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Tolterodine Causes Measurable Restoration of Urethral Sensation in Women With Urge Urinary Incontinence

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Introduction & Hypothesis: Determine if treatment of urge incontinence with tolterodine results in changes in bladder and/or urethral sensation using Current Perception Threshold (CPT) testing. **Methods:** Women with ≥1 incontinence episode on 7-day diary were treated with 4 mg of long-acting tolterodine for 2-months. At baseline and 2-months, participants had CPT testing of the urethral and bladder at 3 frequencies 2000, 250, and 5 Hz. Baseline and post-treatment measures were compared using Wilcoxon Signed Rank Test. **Results:** Seventeen women underwent baseline CPT testing. Four discontinued medication due to side effects and did not have repeated testing. Urethral CPT at 250 Hz was lower after treatment (median 1.3 [Interquartile range .69–2.1] and .75 [.45–1.2], $p = .003$) and at 5 Hz trended toward a significant decrease (1.1 [1–1.9] and .84 [.32–1.1], $p = .06$). **Conclusions:** Urethral sensitivity improves after 2-months of tolterodine, suggesting it may restore urethral sensory nerves in addition to known motor effects. *Neurourol. Urodynam. 29:555–557, 2010.* © 2010 Wiley-Liss, Inc.

Key words: antimuscarinic; CPT; current perception threshold; sensory threshold; urethra; urge incontinence

INTRODUCTION

Antimuscarinic agents remain a mainstay of pharmacologic treatment for urge urinary incontinence (UUI). The mechanism of action of antimuscarinics is reportedly via muscarinic receptors in the detrusor smooth muscle where they bind to muscarinic receptors and inhibit parasympathetically mediated detrusor contractions.[1,2] The precise mechanism of benefit with antimuscarinic agents is not fully elucidated as increasing data suggest that alterations in afferent nerve fibers also play a role in treatment response. After taking antimuscarinic agents, patients frequently report decreased sensation or urgency during bladder filling; yet, efferent parasympathetic input is not active during this time.[3] In addition, intravesical and systemic oxybutynin reduce afferent sensitivity in A-δ and C fibers in rats.[4,5] Likewise, low doses of tolterodine have an inhibitory effect on C fibers and increase bladder capacity during filling in rats after cerebral infarction.[6] This is consistent with other data suggesting changes in afferent innervation in the lower urinary tract plays an important role in lower urinary tract dysfunction.[7,8] Afferent signals from the urinary tract are transmitted via A-δ and C fibers along the sympathetic and parasympathetic nervous systems.[9] A-δ fibers are activated by increases in the tension of the bladder wall. C fibers are activated in certain diseased states and begin firing spontaneously as well as increase firing with bladder distension.[10]

Increasing reports use electrical stimulation in the lower urinary tract of humans to further the clinical investigation of afferent innervation in lower urinary tract dysfunction.[7,11–15] Current perception threshold (CPT) testing reliably uses electrical stimuli at varying frequencies to activate different subpopulations of afferent nerve fibers.[16–18] A constant current electrical stimulator delivers sine wave stimuli at three different frequencies, which selectively depolarize different types of sensory nerves. The three major populations of sensory nerves, A-β, A-δ, and C fibers, can then be compared clinically. This method has been described by multiple authors in the bladder and urethra of women with UUI and asymptomatic controls.[7,14,19]

The aim of this pilot study was to determine if long-acting tolterodine for UUI results in afferent neural changes quantified as changes in bladder and/or urethral sensation using CPT testing.

MATERIALS AND METHODS

Following IRB approval, we recruited women seeking treatment for UUI from our tertiary care urogynecologic practice to this pilot study. Women, who desired pharmacologic treatment for UUI, reported no contraindications to or prior history of antimuscarinic therapy; had a postvoid residual urine volume less than 100 ml, a negative urine dipstick analysis, and no known neurologic disease were enrolled. Consenting participants completed a 7-day urinary diary and categorized incontinence episodes as UUI, stress urinary incontinence or other. Participants also self-completed the Medical Epidemiological and Social Aspects of Aging questionnaire (MESA)[20] in addition to a routine urogynecologic history and physical exam including neurourologic evaluation with lower limb deep tendon reflexes. Participants with at least 1 UUI episode on the 7-day diary at their return visit underwent repeat urine dipstick to exclude active urinary tract infection followed by standardized CPT testing in the urethra and bladder.

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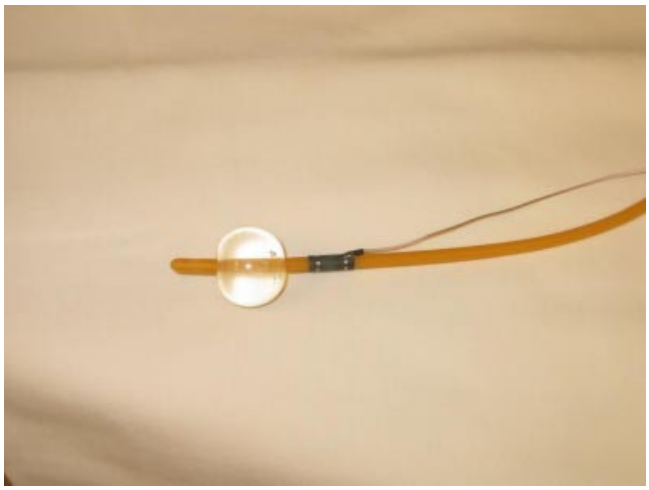

Fig. 1. Urethral ring electrode on 14 French Foley catheter.

We performed CPT testing in the bladder and urethra using a Neurometer® device (Neurotron Inc., Baltimore, MD).[19] The Neurometer® is a constant current stimulator capable of delivering sine wave electrical stimuli at three frequencies, 2,000, 250, and 5 Hz, which selectively depolarize A-β, A-δ, and C fibers, respectively. At completion of baseline CPT testing, we supplied participants with a 2-month supply of 4 mg of long-acting tolterodine. Participants returned during week 8, to undergo repeat CPT testing after catheterized post-void residual urine volume and urine dipstick analysis.

Participants underwent standardized CPT testing in urethra followed by bladder while in the dorsal lithotomy position at baseline and post-treatment. Stimuli were applied to the urinary tract via a ring electrode, consisting of two pieces of platinum wire wound around a thin cylinder and coated with plastic, which was positioned 1 cm distal the balloon on a 14 French Foley catheter (Fig. 1).

Urethral CPT Testing

After draining the bladder and inflating the Foley balloon, we gently positioned the balloon at the urethrovesical junction, so the ring electrode lied at the mid-urethra. The ring electrode was connected to the Neurometer®, and testing initiated at 2,000 Hz. Stimulus intensity was gradually increased until first perceived by the participant, and then decreased until it was no longer perceptible. CPT values were obtained using a semi-automated forced choice paradigm where randomly chosen pairs of stimuli are presented as "A" or "B" with a brief rest period until a consistent perception threshold is reached. We repeated the process at 250 and 5 Hz.

Bladder CPT Testing

After obtaining the final urethral CPT measurement, we deflated the Foley balloon and advance the catheter into the bladder. The catheter was left open to drain during the bladder testing. To ensure mucosal contact, we measured impedance using a Nicolet Viking IV p electrodiagnostic instrument. When impedance was less than 10 kΩ the catheter was taped securely in place. The electrode was reconnected to the Neurometer® and bladder CPT measurements obtained as described for the urethra.

SPSS Version 13 (Chicago, IL) was used for data management and statistical analysis. Baseline and post-treatment measures were compared using the Wilcoxon Signed Rank Test. We only included women who underwent baseline CPT testing, completed 2 months of tolterodine, and had repeat CPT testing in the analysis. All tests were considered significant at a 0.05 level.

RESULTS

Seventeen women underwent baseline CPT testing. Four of 17 (24%) discontinued medication due to side effects and did not undergo repeat testing. Participants had a mean ± SD age of 62 ± 14 and a median vaginal parity of 2 (range 0–4). Ninety-three percent (N = 12) were Caucasian. All participants had intact bulbocavernosus, patellar, and Achilles reflexes. Women had a median of 14 (1–40) UUI episodes per week on urinary diary. Mean MESA urge subscale scores improved significantly from baseline after treatment (10 ± 3.5 and 6.5 ± 3.7, $P = 0.007$). Table I shows baseline and post-treatment urethral and bladder CPT values. Urethral CPT at 250 Hz was significantly lower (more sensitive) after treatment with tolterodine, and urethral CPT at 5 Hz trended toward a significant decrease (more sensitive). Decrease in urethral CPT at 250 Hz and improvement in MESA scores after treatment were strongly correlated (Spearman's $\rho = 0.76$, $P = 0.01$). We did not detect significant changes in bladder CPT after treatment with tolterodine.

DISCUSSION

This is the first report of recording a significant post-treatment decrease in urethral CPT values at 250 Hz consistent with small, myelinated A-δ fibers) and a similar trend at 5 Hz (consistent with C fibers) in women with UUI. High CPT values are consistent with loss of afferent neural function; therefore, the decrease in urethral CPT values after successful treatment with tolterodine suggests that treatment modifies or improves afferent innervation. We previously reported normative urethral and bladder CPT values in 48 women without lower urinary tract symptoms.[13] We also found that urethral CPT values were significantly higher in women with UUI when

TABLE I. Baseline and Post-Tolterodine Treatment CPT Values

	OAB (N = 13)		
	Baseline CPT median (25th–75th IQR)	Post-treatment CPT median (25th–75th IQR)	*P*-value*
Urethra (2,000 Hz)	2.6 (1.3–5.4)	1.7 (1.1–2.7)	0.91
Urethra (250 Hz)	1.3 (0.69–2.1)	0.75 (0.41–1.2)	0.003
Urethra (5 Hz)	1.1 (1–1.9)	0.84 (0.32–1.1)	0.06
Bladder (2,000 Hz)	1.9 (1.1–8.2)	1.4 (1.2–8.4)	0.86
Bladder (250 Hz)	1.0 (0.39–4.6)	1.0 (0.63–5.0)	0.88
Bladder (5 Hz)	0.55 (0.07–3.1)	0.46 (0.33–1.5)	0.87

*Wilcoxon sign rank test.

compared to controls.[13] After treatment with tolterodine, CPT measures of women with UUI in this study approach those of our previously reported control group without urinary symptoms, further supporting that antimuscarinic drugs may have affects on urethral afferent nerve fibers, which mediate uninhibited detrusor contractions.

While this is one of only a few reports in humans quantifying differences in urethral afferent innervation in women with UUI, the relationship between urethral afferent nerves and uninhibited detrusor contractions was described nearly a century ago in cats.[21] More recently, investigators demonstrated urethral pressure increases with bladder filling, which result in a negative feedback loop to inhibit spontaneous detrusor contractions.[22,23] Chaliha et al.[24] reported a drop in urethral pressure during multichannel urodynamics in women with detrusor overactivity that was not seen in women with urodynamic stress incontinence. Yokoyama et al.[25] used intraurethral capsaicin in rats to desensitize urethral afferent fibers and found a marked decrease in detrusor activity after a brief initial increase in activity. Similar to our findings of restoration of urethral sensation after treatment with antimuscarinics, these data also suggest that alterations in afferent urethral innervation effect detrusor activity.

We did not find changes in CPT values in the bladders of women with UUI before and after treatment with tolterodine. Other investigators reported mixed effects of tolterodine on bladder sensory thresholds in asymptomatic volunteers.[15,26] Boy et al.[26] performed sensory threshold testing on seven women without lower urinary tract symptoms before and 2-hr after a single 4-mg oral dose of immediate release tolterodine. They applied square wave electrical stimuli to the bladder mucosa 1 cm above the bladder neck using a bipolar electrode mounted on a micro-tip urodynamic catheter and reported significant increases in sensory thresholds after taking tolterodine. Mehnert et al.[15] used a similar technique after randomizing 30 asymptomatic women to one of three-groups: placebo; 4-mg long-acting tolterodine; and 8-mg long-acting tolterodine. They did not find significant changes in any group before and 4-hr after medication. Important differences in our study compared to the others, which may impact the results include: subjects with UUI rather than absence of urinary tract symptoms; sine versus square wave stimuli; duration of tolterodine therapy; and position of the stimulating electrode in the bladder. Investigators have reported significant differences in bladder sensory thresholds depending on electrode positioning in the bladder[4] and use of sine or square wave electrical stimuli.[14] In our study, standard deviations of CPT measures in the bladder at all frequencies are much larger than those in the urethra. This increased variability and reported differences in sensory thresholds depending on electrode positioning in the bladder suggest our lack significant findings in the bladder may be related to technical inconsistencies and/or variation. Future studies will confirm precise electrode positioning in the bladder to improve the reproducibility in the bladder.

Urethral sensitivity improves after 2 months of treatment with long-acting tolterodine. These findings suggest that this class of drugs may restore urethral sensory nerves in addition to their known motor effects.

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