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# Neurogenic Bladder Treatment by Doubling the Recommended Antimuscarinic Dosage

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**Introduction and Objectives:** The dosage of the antimuscarinic drugs: Tolterodine ER or Trospium was increased to a higher-than-recommended dosage in patients where the manufacturer's recommended dosage had failed. All patients were suffering from neurogenic detrusor overactivity incontinence. Tolerability and success were evaluated in the present study. **Materials and Methods:** Twenty-one patients with neurogenic detrusor overactivity were evaluated: 17 with spinal cord injury, 3 with multiple sclerosis, and 1 with a meningomyelocele. All patients catheterized themselves or were catheterized. If neurogenic detrusor overactivity continued and the medication was well tolerated, the dosage was doubled to either 8 mg of Tolterodine ER [$2 \times 4$ mg ($n = 11$)] or 90 mg of Trospium [$3 \times 30$ mg ($n = 10$)]. The follow-up was monitored by a bladder diary and urodynamic evaluation. **Results:** Sixteen patients significantly decreased their incontinence episodes from 8–12 episodes before to 0–2 episodes during the doubled treatment. The reflex volume increased from $202 \pm 68$ to $332 \pm 50$ ml ($P < 0.001$). Cystometric capacity enlarged from $290 \pm 56$ to $453 \pm 63$ ml ($P < 0.001$). One patient had to stop the medication because of intolerable side effects and five patients did not experience satisfactory benefit. **Conclusion:** The increased dosage of Tolterodine or Trospium is an effective treatment in patients with neurogenic bladder. *Neurourol. Urodynam. 25:441–445, 2006.* © 2006 Wiley-Liss, Inc.

**Key words: antimuscarinics; neurogenic bladder; urodynamics**

## INTRODUCTION

Antimuscarinic drugs remain the first choice of treatment for patients with neurogenic detrusor overactivity [Aslan and Kogan, 2002]. As it has been shown in several studies, these drugs are safe, efficient, and generally well tolerated [Van Kerrebroeck et al., 2001; Kreder et al., 2002; Halaska et al., 2003]. However, oral antimuscarinic treatment with the manufacturer's recommended maximum dosage of a single antimuscarinic drug does not always lead to the desired effect of detrusor stability and continence. This is especially true for tetra- or paraplegic patients after spinal cord injury or patients with severe neurological disorders such as multiple sclerosis or meningomyelocele. In those patients, the situation is often complicated by detrusor sphincter dyssynergia, which despite persistent incontinence episodes, forces patients to perform even more frequently clean intermittent catheterization that significantly impacts their quality of life.

According to Madersbacher et al. [2004], approximately 30% of the patients undergoing antimuscarinic treatment at the recommended dosage had persistent detrusor overactivity (max. pressure >40 cm $H_2O$), low compliance (<20 ml/cm $H_2O$), or a low capacity (<250 ml). As we know, this situation may lead to persistent incontinence, repeated urinary infections, and threaten long-term renal function. In order to effectively deal with these problems, further treatment options are needed. For this reason, dose-ranging studies were performed to adjust antimuscarinic treatment to better protect the urinary tract and meet the patients' needs. In 1995, Madersbacher et al. [1995] first used Trospium to treat neurogenic detrusor overactivity; in 1998, Van Kerrebroeck et al. [1998] used Tolterodine; and in 2004, Steers et al. [2005] tested Darifenacin. In these studies, the treatment effectiveness increased linearly to the amount of the administered antimuscarinic drugs.

In order to prevent urinary retention in patients, higher-than-recommended manufacturer's dosages (recommended dosage of Tolterodine ER is $1 \times 4$ mg/day and of Trospium $3 \times 15$ mg/day) are usually not prescribed for spontaneously voiding patients, who do not perform clean intermittent catheterization. Due to the fact that the patients included in this study practiced clean intermittent catheterization, we believed that higher-than-recommended antimuscarinic dosages could be an effective treatment option. For this reason we evaluated the effect of an antimuscarinic treatment in 21 patients, where the normal antimuscarinic dosage failed. The drug

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prescription was doubled to a 2 × 4 mg dosage per day of Tolterodine (n = 11) or a 3 × 30 mg dosage per day of Trospium (n = 10).

## MATERIALS AND METHODS

### Patients

All patients enrolled in this study suffered from neurogenic detrusor overactivity incontinence. Seventeen were attributable to spinal cord injury, 3 to multiple sclerosis, and 1 to meningomyelocele. The group of patients with spinal cord injury was further subdivided into 2 groups: 10 tetraplegic and 7 paraplegic patients. Fifteen patients were male and six were female. The mean age was 34 years (18–55 years) (Table I). All patients (n = 21) either practiced clean intermittent self-catheterization or were catheterized by a nurse or a family member. After the detrusor overactivity was diagnosed, an antimuscarinic treatment with the manufacturer's recommended dosage of either Tolterodine ER (1 × 4 mg) or Trospium (3 × 15 mg) was administered. The medication was chosen randomly and dependent upon the treating physician's preferred medication. Detrusor overactivity was defined by the discovery of uninhibited detrusor contractions resulting in pressures exceeding 40 cm $H_2O$ while performing a filling cystotonometry. The follow-up was done by a bladder diary and urodynamic evaluations. Any reported incontinence or unintended side effects were also noted in the diary.

For all patients in this group, the treatment benefit after 4 weeks was unsatisfying at the manufacturer's highest recommended dosage. For this reason, the initial dosage was then doubled to either Tolterodine (2 × 4 mg daily) or Trospium (3 × 30 mg daily). The success of the treatment was then re-evaluated by bladder diaries, urodynamics, and the clinical outcome.

### Urodynamic Studies

The urodynamic investigations were carried out after exclusion of urinary infection. The urodynamic evaluation was done with a SEDIA device using a double micro tip catheter (9°F) to measure intravesical pressure. The bladder was filled with 37°C saline via the urethral catheter at a filling rate of 20 ml/min mixed with contrast medium (Ultravist®-300 Schering, Germany) to perform video urodynamics. A rectal catheter was inserted in order to evaluate the intra-abdominal pressure and determine detrusor activity. Simultaneously, a pelvic floor electromyogram was recorded with adhesive electrodes attached to the perineum. Maximum bladder capacity, maximum detrusor pressure (leak point pressure), and detrusor compliance were determined during a filling cystotonometry.

In addition to the urodynamic evaluation, the patient documented bladder diaries prior to the initial recommended dosage and 4 weeks after the drug was increased. The patient also documented any new or increased side effects.

**TABLE I. Patients' Characteristics**

| | |
|---|---|
| Patients (n) | 21 |
| Males (n) | 15 |
| Females (n) | 6 |
| Age (years) | 34 (18–55) |
| Spinal cord injury (n) | 17 |
| Multiple sclerosis (n) | 3 |
| Meningomyelocele (n) | 1 |

### Statistical Analysis

A Wilcoxon/Kruskal–Wallis test (jmp software, SAS Institute, Cary, NC, USA) was applied to compare the different treatment groups before and after the increased antimuscarinic treatment. *P*-values of $\leq 0.05$ were considered as statistically significant.

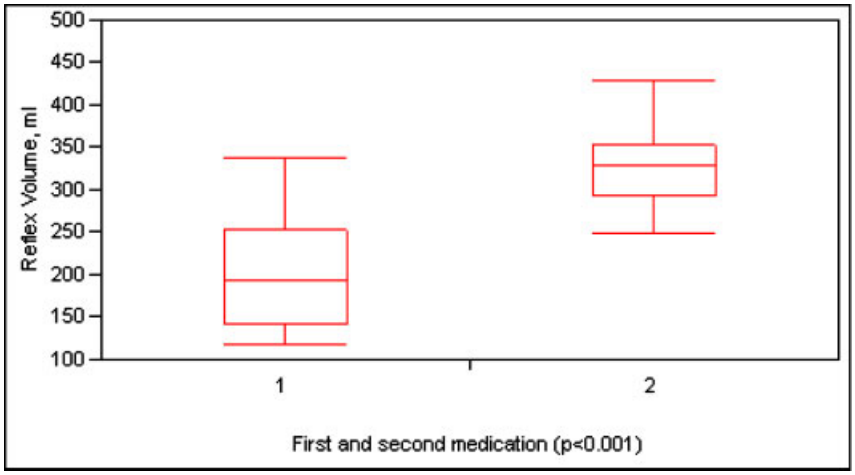
## RESULTS

All patients included in this study did not experience satisfactory treatment at the manufacturer's recommended dosage. They also did not note any side effects. Because of this negative outcome, this alternative treatment option was offered to the patients. With their agreement, we administered the increased dosage of the antimuscarinic drugs with a close follow-up. In an effort to effectively treat the patient, the dosage of either Tolterodine or Trospium was doubled. The increased dosage of Tolterodine and Trospium was generally well tolerated. Sixteen patients demonstrated a significant decrease of incontinence episodes from 8 to 12 under the recommended dosage to 0–2 with the new treatment regime. Urodynamic findings confirmed this clinical observation. The average reflex volume increased from 202 ± 68 to 332 ± 63 ml ($P < 0.001$) (Fig. 1). The cystometric capacity enlarged from 290 ± 56 to 453 ± 63 ml ($P < 0.001$) (Fig. 2). The maximum detrusor pressure dropped from 60 to 47 cm $H_2O$ ($P < 0.05$) (Fig. 3). In both groups, these results confirmed the increased effectiveness of the doubled antimuscarinic dosage.

In the 10 patients treated with Trospium, the average reflex volume increased from 177 ± 63 to 314 ± 59 ml ($P < 0.05$). The cystometric capacity enlarged from 271 ± 44 to 430 ± 51 ml ($P < 0.005$). The maximum detrusor pressure decreased from 66 to 51 cm $H_2O$ ($P < 0.05$) (Table II).

The results for the 11 patients treated by Tolterodine showed a slightly more effective treatment. The average reflex volume increased from 225 ± 68 to 350 ± 38 ml ($P < 0.05$). The bladder capacity enlarged from 308 ± 61 to 480 ± 65 ml ($P < 0.001$). The average maximum detrusor pressure dropped from 54 to 43 cm $H_2O$ ($P < 0.05$) (Table II).

In five patients the doubled medication (three using Trospium, two using Tolterodine) was stopped because of a lack of treatment benefit due to persistent clinical urinary incontinence and pathological maximum detrusor pressures still




Differences were significant between both groups ($P < 0.001$).

**Fig. 1.** Reflex Volume During First (1) and Second (2) Medication With Either Tolterodine or Tospium.

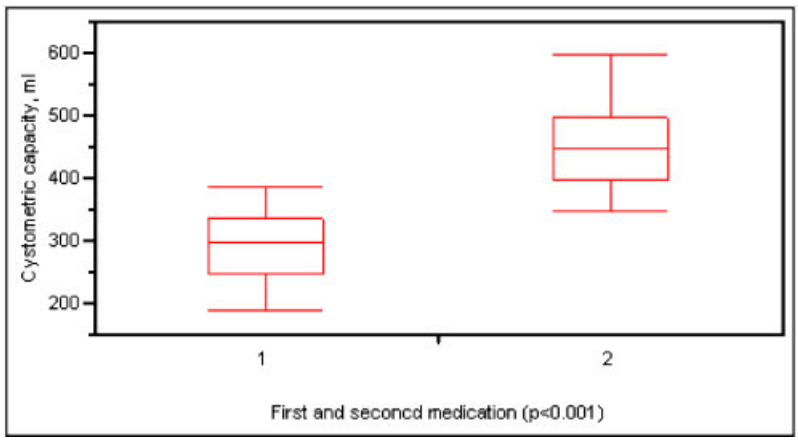
exceeding the recommended 40 cm $H_2O$. Despite the lack of clinical benefit, we observed that urodynamic parameters improved in these five patients. Reflex volume increased from 195 to 275 ml. Cystometric capacity enlarged from 245 to 345 ml. The maximum detrusor pressure dropped from 72 to 56 cm $H_2O$. Of these five patients, one patient suffered from a menigomyelocele, the second from multiple sclerosis and the other three had neurogenic bladders due to spinal cord injuries. Although these patients improved their urodynamic parameters, they did not attain the agreed upon urodymanic parameters judged as a success. These patients were then treated with either botulinum toxin or alternatively with a combination of the present antimuscarinic drug with another antimuscarinic drug.

Despite significant improvement in parameters, one patient suffering from tetraplegia while using the medication of Trospium had to stop the drug intake because of severe side effects (e.g., dizziness, dry mouth, tachycardia, and dry skin).

Mild side effects were noted in some patients. Dry mouth was noted in two patients treated by Trospium and in one patient treated by Tolterodine. Dysopia was recorded in one case and dry skin in another case (Table III). These patients continued the medication because the side effects were considered acceptable in relationship to the treatment benefit. There were no side effects affecting the central nervous system (Table III).

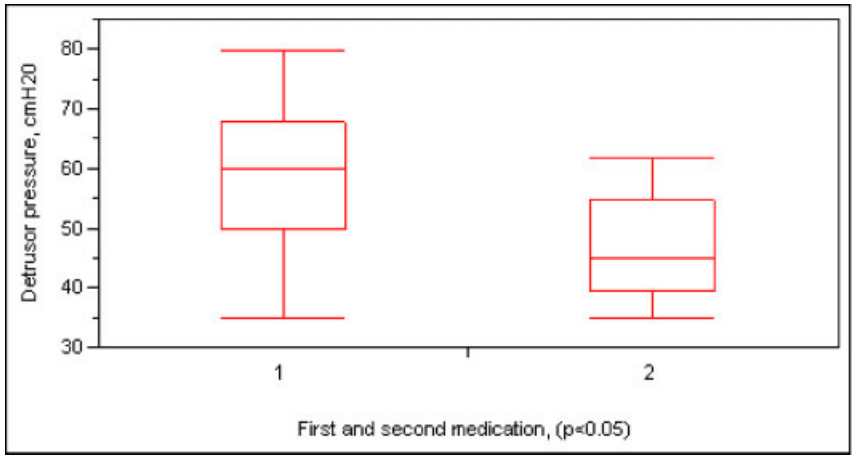
## DISCUSSION

In general, antimuscarinic drugs are a safe, well-tolerated, and effective treatment in detrusor overactivity. This was demonstrated in clinical studies performed by Halaska et al.




Differences were significant between both groups ($P < 0.001$).

**Fig. 2.** Cystometric Capacity During First (1) and Second (2) Medication With Either Tolterodine or Tospium.




Differences were significant between both groups ($P < 0.05$).

**Fig. 3.** Detrusor Pressure During First (1) and Second (2) Medication With Either Tolterodine or Tospium.

[2003] and Alloussi et al. [1998] for Trospium and Kreder et al. [2002] and Van Kerrebroeck et al. [2001] for Tolterodine. In several other studies, both drugs also proved to be effective in patients with detrusor overactivity due to neurogenic disorders [Stöhrer et al., 1991; Madersbacher et al., 1995; Osca-Garcia et al., 1997].

Still it is estimated that for approximately 30% of the patients with neurogenic detrusor overactivity, the recommended dosage of Trospium is insufficient in the treatment of incontinence, neurogenic detrusor overactivity, and low capacity bladder [Madersbacher et al., 2004]. Similar unsatisfactory results have been reported for Tolterodine [Van Kerrebroeck et al., 2001].

In addition to several other authors Ethans et al. [1995] first reported an enhanced bladder capacity and a better continence rate in 10 patients with neurogenic bladders treated by a 2 × 2 mg/day dose of Tolterodine compared to the placebo group. The same 10 patients increased the dosage of Tolterodine to a self-selected average of 8 mg/day, still improving their continence rates and bladder capacities.

In Tolterodine studies, Ethans et al. [1995] and Van Kerrebroeck et al. [1998] reported improved urodynamic parameters as well as satisfactory clinical outcome at higher-than-recommended dosages. Madersbacher et al. [2004], reported for Trospium that he noted a treatment benefit in some of the patients where the treatment dosage was increased up to 135 mg/day of Trospium. Thus, increased effectiveness was reported for both drugs at the higher treatment dosages.

The result of the present study parallels the similar clinical findings of the above noted studies. With the doubled dose, we noted significant effectiveness while recording urodynamic parameters. These results correspond to already published data in patients with neurogenic bladders [Ethans et al., 1995; Van Kerrebroeck et al., 1998; Madersbacher et al., 2004].

Statistical calculations showed highly significant improved urodynamic parameters for boths drugs regarding reflex volume, cystometric capacity, and maximum detrusor pressure (Figs. 1–3). These results may not be generalized as the value of these statistics is clearly limited by the small number of patients included in this study. However, it underlines our clinical impression of a clear treatment benefit for patients with an increased antimuscarinic treatment dosage. Further studies with higher numbers of patients are definitely needed to further elucidate this situation.

A major argument against higher than recommended dosages of antimuscarinic drugs is the increase of residual urine in correlation to the amount of administered antimuscarinic drugs, which often leads to an insufficient micturition in spontaneously-voiding patients [Guay, 1999; Todorova et al., 2001]. Fortunately, in this group of patients, this concern was irrelevant because all patients were already performing clean intermittent self-catheterization prior to doubling the

**TABLE II. Improvement of Urodynamic Parameters**

| Drug | Patients (n = 21) | First medication (mg) | Max. det. pressure (cm $H_2O$) | Reflex volume (ml) | Cystometric capacity (ml) | Second medication (mg) | Max. det. pressure (cm $H_2O$) | Reflex volume (ml) | Cystometric capacity (ml) |
|---|---|---|---|---|---|---|---|---|---|
| Trospium | n = 10 | 3 × 15 | 66 | 177 | 271 | 3 × 30 | 51 | 314 | 430 |
| Tolterodine | n = 11 | 1 × 4 | 54 | 225 | 308 | 2 × 4 | 43 | 350 | 480 |

**TABLE III. Number of Patients With Side Effects or Drop out**

| | Trospium, number of pat. (n) | Tolterodine, number of pat. (n) |
|---|---|---|
| Dry mouth | 2 | 1 |
| Dysopia | 0 | 1 |
| Dry skin | 1 | 0 |
| Drop out because of unsatisfactory benefit | 3 | 2 |
| Drop out because of severe side effects | 1 | 0 |

antimuscarinic dosage. Therefore the retention with a low pressure system are intended effects leading to a reduced number of incontinence episodes and a lower intravesical pressure [Ethans et al., 1995].

Another major concern against this form of treatment is the possible increase of unintended side effects.

With bowel constipation, this also seems to play a less important role in this group of patients, as most of them were already dependent on the regular use of laxatives and manual defecation procedures. None of the patients in our group reported about an increased difficulty regarding constipation.

Dry mouth rates were similar to those published in the recent literature on patients with neurogenic bladders. Three patients of the observed group reported dry mouth (n = 2 by Trospium and n = 1 by Tolterodine). This is similar to Van Kerrebroeck et al. [1998] who reported dry mouth in 3 patients out of 17 who were treated with a 2 × 4 mg dose of Tolterodine. Madersbacher et al. [2004] reported dry mouth rates of 36% in a group of 76 patients who were treated with Trospium doses ranging from 45 to 135 mg/day. These results were slightly higher than in our group of patients (20%).

Other side effects (dry skin, dysopia) rates in the observed group were slightly better compared to the previously discussed authors.

Only one patient had to stop the medication due to experiencing a multitude of side effects. Despite experiencing a benefit from the increased oral given drug, he suffered from dizziness, dry mouth, tachycardia, and dry skin.

Other severe side effects, especially those that might affect the central nervous system, were not reported by any of the patients in their diaries.

In conclusion, the medication was generally well tolerated as reported by the patients. Those patients who showed a satisfactory treatment benefit were highly motivated to continue the medical treatment. In comparison, the treatment with Tolterodine was slightly more efficacious especially in regard to the maximum detrusor pressure. In addition fewer side effects were reported than for Trospium. However, the number of patients was too small to show statistical relevant results.

Altogether the patient's improved their quality of life according to our observation. This was achieved without major side effects. According to our opinion, the doubled dosage became a good treatment option for the conservative management of detrusor overactivity in patients with neurogenic detrusor overactivity if the normal dosage of anticholinergic treatment fails. Due to the success of this treatment, other more invasive treatments such as the injection of botulinum toxin or surgical procedures might be postponed or even become unnecessary.

In order to confirm this treatment option, we strongly suggest continued studies with higher numbers of patients and an extended observation time.

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