center, Durham, NC.

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TABLE 6. Adverse events reported in more than 10% of patients in study 2

| Adverse Event | No. Pts (%) |
|-------------------------|-------------|
| Urinary tract infection | 3 (18.9) |
| Vasodilation | 2 (12.5) |
| Constipation | 2 (12.5) |
| Diarrhea | 2 (12.5) |
| Ecchymosis | 2 (12.5) |
| Otitis media | 2 (12.5) |

bifida. All measured urodynamic parameters improved after oxybutynin treatment, indicating an overall improvement in bladder function. These patients experienced noticeable clinical improvement for up to 24 weeks, including increases in the proportion of incontinence-free intervals between catheterizations and average volume of urine per catheterization.

In study 2, where younger children with detrusor hyperreflexia due to spina bifida were treated for a shorter duration, oxybutynin syrup produced a significant improvement in maximal cystometric capacity and a significant decrease in the proportion of patients exhibiting uninhibited detrusor contractions 15 cm H₂O or greater. These findings are consistent with improved bladder function, despite the fact that decreases in detrusor and intravesical pressures were not observed here.

We observed roughly comparable efficacy and safety among the 3 oxybutynin formulations in study 1. Youdim and Kogan performed a retrospective study comparing extended release and traditional oxybutynin formulations in 25 children, 14 with neurogenic bladder dysfunction.⁵ In patients previously treated with oxybutynin extended release tablets were equally or more effective and produced the same or fewer side effects, especially with regard to dry mouth, compared to oxybutynin immediate release tablets. Families reported better patient compliance with oxybutynin extended release tablets, and patient and family satisfaction with the extended release formulation was high. The investigators concluded that oxybutynin extended release tablets offer therapeutic benefits beyond those of traditional, immediate release oxybutynin tablets. However, this trial did not include physiological assessments to compare the urodynamic effects of the 2 formulations.

The goal of conservative treatment of neurogenic bladder dysfunction in children is to keep the intravesical pressure low to prevent damage to the upper urinary tract. Bladder pressures less than 40 cm H₂O are essential to maintain kidney function. Anticholinergic therapy with CIC is the cornerstone of conservative management, and long-term use has been shown to prevent development of a high pressure, low volume bladder, improve urodynamic measures and continence, and decrease the risk of bladder dysfunction.^{1,2,6,9-12} Moreover, after a followup of at least 2 years only 2 patients had discontinued treatment because of adverse effects, and treatment effectively protected renal function in the vast majority of children (90% or more).¹ The open label design of the 2 studies presented here limits their interpretation, and no comparison of the 3 formulations was prospectively planned. However, these results are consistent with the urodynamic findings of Goessl et al,¹ and extend the documented safety and efficacy of oxybutynin and CIC therapy in this population to 3 available formulations of oxybutynin.

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