Neurourology and Urodynamics 23:48–53 (2004)

Clinical Efficacy of Tolterodine With or Without a Simplified Pelvic Floor Exercise Regimen

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Objectives: To investigate whether the combination of tolterodine plus (Tp) a simple pelvic floor muscle exercise (PFME) program would provide improved treatment benefits compared with tolterodine alone (Ta) in patients with symptoms of overactive bladder (OAB). **Methods:** After a 1–2 week run-in period, 480 patients with symptoms of urinary frequency (≥8 micturitions/24 hr), urgency, and urge incontinence (≥1 episode/24 hr), were randomized to receive tolterodine 2 mg bid with or without a simple PFME program for 24 weeks in this multinational study. Treatment efficacy was assessed by comparing the change from baseline in 3-day micturition diary recordings. **Results:** After 24 weeks' treatment, in the Ta group the urgency episodes reduced from mean of 4.1 to 1.5 (83% reduction) while in the Tp group the urgency episodes reduced from 4.2 to 2.1 (78.7% reduction). Mean incontinence episodes per day decreased from 3.21 (standard deviation (SD) 3.4) to 0.95 (SD 1.9) in Ta group and from 3.44 (SD 3.4) to 1.25 (SD 2.7) in the Tp group. Similarly, the number of micturition/24 hr were significantly reduced, from 12.78 to 9.20 (27.3% reduction) in the Ta group and from 11.87 to 9.29 (23% reduction) in the Tp group. There was an improvement in the patients' perception of urinary symptoms in 85.9% of patients on Ta and 81.7% patients on Tp PFME. There were no statistically significant differences between the groups with regard to any of the outcome parameters. **Conclusions:** Tolterodine therapy for 24 weeks results in significant improvement in urgency, frequency, and incontinence, however, no additional benefit was demonstrated for a simple PFME program. *Neurourol. Urodynam. 23:48–53, 2004.*

Key words: bladder training; incontinence; overactive bladder; pelvic floor exercise; tolterodine

INTRODUCTION

Tolterodine has been shown, in many studies, to be a safe and effective antimuscarinic agent for the treatment of symptoms of detrusor overactivity [Appell, 1997; Jonas et al., 1997; Abrams et al., 1998, 2001; Drutz et al., 1999; Millard et al., 1999; Jacquetin and Wyndaele, 2001; Malone-Lee et al., 2001a,b]. Indeed, worldwide, it is now the most widely studied drug for the condition. For patients presenting with symptoms of overactive bladder (OAB), treatment often consists of behavioral bladder training, with or without antimuscarinic support. Approximately half of the patients require some pharmacological support. The National Overactive Bladder Evaluation (NOBLE) Program of prevalence studies in the USA indicate that 16.9% of the population has symptoms of bladder overactivity [Stewart et al., 2001], suggesting that the condition is too common for treatment to rely upon specialist referral. However, if urge incontinence and symptoms of OAB are to be treated in the primary care setting, adjunctive treatment like bladder training must be simple, fast, and effective enough for these busy practitioners to administer at the initial consultation. This study was designed to test the hypothesis that even a simple pelvic floor exercise program for 24 weeks might significantly augment the effects of tolterodine alone (Ta) in patients with symptoms of OAB.

METHODS

This was conducted as an international multicenter study with 54 sites. All centers secured ethics committee approval and informed individual patient consent was obtained. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Patients, aged 18–90 years, with urinary frequency (≥8 micturitions/24 hr), urgency, and urge incontinence (≥1 episode/24 hr), of at least 6 months duration, were eligible for inclusion. Exclusion criteria included symptomatic stress incontinence, significant postvoid residual volume, neuropathy, glaucoma, urinary tract infection, or positive urine cytology. Use of concomitant anticholinergic therapy within 14 days of randomization was not permitted.

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Received 12 November 2002; Accepted 11 September 2003
Published online in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/nau.10167

Study Design

After a 1–2 week washout/run-in period, patients were randomized in a ratio of 1:1 to receive 24 weeks' treatment with tolterodine 2 mg twice daily (bid) orally alone (Ta) or tolterodine 2 mg bid combined with a simple pelvic floor muscle exercise (PFME) program provided on an instruction card tolterodine plus (Tp group). Patients were not permitted to engage in bladder training or other exercise programs, and patients in group Ta were kept segregated from those in the other group.

The PFME program consisted of a two-page set of instructions which included the following: how to identify the correct muscles, the exercise program, how to use pelvic floor muscle contraction to avoid leakage ('the knack'), and having realistic expectations. Patients were expected to contract the muscles for 10 sec with a rest of 10 sec between each contraction. Patients were initially to perform 15 contractions in the morning and afternoon, with 20 contractions in the evening. The number of contractions was to be increased to 25 as muscle strength increased.

Patients' perceptions of their bladder condition at 12 and 24 weeks was determined by a 6-point Likert-type rating scale with the following categories: "no problems," "very minor problem," "minor problem," "moderate problem," "severe problem," and "many severe problems."

At screening, demographic data were collected together with history, physical examination, urinalysis, urine cytology and, where appropriate, pregnancy testing. Prior to each visit, patients completed a 3-day micturition diary. Treatment efficacy was assessed by comparing the change in micturition diary recordings from baseline (run-in period) to weeks 12 and 24 for the following variables: number of micturitions/24 hr, urinary volume voided per micturition, number of episodes of urgency, and episodes of urge incontinence/24 hr.

The safety and tolerability of treatment were assessed over the entire 24-week treatment period in terms of adverse events recorded at each visit.

Statistical Analyses

Sample size calculations were based on previous phase III studies of tolterodine 2 mg bid. Assuming a mean number of incontinence episodes/24 hr of 3.5 (standard deviation (SD) 3), in order to detect a reduction of 1 incontinence episode/24 hr after 24 weeks with alpha = 0.05 and a power of 80%, 143 patients would need to be recruited to each group. Assuming a dropout rate of 20% and accounting for non-compliance, the recommended total sample size was 500 patients.

Results were analyzed on an intention-to-treat (ITT) basis and included all randomized patients who had taken at least one dose of medication. Missing data was imputed on the principle of Last Observation Carried Forward (LOCF). Safety data were analyzed for all randomized patients. Within-group changes from baseline were analyzed using the Wilcoxon signed rank test. Between-group comparisons were made using the non-parametric Wilcoxon rank sum test. Between-group comparison of patient perception of bladder symptoms was made using the Chi-square test.

RESULTS

Of 482 patients screened for the study, 480 were randomized to treatment with either tolterodine 2 mg bid alone (group Ta; n = 253) or tolterodine 2 mg bid with PFME (group Tp; n = 227) and comprised the ITT population. Baseline demographic data for the ITT population is listed in Table I. Mean age was 53.6 and 53.2 years in the Ta and Tp groups, respectively. The majority of subjects were women (75.4%) of Asian descent (79.6%) with a duration of OAB symptoms between 6 months and 5 years. Subjects (40.3%) had prior pharmacological therapy for OAB, of which only 6.9% had previous anticholinergic therapy. There were no significant differences between groups for any of the demographic variables (Table I).

In the Ta group 81.0 and 75.5% of subjects completed 12 and 24 weeks of treatment. The addition of pelvic floor exercises did not significantly impact continuation, with 79.7 and 71.4% completing 12 and 24 weeks (group Tp). Reasons for discontinuation were similar in both groups as follows; consent withdrawn and failure to take the medication 5.6%, protocol violation 5.2%, adverse event 9.4%. Only 1.9% discontinued due to lack of efficacy.

Median baseline micturition diary variables for the Ta and Tp groups (25th and 75th centiles) were 3.0 (1.3–6.0) and 3.6 (1.3–6.0) episodes of urgency per 24-hr period, 11.3 (9.0–15.0) and 10.7 (9.0–13.7) micturitions per 24-hr period, 2.9 (1.3–3.7) and 2.3 (1.3–4.0) incontinence episodes per 24 hr, respectively. Volume voided was 132 (99–189) and 137 (98–186) ml, respectively. There were no statistically significant differences in baseline parameters between the groups (Table II).

Compliance with the BID medication regimen as assessed by unused pills, was 90% for both groups at 12 and 24 weeks. The majority of patients did not require any dose reduction. Only 3.3% of subjects had the dose lowered to 1 mg BID of tolterodine over the 24-week study period.

At both 12 and 24 weeks there were significant ($P = 0.0001$) reductions in incontinence episodes/24 hr relative to baseline in both groups. Mean incontinence episodes decreased from 3.21 (SD 3.4) to 1.1 (SD 2.2) and to 0.95 (SD 1.9) at 12 and 24 weeks in the Ta group and from 3.44 (SD 3.4) to 1.3 (SD 2.6) and 1.25 (SD 2.7) in the Tp group (Table III). A 70% reduction in mean incontinence episodes in the Ta group and a 64% change in the Tp group was seen at 24 weeks. Median values for IE were zero at 12 and 24 weeks.

Similarly, the number of micturition/24 hr were significantly reduced, from 12.78 to 9.36 (26% reduction) and 9.20 (27.3%reduction) in the Ta group and from 11.87 to 9.19 (22% reduction) to 9.29 (23% reduction) in the Tp group at 12 and 24 weeks (Table IV).

TABLE I. Baseline Demographic Data at Screening—Intention-to-Treat (ITT) Population

	Group tolterodine alone (Ta)	Group tolterodine plus (Tp) PFME	Total
No. of patients	252	223	475
Age (yrs): mean (SD), range	53.2 (17.4), 18–87	53.6 (16.9), 18–90	53.4 (17.4), 18–90
Gender = female	190 (75.4%)	169 (75.4%)	359 (75.4%)
Race			
Asian	203 (80.6%)	176 (78.6%)	379 (79.6%)
White/mix	49 (19.4%)	48 (21.4%)	97 (20.4%)
Wt (kg): mean (SD)	63.3 (14.1)	63.4 (14.2)	63.3 (14.2)
Height (cm): mean (SD)	158.4 (9.0)	158.3 (10.0)	158.3 (9.5)
Duration			
6 mo–5 yr	173 (68.7%)	166 (74.1%)	339 (71.2%)
>5 yr	78 (31%)	56 (25%)	134 (28.2%)
Prev UT surgery	43 (17.1%)	44 (19.6%)	87 (18.3%)
Prev anticholinergics	14 (5.6%)	19 (8.5%)	33 (6.9%)
Prev UUI drug	91 (36.1%)	101 (45.1%)	192 (40.3%)
Incont episodes/24 hr	3.21 (3.4)	3.44 (3.4)	3.32 (3.4)
No. of voids/24 hr	12.78 (5.6)	11.87 (4.3)	12.36 (5.0)
Mean vol./void (ml)	146.0 (83.3)	146.1 (67.7)	146.1 (76.3)
Urgency episodes/24 hr	4.1 (4.0)	4.2 (3.6)	4.2 (3.8)

No significant differences between groups.

Urgency episodes per 24 hr declined significantly in both group Ta and Tp groups (Table V). The median change between 12 and 24 weeks was statistically significant for both the Ta ($P < 0.0001$) and Tp ($P = 0.028$) groups compared with baseline. In the Ta group, urgency episodes reduced from mean of 4.1–1.9 (69.8% reduction) and 1.5 (83% reduction) at 12 and 24 weeks, respectively while in the Tp group the urgency episodes reduced from 4.2 to 2.4 (64.5% reduction) and 2.1 (78.7% reduction) (Table V). The percentage change from baseline in the medians of these parameters is depicted in Figure 1.

Median improvement in volume voided per micturition at 12 and 24 weeks was 17.5 and 19.1 ml in the Ta group which was similar to the 20.4 and 21.1 ml observed in the Tp group. There was no statistical differences with respect to any of the micturition diary variables between the two treatment groups. Mean voided volume per micturition also increased from baseline, at 12 and 24 weeks, by 15.8 and 15.4% in Ta group, and by 17.2 and 18.1% in Tp group.

Patient Perception of Bladder Symptoms

The distribution of patients' perceptions of urinary symptoms at baseline showed that, overall, the proportion of patients with "severe" or "many severe" problems was well balanced between the two groups (Ta group 56.8%, Tp group 54.0%). At 12 and 24 weeks 83.9 and 85.9% of patients in the Ta group reported an improvement in their bladder condition. The 82.6 and 81.7% of subjects in the Tp group reported improvement at 12 and 24 weeks, respectively. There were some subjects who reported at baseline that their bladder condition did not cause them any problems. It is therefore impossible for these subjects to demonstrate any improvement with the scale employed in this study. When these subjects are

TABLE II. Patient Disposition

	Group Ta N (%)	Group Tp PFME N (%)	Total N (%)
Patients randomized	253	227	448 (100)
Took medication	252 (99.6)	226 (99.6)	478 (99.6)
Completed week 2	241 (95.3)	211 (93.0)	452 (94.2)
Completed 12 weeks	205 (81.0)	181 (79.7)	386 (80.4)
Completed 24 weeks	190 (75.1)	164 (72.2)	354 (73.8)
Patients withdrawn	62 (24.5)	65 (28.6)	127 (26.5)
Adverse event	23 (9.1)	22 (9.7)	45 (9.4)
Protocol violation	10 (4.0)	15 (6.6)	25 (5.2)
Consent withdrawn	13 (5.1)	12 (5.3)	25 (5.2)
Lost to follow up	13 (5.1)	10 (4.4)	23 (4.8)
Lack of efficacy	3 (1.2)	6 (2.6)	9 (1.9)

TABLE III. Incontinence Episodes per 24 hr—ITT Population

	Group Ta	Group Tp PFME	Total	*P* value
Baseline				
No. of patients	252	224	476	
Mean (SD)	3.21 (3.4)	3.44 (3.4)	3.32 (3.4)	0.3588
Week 12				
No. of patients	242	210	452	
Mean (SD)	1.1 (2.2)	1.30 (2.6)	1.2 (2.4)	0.2215
Change (SD)	−2.15 (2.7)	−2.15 (3.0)	−2.19 (2.8)	
Median	−1.6	−1.6	−1.6	0.8251
P value within group	0.0001	0.0001	0.0001	
Week 24				
No. of patients	242	211	453	
Mean (SD)	0.95 (1.9)	1.29 (2.7)	1.1 (2.3)	
Change (SD)	−2.26 (3.0)	−2.23 (3.0)	−2.25 (3.0)	
Median	−1.6	−1.60	−1.60	0.8341
P value within group	0.0001	0.0001	0.0001	

P value within group refer to changes compared with baseline using Wilcoxon signed rank test. Test for difference based on non-parametric Wilcoxon rank sum test.

excluded to yield a population of patients with the potential for demonstrating improvement, 87.8 and 89.9% of subjects in the Ta group and 85.9 and 85.0% of subjects in the Tp group report improvement in their bladder condition at 12 and 24 weeks, respectively (Table III). There is no statistically significant difference between groups noted in patient perception of their bladder condition at any time point.

Dry mouth was the most common adverse event reported of which the majority were mild. Reported rates of mild, moderate, and severe dry mouth were 21.3, 5.1, and 3.2% in the Ta group, 18.1, 7.5, and 4.0% in the Tp group. Headache occurred in 6.0% of patients, constipation in 4.8%, nausea in 2.7%, dry eyes in 2.5%, and dizziness in 2.4%. Most of these events were of mild or moderate intensity. No other adverse event occurred in >1% of subjects.

DISCUSSION

The primary objective of this study was to test the hypothesis that the combination of tolterodine with PFME would improve the results of treatment compared with Ta. The results show significant improvements in both groups compared with baseline with respect to reduction in incontinence episodes, episodes of urgency, and number of micturitions per 24-hr period, and an increase in voided volume per micturition. However, an added benefit of PFME was not demonstrated in this trial. The results can not be interpreted as demonstrating that pelvic floor exercises are without value. Pelvic floor exercises administered alone have been shown to improve incontinence [Nygaard et al., 1996; Burgio et al., 1998, 1999]. Given the highly significant effects obtained with Ta, an additional intervention would need to act in an additive or synergistic manner to tolterodine and would need to be of sufficient magnitude to be detected with this experimental design.

TABLE IV. Number of Micturitions per 24 hr—ITT Population

	Group Ta	Group Tp PFME	Total	*P* value
Baseline				
No. of patients	252	224	476	
Mean (SD)	12.78 (5.6)	11.87 (4.3)	12.36 (5.0)	0.1331
Week 12				
No. of patients	242	210	452	
Mean (SD)	9.36 (4.6)	9.19 (3.8)	9.28 (4.3)	0.9478
Week 24				
No. of patients	242	211	453	
Mean (SD)	9.20 (5.2)	9.29 (5.0)	9.25 (5.1)	0.3549

Several RCTs have failed to demonstrate a treatment benefit for PFME [Burns et al., 1990; Lagro-Janssen et al., 1992; Sherman et al., 1997]. Clinical studies on PFME have been criticized for including a heterogeneous population of subjects with both stress and urge incontinence [Payne et al., 2000]. Nygaard et al. [1996] reported subjects with detrusor instability separately, and demonstrated improvement in: incontinence episodes, number of voids per night, urge score, and muscle strength. Number of voids per day, number of pads used, and pad weight gain did not change significantly. Burgio conducted a 3-arm study with randomization to either behavioral treatment which included PFME, oxybutynin, or placebo. The patients were postmenopausal women with urge or mixed incontinence, the latter with predominantly urge incontinence symptoms. Improvement in urge incontinence episodes was statistically significantly better in the behavioral group (80.7%) compared to the oxybutynin group (68.5%) and the placebo group (39.4%) [Burgio et al., 1998].

This study is the first to report on a population with OAB, that excluded subjects with stress and mixed incontinence.

TABLE V. Urgency Episodes per 24 hr—ITT Population

	Group Ta	Group Tp PFME	Total	*P* value
Baseline				
No. of patients	252	224	476	
Mean (SD)	4.1 (4.0)	4.2 (3.6)	4.2 (3.8)	
Week 12				
No. of patients	242	211	452	
Mean (SD)	1.9 (3.0)	2.4 (3.6)	2.1 (3.3)	NS
Change (SD)	−2.2 (3.6)	−1.9 (4.0)	−2.1 (3.8)	
Median	−1.3	−1.6	−1.4	0.7658
P value within group	0.0001	0.0001	0.0001	
Week 24				
No. of patients	242	211	453	
Mean (SD)	1.5 (2.3)	2.1 (3.1)	1.7 (2.7)	NS
Change (SD)	−2.7 (3.5)	−2.2 (3.6)	−2.5 (3.5)	
Median	−2.0	−1.9	−2.0	0.3029
P value within group	0.0001	0.0001	0.0001	

The magnitude of the effect seen on micturition diary variables and the patient perception of their bladder condition with tolterodine, is such that demonstrating an independent benefit of PFME in a pure OAB population will be very difficult. The efficacy of PFME alone in an OAB population needs to be defined in order to determine whether PFME should be instituted prior to drug therapy. The added role of PFME may still be of value in subject with mixed or stress urinary incontinence.

Mattiasson [2001] recently reported a significant benefit in micturitions/24 hr and voided volume/micturition in OAB patients who received a simple bladder training instruction sheet with tolterodine, compared to Ta. Although, in that study, the change in incontinence episodes between groups (−87% vs. −81%) was not statistically significant, there was a trend in favor of the bladder training group. The difference between those results and the results of our study show that non-pharmacological interventions are valuable, and that they are dependent on the instruction set utilized stated by Bo [1996, 2000].

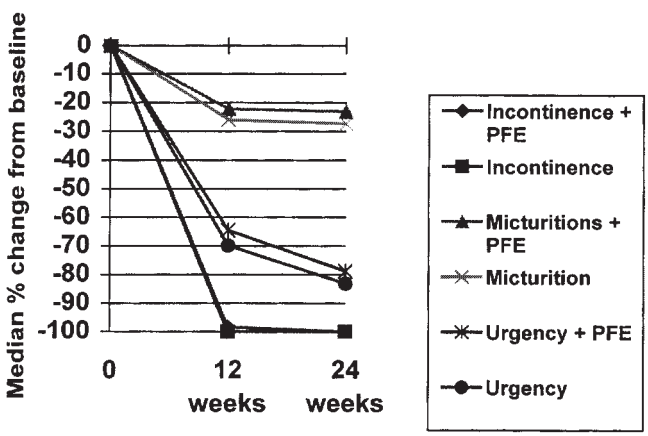

Fig. 1. Graph of median % changes from baseline for incontinence, micturitions, and urgency.

The efficacy achieved in both groups with respect to incontinence episodes was slightly higher than that reported in other studies. The median percentage improvement in incontinence episodes was 98.3 and 100% for the two groups at 12 weeks, compared to 60% reported by Van Kerrebroeck. The most likely reason for the apparent disparity is probably related to patient selection. In most studies on tolterodine between 40 and 60% of subjects have been previously treated with antimuscarinic therapy. In this study the majority of subjects were new patients, in that only 6.9% had been previously treated with antimuscarinics. Since 93.1% of the subjects in this study were in effect "new patients," the results most likely represent what one would expect when treating new patients. This is consistent with other investigators studying tolterodine who reported improved efficacy in new patients compared to those who had received prior antimuscarinic therapy.

The majority of clinical studies with antimuscarinic compounds for OAB are of 8–12 weeks in duration. Clinically, it is important to know when the maximal effect of tolterodine is achieved, and whether its effect is sustained, or tachyphylaxis occurs. This trial is the first to document micturition diary variables at 12 and 24 weeks. Figure 1 clearly illustrates that symptoms of frequency and incontinence are at maximal levels by 12 weeks of treatment. Urgency continues to improve through 24 weeks. There is no evidence of tolerance developing in that the clinical efficacy is maintained through 24 weeks. This is consistent with the data of Kreder et al. [2002] who reported maintenance of efficacy for 1 year.

Evaluating efficacy solely through micturition diaries is limited in that it does not measure the perceived value to the patient in treating their OAB symptoms [Fonda et al., 1998]. Thus improvement in diaries must be accompanied by improvements in patients' perception of their bladder condition to be clinically meaningful. Patient perception also

improved to near maximal levels at 12 weeks and was sustained through 24 weeks. For those subjects who rated their bladder condition as problematic, by the end of the study approximately 85–90% of subjects in the two groups reported improvement (Table III).

The most common side effect noted was dry mouth. Interestingly only 3.3% of subjects required a decrease in their dose from 2 mg to 1 mg BID. One may infer from this finding that starting therapy with a daily dose of 4 mg of tolterodine will provide the optimal combination of efficacy and tolerability for this drug, and very few dose adjustments will be required.

In summary, although this clinical trial did not demonstrate a therapeutic benefit for the concurrent performance of pelvic floor exercises with tolterodine, compared to administration of Ta, important information pertinent to the management of OAB was obtained. Specifically, this study provides estimates of efficacy from a diary and patient perception perspective representative of a population of subjects who have not previously received antimuscarinic therapy for their OAB. It also demonstrates that a starting dosage of 4 mg daily is well tolerated, and that 12 weeks is a sufficient duration of time to achieve maximal effect for most OAB symptoms, with the exception of urgency which requires a longer time.

ACKNOWLEDGMENTS

The following investigators took part in this study and their contribution to these results is thanked:

Australia: R.J. Millard, K. Moore, R.A. Gardiner, B. Clarke, J. Yaxley, H. O'Connell, A. McLennan, M. Chamberlain, S. Wisniewski; Indonesia: R. Yuwana, R. Sumardi, S. Hardjowijoto; Hong Kong: E.M.F. Leung, C.P. Wong; Malaysia: S. Raja Mohamed, C.S. Loh, K. Noordin; Philippines: D.T. Bolong, E. Gatchalian, E. Tan-Yap, R. Abiog, B. Cabahug, O. Escudero, V. Santos-Abalos; Singapore: P. Lim, D. Consigliere, M.K. Li, H.C. Han, M. Wong; Pakistan: S. Majeed, R. Chaudnri, R.M. Malik, S. Asif, N.H. Khan, K.J. Noorani; Taiwan: C.-P. Chang, C.-L. Cheng, W.-H. Chiu, S.-T. Huang, T.I. Hwang, Y.-H. Lee, T.H. Su, Y.-C. Tong, A.C. Wang, H.-C. Wu, C.-H. Yang, K.-J. Yu; Thailand: D. Akarasakul, P. Bunyaratavej, W. Kochakarn, S. Ruangdilokrat, S. Wudhikarn, S. Soontrapa, C. Pripatnanont.

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