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Original Article

Clinical Efficacy and Safety of Tolterodine Compared to Oxybutynin and Placebo in Patients with Overactive Bladder

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Abstract: This study compared the clinical efficacy (determined from micturition diaries) and safety of 12 weeks' treatment with either tolterodine 2 mg twice daily, oxybutynin 5 mg three times daily or placebo in patients with an overactive bladder. A total of 277 patients were randomized and treated at 25 centers. Both tolterodine and oxybutynin significantly increased volume voided/micturition compared to placebo. Both treatment groups evoked greater decreases in micturitions per 24 hours and incontinence episodes per 24 hours compared to placebo; however, only tolterodine was significantly better than placebo in reducing micturition frequency. Tolterodine and oxybutynin were equivalent in their effectiveness. Tolterodine was significantly better tolerated than oxybutynin when adverse events (particularly frequency and intensity of dry mouth), dose reduction and patient withdrawals were considered. Oxybutynin is an effective drug whose frequent adverse effects limit its clinical usefulness. Tolterodine has equivalent efficacy to oxybutynin, but with less severe adverse effects. This will allow patients to receive more effective treatment for their condition, with better compliance.

Keywords: Comparative study; Overactive bladder; Oxybutynin; Tolterodine

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Introduction

The symptoms of an overactive bladder are urgency, frequency and urge incontinence, and are caused by inappropriate contractions of the detrusor muscle during bladder filling. As detrusor contractions are mediated by cholinergic muscarinic receptor stimulation, antimuscarinic drugs have been used for the treatment of this condition [1]. The most commonly used is oxybutynin, which has been shown to be effective in controlled clinical studies [2]. However, its clinical usefulness is limited by systemic adverse effects [3], in particular a dry mouth [4,5], which may be of sufficient severity to result in poor compliance or even discontinuation of the treatment [1,6].

Tolterodine is a new, potent and competitive muscarinic receptor antagonist developed for the treatment of overactive bladder. This compound was selected for development with the objective of achieving a separation of the antimuscarinic effects on urinary bladder and salivary glands. The differences between tolterodine and oxybutynin have been demonstrated in a number of preclinical studies, including pharmacological in vitro and in vivo studies. For example, it has been shown that the two compounds are equipotent at bladder muscarinic receptors, as shown by radioligand binding and functional data. However, radioligand binding data show that tolterodine has eight times less potency than oxybutynin at the muscarinic receptors in the parotid gland [7,8]. These findings suggested that tolterodine might be an interesting therapeutic alternative for the treatment of overactive bladder.

This study was undertaken to compare the clinical efficacy and safety of tolterodine 2 mg twice daily (bid),

oxybutynin 5 mg three times daily (tid) and placebo after 12 weeks' treatment in patients with detrusor overactivity and symptoms of frequency and either urge incontinence and/or urgency.

Materials and Methods

This was a randomized, double-blind, parallel, placebo- and comparator-controlled multicenter study that was intended to enroll a total of 250 patients (100 in each active treatment group and 50 placebo patients) at 25 centers in the United States and Canada. Patients completed a 2-week washout/run-in period before randomization to treatment with tolterodine 2 mg bid, oxybutynin 5 mg tid, or placebo, for 12 weeks. To maintain blinding, a double-dummy blinding procedure was utilized. All patients took the same number of tablets in the morning, afternoon and evening. The doses were made up of both placebo and active drug. Placebo tablets had the same appearance as the tolterodine and oxybutynin tablets. Patients were seen at entry, at baseline and after 2, 4, 8 and 12 weeks of treatment. Dose reduction (tolterodine 1 mg bid; oxybutynin 5 mg bid; placebo) was permitted within the first 2 weeks of treatment in cases of intolerance to the study medication, but only as an alternative to withdrawal.

To be eligible for study inclusion the subjects (age $\geqslant$18 years) were to have understood and provided written informed consent. All female patients were to be postmenopausal, surgically sterile, or using an adequate contraceptive method before and during the study. Further inclusion criteria included evidence of detrusor overactivity on subtracted cystometry (phasic detrusor contraction with an amplitude $\geqslant$10 cmH_2O), along with urinary frequency ($\geqslant$8 micturitions on average per 24 hours) and either urge incontinence ($\geqslant$1 incontinence episode on average per 24 hours), as confirmed by micturition diaries during the run-in period, and/or urinary urgency.

Patients were excluded from the study if they fulfilled any of the following criteria: clinically significant stress incontinence as determined by the investigator during a cough stress test maneuver; hepatic or renal disease; any disease which the investigator thought made the patient unsuitable for inclusion; recurrent urinary tract infections; interstitial cystitis; uninvestigated hematuria or hematuria secondary to malignant disease; indwelling catheter or intermittent catheterization; treatment with any investigational drug in the 2 months prior to entry; previous treatment with tolterodine; electrostimulation therapy or bladder training within 14 days prior to entry or initiation during the study; treatment with any anticholinergic drug, or any drug for urinary urge incontinence within 14 days prior to the baseline visit or initiation during the study; unstable dosage of any treatment with anticholinergic adverse effects or initiation of such treatment during the study; previously demonstrated serious adverse effects on oxybutynin; average total voided volume/24 hours of >3000 ml; or clinically significant voiding difficulty with risk of urinary retention (such as residual volume >200 ml or urine flow rate <10 ml/s).

The efficacy of the different treatments was assessed for the protocol correct (PC) population (i.e. patients who completed 12 weeks' treatment, did not reduce their dosage and did not have a major protocol violation) from micturition diaries completed by the patient for 7 days prior to each visit. Treatment efficacy was measured by comparing the values after 12 weeks' treatment relative to baseline. Efficacy measures included the number of micturitions per 24 hours (primary variable), the number of incontinence episodes per 24 hours, and mean urinary volume voided per micturition.

Safety was assessed for the overall population (OP) through spontaneously reported and observed adverse events, blood pressure, and measurement of routine laboratory parameters. The severity of each adverse event was assessed by the investigator after discussion with the patient and a review of pertinent laboratory and physical findings.

Preliminary micturition diary data suggested a standard deviation (SD) of three micturitions per 24 hours. Thus, in order to have an 80% chance of detecting a difference of 1.5 in reduction of micturitions per 24 hours (α 5%), using a 1:2:2 randomization ratio, it was necessary to recruit at least 47 patients into the placebo group and 95 into the tolterodine and oxybutynin groups. A difference of 1.5 micturitions was selected based upon earlier studies, where mean baseline micturition frequency was approximately 10 micturitions per day and data indicated that a 1.5 micturition decrease would be clinically relevant to the patient [9].

Parametric and non-parametric statistical methods were used for analysis and statistical significance was set at the 5% level. The efficacy variables were analyzed using analysis of variance with the factors treatment, visit and patient within treatment and a treatment-by-visit interaction in the model. Equivalence between tolterodine and oxybutynin (for mean number of micturitions and incontinence episodes per 24 hours) was analyzed with 95% confidence intervals. As defined in the study protocol, for the micturition and incontinence variables the active treatments were considered to be equivalent if the 95% confidence for the difference with respect to reduction from baseline was within the limit of -1.5 to 1.5. Mean relative changes in laboratory safety parameters were estimated using geometric means. The percentage of patients with at least one adverse event, the percentage with dry mouth, the percentage who required dose reduction, and the percentage of withdrawals were compared between groups using the χ^2 test.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and the study protocol was approved by the Ethics Committee of each participating center.

Results

A total of 277 patients (63 males, 214 females) were randomized into the study and comprised the overall population (OP). The protocol correct (PC) population consisted of 147 patients (36 placebo, 70 tolterodine 2 mg and 41 oxybutynin), with 130 patients excluded owing to early withdrawal from the study (57 patients), dose reduction (27 patients) or protocol violation (46 patients).

The treatment groups in the OP were well balanced with regard to baseline demographic and disease characteristics and micturition diary/urodynamic variables (Table 1). No significant differences were apparent

Table 1. Demographic and baseline clinical characteristics

Variable	Treatment group		
	Placebo (n=56)	Tolterodine 2 mg bid (n=109)	Oxybutynin 5 mg tid (n=112)
Demographics			
Mean age, years (range)	62.1 (26–87)	63.0 (31–88)	66.3 (23–91)
Gender, male:female (%)	11:45 (20:80)	21:88 (19:81)	31:81 (28:72)
Caucasian (%)	52 (93)	95 (87)	105 (94)
Mean body mass index, kg/m^2	29.1 (17.2–52.8)	29.0 (18.3–56.2)	28.0 (16.0–51.4)
Disease characteristics			
Duration of symptoms >5 years (%)	25 (45)	47 (43)	41 (37)
Instability:hyperreflexia (%)	53:3 (95:5)	101:8 (93:7)	100:8 (89:7)
Urgency (%)	55 (98)	104 (95)	111 (99)
Previous drug therapy for urge incontinence, (%)	31 (55)	49 (45)	50 (45)
of which showed good efficacy response	12 (39)	20 (41)	20 (40)
Previous surgery affecting the lower urinary tract (%)	19 (34)	29 (27)	50 (45)*
Micturition diary variables			
No. of patients with $\geqslant$8 micturitions/24 h (%)	55 (98)	108 (99)	110 (98)
Mean no. of micturitions/24 h (range)	11.6 (6.6–21.9)	11.6 (7.7–22.0)	11.5 (7.1–31.4)
No. of patients with incontinence episodes (%)	50 (89)	90 (83)	103 (92)
Mean no. of incontinence episodes/24 h (range)	3.5 (0.1–14.9)	3.7 (0.1–19.9)	3.4 (0.1–13.4)
Mean volume voided/micturition, ml (range)	160 (33–371)	155 (48–290)	149 (42–315)

bid, twice daily; tid, three times daily; *P<0.05 vs placebo and tolterodine treatment groups.

Table 2. Mean micturition diary variables at baseline and after 12 weeks' treatment with placebo, tolterodine or oxybutynin for overactive bladder

Treatment group	Variable		
	Micturitions/24 h	Incontinence episodes/24 h	Volume voided/micturition (ml)
Placebo			
n	36	33	36
Baseline (SD)	11.4 (3.0)	3.6 (3.2)	160 (71)
Week 12 (SD)	10.3 (3.2)	2.6 (3.1)	172 (78)
Change from baseline (SD)	−1.1 (2.9)	−1.0 (2.2)	+12 (41)
Tolterodine 2 mg bid			
n	70	60	70
Baseline (SD)	11.7 (2.9)	3.7 (3.3)	159 (55)
Week 12 (SD)	9.7 (2.5)	1.9 (2.9)	193 (81)
Change from baseline (SD)	−2.0 (2.5)	−1.7 (2.0)	+34 (41)
P value vs placebo	0.036	0.063	0.0075
Oxybutynin 5 mg tid			
n	41	39	41
Baseline (SD)	11.6 (3.1)	3.3 (2.9)	147 (53)
Week 12 (SD)	9.6 (3.2)	1.6 (2.6)	197 (74)
Change from baseline (SD)	−2.0 (2.3)	−1.7 (1.7)	+50 (43)
P value vs placebo	0.066	0.10	0.0001
Tolterodine vs oxybutynin			
Mean difference (SEM)	0.0 (0.4)	0.0 (0.4)	NA
95% CI	−0.8 to 0.8	−0.7 to 0.7	NA

bid, twice daily; tid, three times daily; NA, not applicable.

between the treatment groups, with the exception that significantly more patients in the oxybutynin group had had previous lower urinary tract surgery than in the placebo and tolterodine groups (Table 1). Demographic and baseline characteristics of the PC population were similar to those of the OP.

A significant decrease in the number of micturitions per 24 hours was observed for each of the treatment groups between baseline and week 12 (P = 0.026 for placebo and $P < 0.001$ for tolterodine and oxybutynin groups); however, only tolterodine 2 mg bid was significantly more effective than placebo (P= 0.036) (Table 2, Fig. 1). For the variable number of incontinence episodes per 24 hours, a significant decrease was also observed for each treatment group between baseline and week 12 ($P = 0.013$ for placebo and $P < 0.001$ for tolterodine and oxybutynin groups); however, there were no significant differences between the groups after 12 weeks' treatment (Table 2, Fig. 2).

Using the predefined equivalence definitions, equivalence was demonstrated between the tolterodine and oxybutynin treatment groups for the mean change in number of micturitions and incontinence episodes per 24 hours after 12 weeks' treatment (Table 2). Equivalence between oxybutynin 5 mg tid and tolterodine 2 mg bid was also noted with other comparisons. A total of 65% oxybutynin- and 63% tolterodine-treated patients experienced at least a 50% reduction in frequency of incontinence compared to baseline. In addition, 22% of oxybutynin recipients and 21% of tolterodine-treated patients experienced a cure (i.e. no incontinence episodes during the 7-day diary collection period) of their incontinence after 12 weeks' treatment.

Both tolterodine and oxybutynin showed a significant increase from baseline in the mean volume voided/micturition compared to placebo (Table 2), and the benefit was observed throughout the treatment period. In the placebo group, the change from baseline to week 12 was not statistically significant (Fig. 3).

Adverse events were reported by 75%, 78% and 90% of patients treated with placebo, tolterodine and oxybutynin, respectively. The percentage of patients reporting at least one adverse event was significantly higher in the oxybutynin group than in either the tolterodine or placebo treatment groups ($P = 0.013$ and $P = 0.008$, respectively). The most frequently reported adverse events were autonomic nervous system disorders (22%, 32% and 73% of patients, respectively, in the placebo, tolterodine and oxybutynin treatment groups), general body disorders (placebo 26%; tolterodine 37%; oxybutynin 30%) and gastrointestinal disorders (placebo 26%; tolterodine 21%; oxybutynin 39%).

Dry mouth was the most frequently reported adverse event in each treatment group (reported by 15%, 30% and 69% of patients, respectively, in the placebo, tolterodine and oxybutynin treatment groups). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine group ($P < 0.001$). Also, the percentage of patients reporting moderate or severe dry mouth was much higher in the oxybutynin group (44%) than in the tolterodine and placebo treatment groups (9% and 7%, respectively) (Fig. 4). Other more commonly reported adverse events in the oxybutynin treatment group were dizziness (11%) and headache (10%), and in the tolterodine treatment group, headache (15%). Adverse events of possible cardiovascular origin (e.g. angina, chest pain, hypertension, hypotension and palpitation) were reported most commonly in the oxybutynin group (8.1%), with a slightly lower (but not significant)

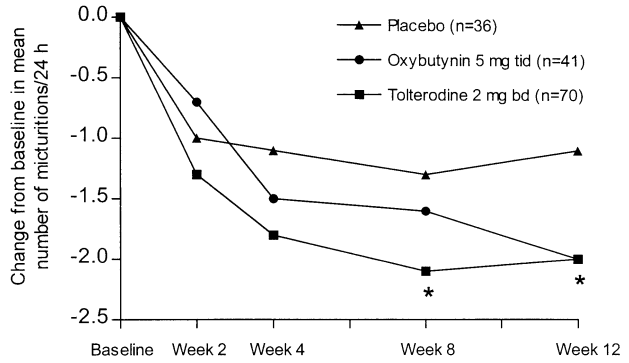

Fig. 1. Mean change from baseline in the mean number of micturitions per 24 hours; *$P \leqslant 0.05$ for tolterodine vs. placebo.

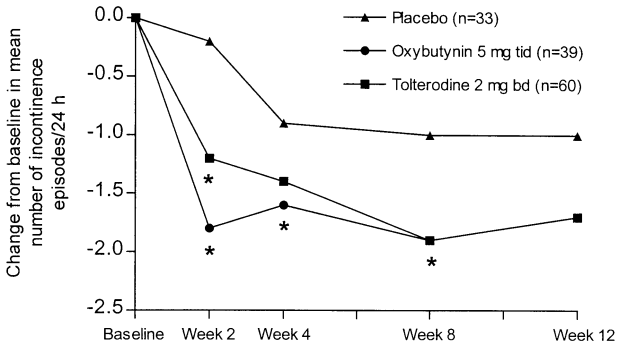

Fig. 2. Mean change from baseline in the mean number of incontinence episodes per 24 hours; *$P \leqslant 0.05$ vs. placebo.

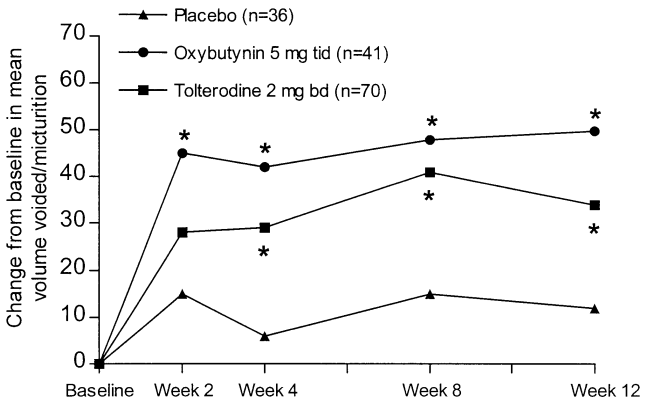

Fig. 3. Mean change from baseline in the mean volume voided per micturition; *$P \leqslant 0.05$ vs. placebo.

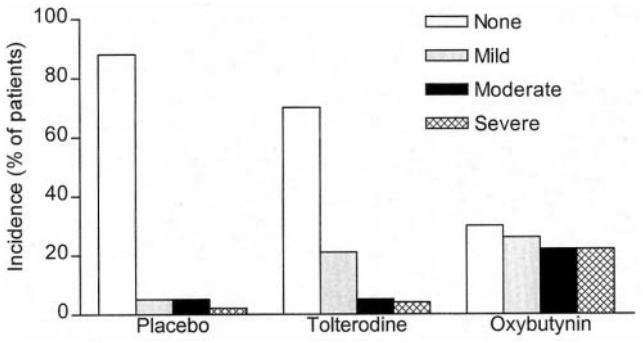

Fig. 4. Frequency and maximum intensity of dry mouth during 12 weeks' treatment with placebo, tolterodine 2 mg twice daily or oxybutynin 5 mg three times daily for overactive bladder.

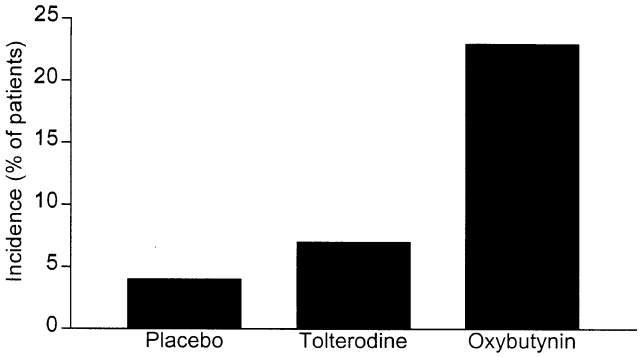

Fig. 6. Incidence of dose reduction during the first 2 weeks of treatment as a result of intolerable adverse events.

percentage in the tolterodine group (7.4%). No cardiovascular adverse events were reported in the placebo group.

A total of 57 patients withdrew from the study prior to completion of the 12-week treatment period (placebo $n = 8$ (14%); tolterodine $n = 14$ (13%); oxybutynin $n = 35$ (31%)). The primary reason was adverse events. A total of 34 patients were withdrawn because of adverse events: 4 (7%) in the placebo group, 7 (6%) in the tolterodine group and 23 (21%) in the oxybutynin group (Fig. 5). The proportion of such patients was significantly higher in the oxybutynin group than in either the tolterodine or the placebo groups ($P = 0.002$ and $P = 0.026$, respectively). The percentage of patients who withdrew for reasons other than adverse events (i.e. lost to follow-up, withdrawal of consent and protocol violation) was comparable between the groups.

Serious adverse events were reported for 6 patients: 2 (4%) in the placebo group, 1 (1%) in the tolterodine group and 3 (3%) in the oxybutynin group. None of these was considered related to the study drug by the investigator who reported the event.

Dose reduction was permitted within the first 2 weeks of treatment in the case of intolerance to the study medication, but only as an alternative to withdrawal. Dose reduction was reported for 4% ($n = 2$), 7% ($n = 8$) and 23% ($n = 26$) of placebo, tolterodine and oxybutynin patients, respectively (Fig. 6). The proportion of patients who required dose reduction was significantly higher in the oxybutynin group than in either the tolterodine or placebo treatment groups ($P < 0.001$ and $P < 0.001$, respectively). Of the dose reducers, 1 of 8 (13%) tolterodine and 8 of 26 (31%) oxybutynin patients ultimately withdrew from treatment.

Evaluation of blood pressure and laboratory safety parameters indicated no clinically significant differences between the treatment groups during the study.

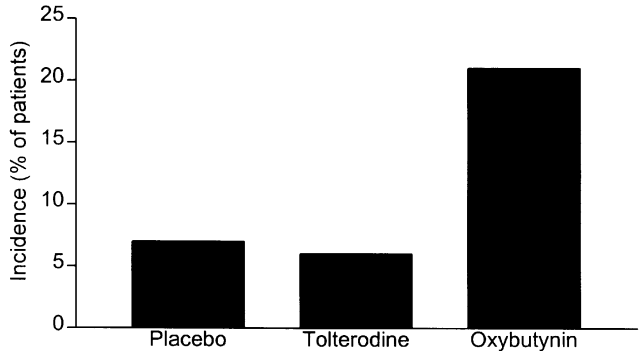

Fig. 5. Incidence of withdrawals due to adverse events.

Discussion

This well controlled study shows that at equivalent effect on micturitions and incontinence episodes, tolterodine has a superior tolerability profile to oxybutynin. Patients treated with tolterodine experienced significantly fewer episodes of dry mouth (in terms of both frequency and severity), overall adverse events, withdrawals and dose reductions than did oxybutynin-treated patients.

The efficacy variables used in the study were selected based upon their relevance to patients with overactive bladder. Change in the number of micturitions per 24 hours was selected as the primary efficacy variable. Change in the number of incontinence episodes per 24 hours, although also of relevance to the patient, was selected only as a secondary efficacy variable because not all patients with overactive bladder experience incontinence, and historically it has been difficult to demonstrate antimuscarinic efficacy on this symptom of overactive bladder [10–12]. Volume voided/micturition was selected as a secondary efficacy measure, as an increase in this variable should result in decreases in micturition and incontinence frequency. A urodynamic assessment was not performed because it is a less patient-relevant measure and significant urodynamic improvement has been previously documented with tolterodine [7]. Efficacy comparisons between tolterodine and oxybutynin were based on changes in incontinence episodes per 24 hours and micturitions per 24 hours.

Efficacy evaluations were based on the PC population in order to accurately compare the treatment effects of tolterodine 2 mg bid and oxybutynin 5 mg tid after 12

weeks' treatment. Other evaluation methods were thought to be less accurate because the maximum effect of treatment was not reached in the study until approximately 8 weeks after the initiation of treatment; the percentage of patients who reduced dose in the oxybutynin group was significantly greater than in the tolterodine group (23% versus 7%); and the percentage of oxybutynin patients withdrawing prematurely from treatment was significantly higher than the percentage of tolterodine patients (31% versus 13%). The drawback of using the PC population was that 36%, 36% and 63% of placebo, tolterodine and oxybutynin patients, respectively, were excluded from the analysis.

The efficacy of tolterodine and oxybutynin relative to placebo was most consistently demonstrated in the change in mean volume voided/micturition. A surrogate measure of bladder capacity, this increased by 20%–30% compared to baseline, and was significant for both active treatments compared to placebo. This effect was noted 2 weeks after treatment was initiated and was maintained throughout the study. Interestingly, whereas the volume voided per micturition was increased more in the oxybutynin group than in the tolterodine group, this did not translate into better effect on micturitions and incontinence episodes. This suggests that the numerical difference was not great enough to result in clinicially relevant differences in patient symptoms between tolterodine and oxybutynin.

Results for the other efficacy parameters showed only tolterodine to be significantly more effective than placebo in reducing micturitions, and neither active treatment was more effective for the incontinence variable. It appears that this may be due to two factors, the small sample sizes in the PC population and the high placebo effect. Sample size calculations performed prior to study initiation indicated that a total of 95 patients were required in the tolterodine and oxybutynin groups to have an 80% chance of showing a significant difference versus placebo. With only 41 patients in the oxybutynin and 70 in the tolterodine group, the statistical comparison lacked the power to find such significant differences. Other studies have demonstrated the significant efficacy of tolterodine compared to placebo on micturition frequency and incontinence episodes [13,14]. In addition, the effectiveness of oxybutynin in decreasing these parameters is well documented [2].

A large placebo response was noted in this study. This was not surprising, as it is well known that when treating patients with overactive bladder the placebo effect is considerable [15]. Bladder drill provides a placebo effect and is a common behavior-modifying therapy. In this technique the use of micturition diaries plays an essential role [16]. The placebo effect in this 12-week study was greater than in an earlier 2-week tolterodine study, supporting the idea that the frequent use of micturition diaries strengthens the effect of bladder drill [9]. The drawback of bladder drill is that although it provides good short-term relief in around 80% of patients, it is less effective in the longer term [17]. The clinical experience seems to be that most patients find it hard to keep up the discipline involved in the long term.

Maximum effect was not observed for any of the treatment groups until 8 weeks after treatment was initiated. A possible explanation for this can be found by understanding the coping mechanisms used by patients with overactive bladder. These include urinating to a time schedule; urinating at the first sign of urgency; and limiting fluid intake. It is reasonable to conclude that it takes a period of time after beginning treatment with drugs such as tolterodine, or with methods such as bladder drill, before patients completely trust the new control they achieve.

The equivalent efficacy found between tolterodine and oxybutynin for the effect on micturition diary variables indicated that performing direct tolerability comparisons between the two treatment groups was valid. Comparisons between the tolterodine and oxybutynin treatment groups revealed that tolterodine was significantly better tolerated than oxybutynin when adverse events (in particular dry mouth), study withdrawal and dose reductions were considered. Moreover, the superior tolerability profile of tolterodine was accompanied by improved patient compliance (as per tablet counts) compared to patients treated with oxybutynin.

The general safety of tolterodine and oxybutynin for the treatment of overactive bladder was shown in this study. The percentage of patients experiencing serious adverse events was comparable between the active treatment groups and placebo. Urinary retention was reported by only 1 patient who was treated with oxybutynin. Micturition disorders were only reported rarely, with a lower percentage of tolterodine patients than placebo- or oxybutynin-treated patients. Also, no differences were noted between the groups for blood pressure or laboratory safety parameters. One surprising safety finding was cardiovascualr events reported in the tolterodine and oxybutynin groups but not in the placebo group. This result was contrary to the overall reporting of cardiovascular adverse events in the tolterodine phase III clinical trial program, which showed that the percentage of placebo- and oxybutynin-treated patients experiencing cardiovascular adverse events was about the same (7.7% and 8.0%, respectively), with a lower percentage of tolterodine patients reporting this type of event (5.8%) (unpublished observations). Electrocardiographic measurements were not performed in this study (except at baseline), as the potential effect of tolterodine on the electrocardiogram was extensively studied in both phase I and II studies (121 subjects and 255 patients, respectively). These showed no effect of tolterodine on cardiac conduction in any patient group, including the elderly (unpublished observations).

In conclusion, the encouraging tolerability of tolterodine has implications for the treatment of patients with overactive bladder in terms of effective treatment and compliance. It is well documented that although oxybutynin is a highly effective drug, its systemic adverse effects (particularly dry mouth) may lead to frequent discontinuation of treatment or dose reduction

to dosages that may be of minimal clinical benefit [1,3,6]. In contrast, patients on tolterodine treatment should not experience these limitations and will instead be able to obtain safe and long-term effective treatment for their condition.

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EDITORIAL COMMENT: This multicenter randomized prospective study aims to test the efficacy of tolterodine 2 mg bid against oxybutynin 5 mg tid and placebo. The investigators find tolterodine to be equivalent to ditropan in effectiveness but to have fewer side effects. This increased tolerability of tolterodine should improve patient compliance and therefore the overall response rate over time.

Review of Current Literature

Which Physiologic Tests are Useful in Patients with Constipation?

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Ninety-eight patients underwent physiologic tests for the evaluation of severe constipation refractory to a rigorous bowel management program. The study was designed to identify which physiologic tests could provide a definitive diagnosis, and to assess specific historical factors that might be predictive in diagnosis. An anatomic evaluation was performed on all patients. A pretest diagnostic impression was developed from the history and physical examination, and was confirmed or refuted based on the diagnostic test(s) performed. Physiologic tests included manometry, colonic transit time, defecography, pudendal nerve terminal motor latency, balloon compliance, and pelvic floor and sphincter electromyography. The mean age was 48 years, and 84 of the 98 subjects were female. Physiologic testing did not provide information that influenced the treatment plan in 43 patients (44%). In 46 of the patients, where the pretest impression was unclear, physiologic testing defined the cause and directed management in 43 (93%). Physiologic testing was necessary to reach a diagnosis in 53% of patients tested. A history of hysterectomy, urinary incontinence and symptoms of pelvic outlet obstruction were associated with the finding of rectocele. Symptoms of outlet obstruction or dysmotility were not correlated with any particular test. Defecography and transit time studies were most useful in indiciating a definitive diagnosis. Further testing should be performed selectively based on the results of the above studies. History and physical examination are poor predictors of diagnosis.

Comment

There are no follow-up data regarding patient outcomes with intervention, and it is difficult to interpret whether the tests changed the patients' response to therapeutic intervention. However, an excellent diagnostic work-up has been provided and should be repeated. Patients with severe constipation should have history and physical examination, and some type of anatomic study to rule out a mass. A rigorous bowel program is carried out. Further testing should then consist of transit time study and defecography. Other tests may be required.