

Efficacy and Safety of Oxybutynin Transdermal System in Spinal Cord Injury Patients With Neurogenic Detrusor Overactivity and Incontinence: An Open-label, Dose-titration Study

Michael J. Kennelly, Gary E. Lemack, Jenelle E. Foote, and Cynthia S. Trop

OBJECTIVES

To evaluate the efficacy and safety of oxybutynin transdermal system (oxybutynin-TDS) in spinal cord injury patients with neurogenic detrusor overactivity and incontinence despite use of clean intermittent catheterization (CIC).

METHODS

This multicenter, open-label, dose-titration study included patients ≥ 18 years old. During an 8-week dose-titration period, oxybutynin-TDS doses were adjusted every 2 weeks, depending on symptoms. The primary efficacy end point was a change in daily number of CIC periods without leakage, from baseline to 8 weeks or last observation. Outcome parameters included 3-day voiding diary, CIC volume, and urodynamic parameters. Changes from baseline were analyzed with paired *t* tests.

RESULTS

Of 24 study participants (mean age, 41.9 years), 18 (75.0%) completed the study. Final oxybutynin-TDS doses were 7.8, 9.1, and 11.7 mg/d for 4, 9, and 11 patients, respectively. Daily number of CIC periods without leakage increased significantly (mean change, 1.5 ± 2.2 ; $P = .0036$) from baseline (2.4 ± 1.8) to 8 weeks (3.9 ± 1.9). CIC volume ($P = .0029$), reflex volume ($P = .0466$), maximal cystometric bladder capacity ($P = .0009$), and residual urine volume ($P = .0023$) all increased significantly, whereas detrusor pressure at maximal bladder capacity decreased significantly ($P = .0457$). The most common adverse events were application site reaction (12.5% of patients), dry mouth (8.3%), and abnormal vision (8.3%). No patient discontinued treatment because of an adverse event.

CONCLUSIONS

Oxybutynin-TDS was efficacious in spinal cord injury patients with neurogenic detrusor overactivity and was well tolerated at up to 3 times the standard dose. UROLOGY xx: xxx, xxxx. © 2009 Elsevier Inc.

Neurogenic detrusor overactivity (NDO),¹ which is characterized by hyper-reflexia of the detrusor muscle, is a frequent consequence of suprasacral spinal cord injuries (SCIs).^{2,3} Depending on the nature

and severity of the SCI, NDO may be accompanied by other urodynamic abnormalities, such as detrusor-sphincter dyssynergia, low bladder compliance, and high detrusor leak-point pressure.⁴ All of these conditions contribute to a variety of urological complications in the SCI population, such as urinary leakage, urinary tract infection, bladder and renal calculi, vesicoureteral reflux, and upper urinary tract damage.^{5,6}

Clean intermittent catheterization (CIC) is a method of bladder management that is used widely in patients with SCI; it has been associated with a significantly lower incidence of urological complications when compared with chronic urethral catheterization.⁷ To treat patients with NDO, CIC is often used in combination with an antimuscarinic drug such as oxybutynin,⁸⁻¹⁰ tolterodine,⁸ or trospium.¹⁰ Oral administration of antimuscarinic drugs, although efficacious, frequently causes anticholinergic adverse effects, including dry mouth, constipation, and blurred vision.^{11,12} Intravesical administration of antimuscarinic drugs is associated with a lower frequency of

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anticholinergic adverse effects,¹³ but dissolving the drugs may be inconvenient and may lead to variations in quality.¹⁴

Transdermally delivered oxybutynin offers an alternative to orally or intravesically administered antimuscarinic therapy. The oxybutynin transdermal system (oxybutynin-TDS) has several advantages over orally administered oxybutynin, including a lower therapeutic dose to achieve similar efficacy.^{12,15-17} In addition, transdermal delivery is associated with a lower incidence of anticholinergic adverse events, such as dry mouth and constipation.¹² The adverse effects of orally administered formulations have been attributed to high plasma concentrations of the primary metabolite of oxybutynin, *N*-desethyloxybutynin, relative to the parent drug.¹⁸ Because oxybutynin-TDS largely avoids presystemic metabolism, it generates substantially lower ratios of *N*-desethyloxybutynin to oxybutynin plasma concentrations than are produced by orally administered oxybutynin.^{18,19} For some patients, twice-weekly dosing with oxybutynin-TDS may be more convenient than daily dosing with an orally or intravesically administered medication.

Oxybutynin-TDS is effective and well tolerated in patients with non-neurogenic overactive bladder.^{12,20-23} However, treatment with oxybutynin-TDS has not been described in patients with NDO secondary to SCI. In this open-label, dose-titration study, the efficacy and tolerability of oxybutynin-TDS, given at 1 to 3 times the usual dose, were evaluated in patients with NDO resulting from SCI.

MATERIALS AND METHODS

Patients

This study was performed at 4 US centers. Institutional Review Board approval and informed consent were obtained before patients were enrolled. Participants included men and women with SCI, ≥ 18 years old, who had a history of urinary incontinence between CICs from NDO.²⁴ In accordance with recommendations of the Standardization Subcommittee of the International Continence Society, NDO was confirmed through urodynamic assessments during screening. Patients completed a 3-day urinary diary during screening to document urinary incontinence between scheduled CICs. Female participants were nonpregnant and nonlactating; those with childbearing potential were required to use adequate birth control. Patients were eligible only if they were in good health (excluding the SCI) as evidenced by medical history and physical examination findings and were capable of correctly completing the urinary diary, with or without assistance from a caregiver.

Among the most important exclusion criteria were the following: urinary tract infection (but not asymptomatic bacteriuria), urolithiasis, gastric retention, uncontrolled narrow-angle glaucoma, vesicoureteral reflux, active skin disorder, use of diuretics, urethral stent, intrinsic sphincter deficiency incontinence, stress urinary incontinence, external sphincterotomy, urinary tract surgery (previous 3 months), hypersensitivity to oxybutynin-TDS, and participation in a study of another investigational compound (previous 30 days).

Study Design

This pilot study had a multicenter, open-label, dose-titration design (ClinicalTrials.gov identifier: NCT00224029). The following baseline characteristics were determined during a 3-14-day screening period: CIC frequency (ie, number of catheterizations per day), CIC interval (ie, time between catheterizations during waking hours), and number of incontinence episodes per day. During screening, patients with current antimuscarinic therapy completed a washout period of ≥ 2 (for immediate-release medication) or ≥ 3 days (for extended-release medication). CIC frequency and intervals had to remain constant after washout, as documented in a 3-day urinary diary.

Four doses of oxybutynin-TDS were available: 3.9 mg/d ($1 \times 39\text{-cm}^2$ patch), 7.8 mg/d ($2 \times 39\text{-cm}^2$ patches), 9.1 mg/d ($2 \times 39\text{-cm}^2$ patches + $1 \times 13\text{-cm}^2$ patch), and 11.7 mg/d ($3 \times 39\text{-cm}^2$ patches). Patches were applied to the hip, abdomen, or buttock and were replaced every 3-4 days (ie, twice weekly). The site of application was rotated with every dose. Patients without prestudy therapy and those given prestudy doses of oral oxybutynin < 15 mg/d or tolterodine ≤ 4 mg/d initially received oxybutynin-TDS 3.9 mg/d. Patients given prestudy doses of oral oxybutynin ≥ 15 mg/d or tolterodine > 4 mg/d initially received oxybutynin-TDS 7.8 mg/d. During the 8-week titration period, the investigator could adjust doses by 1 level, every 2 weeks. If complete continence was achieved with tolerable adverse effects, the patient stayed at that dose for the duration of the dose-titration period. If the patient reported unacceptable adverse effects, the dose was reduced by 1 level and held steady afterward.

Assessments

The primary objective of the study was to evaluate the efficacy of oxybutynin-TDS in reducing leakage accidents between scheduled CICs in adults with NDO resulting from SCI. At each CIC, patients recorded in the 3-day diary whether urine had leaked since the previous CIC. The mean daily number of CIC periods per day without leakage was compared at baseline and at week 8.

Urinary void volume was a secondary efficacy parameter that was recorded in the 3-day diary. Secondary efficacy variables based on urodynamic evaluations included volume at first sensation, reflex volume (volume at first detrusor contraction with an amplitude > 15 cm H₂O), amplitude of first detrusor contraction > 15 cm H₂O, amplitude of largest detrusor contraction, maximum cystometric (urodynamic) capacity (volume at which urine leakage occurred, or maximum capacity up to 500 mL), detrusor pressure at maximal bladder capacity, and residual urine volume after urodynamic testing.¹ Urodynamic evaluations were performed at each center according to a standardized protocol.

Primary and secondary variables were measured at baseline and at weeks 2, 4, 6, and 8; urodynamics were assessed at baseline and week 8. Safety was assessed by evaluating the incidence of adverse events (weeks 2, 4, 6, and 8).

Statistical Analysis

The modified intent-to-treat (mITT) population included all patients who received oxybutynin-TDS during the dose-titration period and who had any efficacy data after the first dose. The safety population included all patients who received oxybutynin-TDS during the dose-titration period.

All inference tests were conducted at $\alpha = 0.05$, using 2-sided paired *t* tests. The statistical software program SAS, version 8.2

Table 1. Demographic characteristics of study participants*

Characteristic	Patients (N = 24)
Age, y	
Mean (SD)	41.9 (10.4)
Median (range)	43.7 (23.4, 63.0)
Sex, n (%)	
Male	21 (87.5)
Female	3 (12.5)
Race, n (%)	
African American	14 (58.3)
Caucasian	9 (37.5)
Hispanic	1 (4.2)
ASIA classification, n (%) [†]	
A	17 (70.8)
B	2 (8.3)
C	5 (20.8)

ASIA = American Spinal Injury Association.

* Patients with ASIA class D and E impairment were not included in this study.

[†] ASIA Impairment Scale²³: A = Complete: no motor or sensory function is preserved in the sacral segments S4–S5; B = Incomplete: sensory but no motor function is preserved below the neurologic level, and sacral segments S4–S5 are included; C = Incomplete: motor function is preserved below the neurologic level, and more than half of key muscles below the neurologic level have a muscle grade <3.

(SAS Institute, Cary, NC), was used. Observed cases were analyzed for all time points. For week 8 only, additional inference tests were conducted using last observations carried forward (LOCF) to impute missing values for patients who withdrew.

RESULTS

Patient Disposition and Demographic Characteristics

A total of 24 patients entered the dose-titration period of the study and constituted the safety population. Of the 24 patients, 18 (75.0%) completed the study, 4 (16.7%) withdrew voluntarily, 1 (4.2%) was lost to follow-up, and 1 (4.2%) did not complete the study because it was closed by the sponsor. No patient discontinued the study because of an adverse event. Discontinuation rates showed no dependence on the final dose; patients who left the study included 1 of 4 (25.0%) who were taking 7.8 mg/d, 5 of 9 (55.6%) who were taking 9.1 mg/d, and 0 of 11 (0.0%) who were taking 11.7 mg/d. The mITT population included 22 patients; most were male and African American and had an American Spinal Injury Association Impairment Scale class A SCI (Table 1). Mean age was 41.9 years (range, 23–63). Initial doses of oxybutynin were 3.9 mg/d for 6 patients (25.0%) and 7.8 mg/d for 18 patients (75.0%). Final doses were 7.8 mg/d for 4 patients (16.7%), 9.1 mg/d for 9 (37.5%), and 11.7 mg/d for 11 (45.8%).

Daily Number of CIC Periods Without Leakage

Mean daily total CIC frequency was 5.3 ± 1.4 (mean \pm standard deviation) at baseline. The mean daily number

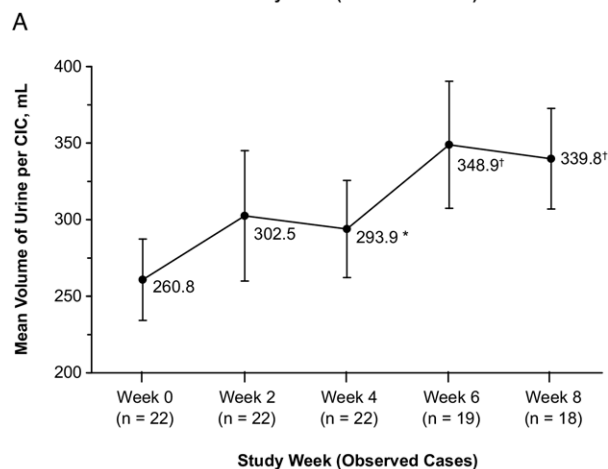
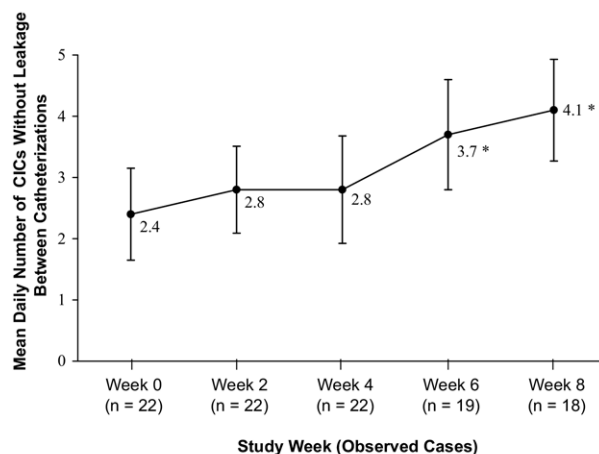


Figure 1. Diary variables at baseline and at each subsequent evaluation. (A) Daily number of clean intermittent catheterizations without leakage between catheterizations and (B) volume of urine collected at each clean intermittent catheterization. * $P < .01$. † $P < .05$, t test for significance of mean change from baseline. Bars depict standard errors of the mean.

of CIC periods without leakage was 2.4 ± 1.8 ; all other CIC periods were associated with leakage. As required by the study protocol, overall mean daily CIC frequency (observed cases) remained constant during the study; mean daily change in CIC frequency was 0.0 ± 0.8 ($P = .8311$) in the mITT population at week 8 (LOCF). In contrast, the mean daily number of CIC periods without leakage (observed cases) increased steadily (Fig. 1A), and mean change in the mITT population at week 8 (LOCF) was 1.5 ± 2.2 ($P = .0036$). The median daily number of CIC periods without leakage doubled from 2.0 at baseline to 4.0 at week 8 (LOCF).

Catheterized Urine Volume

Mean urinary volume (observed cases) increased significantly from baseline to study end (Fig. 1B), with a mean change of 54.7 ± 76.2 mL ($P = .0029$) at week 8 (LOCF).

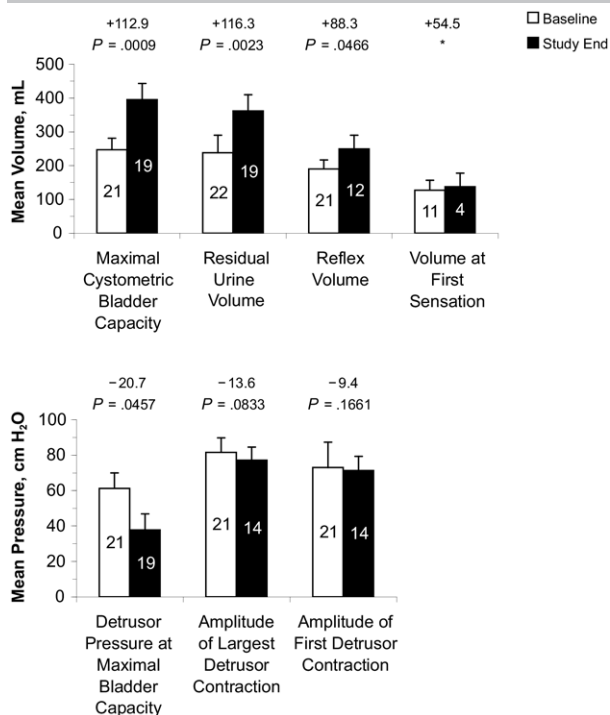


Figure 2. Parameters of urodynamics at baseline and at study end; the number of patients with valid measurements is shown within each column. *P* values were calculated with a *t* test for significance of mean change from baseline. **P* value not calculated because *n* < 10. Bars depict standard errors of the mean.

Urodynamic Parameters

Significant mean improvements ($P < .05$) from baseline to study end were observed for several urodynamic parameters. Reflex volume ($P = .0466$), maximal cystometric bladder capacity ($P = .0009$), and residual urine volume ($P = .0023$) all significantly increased, whereas detrusor pressure at maximal bladder capacity significantly decreased ($P = .0457$) (Fig. 2). Other urodynamic parameters also improved, but changes from baseline were not statistically significant (Fig. 2).

Safety

Fourteen patients experienced 36 adverse events; 22 adverse events in 10 patients were considered related to the study drug. The most common drug-related adverse events were dry mouth (5 separate events in 2 patients [8.3%]), abnormal vision (2 events in 2 patients [8.3%]), constipation (2 events in 1 patient [4.2%]), and excessive sweat (2 events in 1 patient [4.2%]). Three patients experienced a total of 4 application site reactions. Most adverse events (34 of 36; 94.4%) were mild or moderate; 1 patient reported 2 severe adverse events of dry mouth. No event of dry mouth occurred in patients ($n = 11$) receiving the highest dose of oxybutynin-TDS (11.7 mg/d). The incidence of adverse events, whether considered treatment related or not, appeared independent of dose; with oxybutynin-TDS 3.9 mg/d, 2 of 6 (33.3%) patients reported ≥ 1 adverse event; with 7.8 mg/d, 6 of 24

(25.0%); with 9.8 mg/d, 7 of 20 (35.0%); and with 11.7 mg/d, 3 of 11 (27.3%). No deaths or other serious adverse events occurred.

COMMENT

Results of this pilot study show that oxybutynin-TDS promotes significant increases in the daily number of catheterizations without leakage in patients with NDO resulting from SCI. Substantial, statistically significant improvements during the 8-week dose-titration period were observed for several urodynamic parameters, including maximal cystometric bladder capacity and residual urine volume. Urodynamic indicators of a motor effect, for example, amplitude of the largest or first detrusor contraction, were not altered by treatment with oxybutynin-TDS, suggesting that oxybutynin acts at least partially through an afferent mechanism.²⁵ Oxybutynin-TDS was well tolerated, even at 3 times the standard dose (11.7 vs 3.9 mg/d).²³ Nearly all adverse events were mild or moderate in severity, and they did not become more frequent with greater doses; no adverse event led to discontinuation of treatment. Dry mouth, the most common adverse event associated with oral oxybutynin therapy, did not occur with the highest dose of oxybutynin-TDS, and the overall incidence of drug-related dry mouth in this study was consistent with incidences in randomized, double-blind, placebo-controlled clinical studies of oxybutynin-TDS.¹⁵

Despite differences in trial design, the efficacy of oxybutynin-TDS was generally consistent with that of oral oxybutynin in other studies of patients with NDO. A 12-week, open-label, dose-titration study of extended-release oxybutynin (10-30 mg/d) in 10 patients with NDO caused by SCI found significant reductions in the mean number of urge incontinence episodes per week and in daily voids.⁹ The same study showed significant mean increases in maximal cystometric bladder capacity and postvoid residual volume.⁹ Likewise, a study of daily oral doses of 15 mg oxybutynin in patients with NDO reported significant mean changes in maximal bladder capacity, maximum detrusor pressure during voiding, bladder compliance, and residual urine.¹⁰

The tolerability of oxybutynin-TDS in this study compared favorably with that of orally administered oxybutynin in other studies, even though all patients in this study eventually were treated at 2-3 times the standard dose of oxybutynin-TDS. In a study with immediate-release oral oxybutynin 15 mg/d, 56% of patients experienced dryness of mouth, with 23% rating the symptom as severe.¹⁰ In contrast, patients in this study rarely experienced dry mouth (2 of 24; 8.3%). Additional randomized, double-blind studies, in which oxybutynin-TDS up to 3.9 mg/d was used, found no significant difference in the incidence of anticholinergic adverse events (including dry mouth and constipation) between patients given active and placebo treatments.^{20,22}

Limitations of this open-label pilot study include its small population size, which may explain why 3 urodynamic variables exhibited no statistically significant changes. The small population size and the dose-titration design also precluded direct comparison of various doses in terms of efficacy and safety. Thus, it is unclear whether the observed lack of dependence between dose and incidence of adverse events would be found in a parallel-group study. Furthermore, patients previously treated with high doses of orally administered antimuscarinic agents could have been tolerant of anticholinergic adverse effects.

CONCLUSIONS

Oxybutynin-TDS significantly increased the daily number of CIC periods without leakage in SCI patients with NDO. Oxybutynin-TDS was well tolerated in these patients at up to 3 times the standard dose.

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