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Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation

Summary Tolterodine is a new competitive muscarinic receptor antagonist developed for the treatment of the unstable bladder. A total of 242 patients were enrolled in a multicenter, multinational, randomized, double-blind, placebo-controlled study conducted over a period of 4 weeks in patients with detrusor overactivity and symptoms of frequency, urgency, and urge incontinence. The objective of the study was to compare the efficacy and safety of tolterodine given at 1 or 2 mg b.i.d. versus placebo. At week 4 a statistically significant increase in the volume at first contraction ($p = 0.030$) and maximal cystometric capacity ($p = 0.034$) was only in the tolterodine 2 mg b.i.d. group. Tolterodine was safe and generally well tolerated. The incidence of dry mouth, as the most commonly reported adverse event, was only 9% and of mild to moderate intensity.

The symptoms of an unstable bladder are frequency, urge incontinence, and urgency. As detrusor contractions are mediated by cholinergic muscarinic receptor stimulation, antimuscarinic drugs have been used for the treatment of unstable bladders [1]. Oxybutynin is the most commonly used of these substances. Its effectiveness has been documented in controlled clinical studies [8]. However, the clinical usefulness of oxybutynin is limited by systemic side effects, particularly dry mouth [6, 7], which may be of sufficient severity to result in poor compliance or even discontinuation of treatment [1, 3].

Tolterodine is a new potent and competitive muscarinic receptor antagonist developed for the treatment of the unstable bladder. This compound was selected for development with the objective of achieving a separation of the antimuscarinic effects on the urinary bladder and the salivary glands. Data from preclinical pharmacology studies indicate that tolterodine and a major pharmacologically active metabolite (the 5-hydroxymethyl metabolite DD 01), exhibit a favorable tissue selectivity in vivo. Thus, both tolterodine and DD 01 are significantly more potent in inhibiting urinary bladder contraction than in inhibiting salivation in the anesthetized cat. Oxybutynin shows the opposite selectivity profile in this model [5].

The objective of the study was to compare the efficacy of tolterodine given at 1 or 2 mg b.i.d. versus placebo (test for difference) and evaluate the safety after 4 weeks of treatment in patients with detrusor overactivity and symptoms of frequency and either urge incontinence, urgency, or both with regard to the urodynamic variables maximal cystometric capacity, volume of first contraction, and maximal height of wave.

Patients and methods

Study design

This was a multicenter, multinational, randomized, double-blind, placebo-controlled study carried out in patients with detrusor

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overactivity and symptoms of frequency and either urge incontinence, urgency, or both. Patients were initially entered into a 2-week washout/run-in period (1 week of washout followed by 1 week of run-in). Eligible patients were then randomized to undergo treatment with tolterodine 1 or 2 mg b.i.d. or placebo for 4 weeks. Patients who had not received any therapy affecting the bladder (pharmacological treatment, electrostimulation, or bladder training) in the 7 days prior to study entry could be randomized after a run-in period of only 1 week. Patients were seen at entry (visit 1, -1 or -2 weeks), at baseline (visit 2, day 1), and at week 2 (visit 3) and week 4 (visit 4).

Schedule of investigational events

The schedule of investigational events is given in Table 1.

Study population

A total of 242 patients were enrolled in this international multicenter trial. Table 2 summarizes the patients' recruitment by country and treatment groups. The demographic and baseline characteristics are shown in Table 3.

Inclusion criteria

Men or women aged at least 18 years and presenting with detrusor overactivity, defined as the existence of any phasic detrusor contraction with an amplitude of ≥ 10 cmH_2O or the existence of one strong detrusor contraction that caused the end of the infusion, were eligible for the study. Patients were required to show evidence of frequency (≥ 8 micturitions/24 h) in combination with urge incontinence (≥ 1 incontinence episode/24 h), urinary urgency, or both.

Exclusion criteria

Patients with significant stress incontinence or with hepatic disease, defined as twice the upper limit of the reference range for liver-function tests, or renal disease, defined as twice the upper limit of the reference range for creatinine, were excluded from the study. Other exclusion criteria were any condition contraindicating anticholinergic therapy, recurrent urinary tract infections (UTIs), interstitial cystitis, univestigated hematuria, or clinically significant voiding difficulty with risk of urinary retention. In addition, patients on any anticholinergic treatment, patients using an indwelling catheter, or patients who had electrostimulation therapy or bladder training (last 14 days prior to the inclusion visit) were ineligible for the study.

Table 1 Schedule of investigational events

	Run-in/ washout	Treatment			Follow-up post-treatment
Visit	1	2	3	4	–
(days)	(−14 to−7)	(1)	(13–17)	(27–31)	(≥40)
Recording/assessment					
Background information					
Written informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographic data	X	X			
Disease history and prior therapy		X			
Concurrent disease(s) and symptom(s)		X			
Concomitant medication	X	X	X	X	X
Midstream specimen of urine for culture	X				
Efficacy					
Collection and assessment of micturition chart		X			
Patient perception of bladder condition		X		X	
Urodynamics assessment	(X)	X		X	
Safety					
Blood pressure (sitting)		X		X	
Blood samples for clincial chemistry, hematology	X			X	
ECG		X			
Adverse events			X	X	X
Other events					
Blood sample for tolterodine, DD 01	X			X	
Drug dispensing		X			
Drug accountability				X	

Table 2 Recruitment of patients according to country and treatment group

Country	centers (*n*)	Patients (*n*)	Placebo	Tolterodine 1 mg b.i.d.	Tolterodine 2 mg b.i.d.
Germany	43	159	30	63	66
Austria	9	61	11	26	24
Sweden	6	22	3	10	9
Totals	58	242	44	99	99

Treatment period

Following completion of the washout/run-in period, patients were randomized to undergo treatment with tolterodine at 1 or 2 mg b.i.d. or placebo at visit 2 (day 1). Compliance was checked by tablet counts of the returned study medication. Patients were also asked whether they had any problem with compliance. As far as possible, concomitant medication was kept unchanged during the study. Concomitant treatment with anticholinergic drugs or treatment with any agent for urinary urge incontinence (with the exception of any estrogen treatment started at more than 2 months prior to entry) was not permitted in the 14 days prior to entry or during the study. Drugs producing anticholinergic side effects were permitted, provided that the dose was kept constant during the study period. Symptomatic acute UTI occurring during the study was treated and the study medication was continued. Other treatment considered necessary for the patient's welfare was to be given at the discretion of the investigator. Any concomitant medication taken during the study was recorded.

Efficacy assessments

A urodynamic assessment was carried out at, or within the 3-month period before, baseline (visit 1 or 2) and at visit 4 (if possible, within 6 h of the last dose intake) or at withdrawal. The following urodynamic variables were evaluated:

1. Volume at first contraction ≥ 10 cmH_2O [ml]
2. Maximal height of wave ≥ 10 cmH_2O [cmH_2O]
3. Maximal cystometric capacity [ml]
4. Number of waves of contraction ≥ 10 cmH_2O
5. Empty resting pressure [cmH_2O]
6. Full resting pressure [cmH_2O]
7. Bladder compliance [ml/cmH_2O]
8. Bladder sensation, including the volume at first sensation [ml], the volume at normal desire to void [ml], and the volume at strong desire to void [ml]
9. Maximal flow rate [ml/s]
10. Detrusor pressure at maximal flow [cmH_2O]
11. Voided volume [ml]
12. Residual urinary volume [ml]

Safety assessments

The safety of the study medication was to be evaluated on the basis of blood pressure, residual volume, routine laboratory safety assessments (clinical chemistry and hematology), and spontaneously reported and observed adverse events.

A patient was to be withdrawn from treatment if the patient experienced a serious adverse events if, in the opinion of the investigator, it was medically necessary; or if the patient requested it. In the event of pregnancy, the patient was to be immediately withdrawn from the study and the code was to be broken.

Table 3 Demographic and baseline characteristics [expressed as mean values (ranges) except where indicated otherwise]

Variable	Placebo (n = 44)	Tolterodine 1 mg b.i.d. (n = 99)	Tolterodine 2 mg b.i.d. (n = 99)
Age (yrs)	57(23–92)	59(21–81)	57(20–83)
Sex: M:F, *n*(%)	11:33 (25:75)	26:73 (26:74)	23:76 (23:77)
Number (%) of patients with ≥ 8 micturitions/24 h	42 (96)	94 (95)	91 (92)
Number of micturitions/24 h	12.2 (7.3–22.0)	11.7 (0.0–25.9)	11.2 (4.1–23.4)
Number (%) of patients with incontinence episodes	38 (86)	79 (80)	83 (84)
Urodynamic variables:			
Number (%) of patients with detrusor overactivity ≥ 10 cmH_2O	44 (100)	99 (100)	97 (98)
Maximal height of wave (cmH_2O)	47 (10–140)	41 (10–220)	52 (0–224)
Volume at first contraction (ml)	140 (30–370)	142 (5–490)	141 (0–521)
Maximal flow rate (ml/s)	15 (3–60)	16 (3–45)	16 (1–81)
Maximal cystometric capacity (ml)	264 (37–540)	276 (30–682)	272 (52–687)
Residual volume (ml)	38 (0–214)	25 (0–244)	28 (0–262)

Ethical requirements

The study was performed in accordance with the Declaration of Helsinki (Hong Kong revision, 1989) and local legal requirements. The study protocol, patient information sheet, and patient consent form were approved by the relevant ethics committee for each study center. The investigator was responsible for informing the ethics committee of any serious adverse event.

Patient information and consent

The investigator was responsible for obtaining signed informed consent from each patient (or the patient's legally authorized representative) prior to entry into the study. Detailed verbal and written information related to the objective and procedures of the study and the possible risks involved was given and the patient was informed that he/she was free to withdraw from the study at any time without jeopardizing the future course of his/her treatment. Written patient information was given to each patient before enrollment.

Results

Urodynamic evaluation

It was of particular interest to compare the effect of treatment with tolterodine at 1 or 2 mg b.i.d. versus placebo on the three urodynamic variables maximal cystometric capacity, volume at first contraction, and maximal height of wave. The groups were also compared with regard to residual volume, and the results obtained for the other urodynamic variables evaluated have been summarized. There was no evidence of any important difference between the groups at baseline for any of the three urodynamic variables. However, at baseline the residual volume was greater in the placebo group than in either of the tolterodine groups, and the difference was significant for the 1 mg b.i.d. group (tolterodine at 1 mg b.i.d. versus placebo, $p = 0.029$; tolterodine at 2 mg b.i.d. versus placebo, $p = 0.063$).

Results are presented below for each variable in the following order: (a) general, (b) mean and median changes occurring over time within a treatment group, and (c) ranked data analysis of the distribution of changes over time among/between treatment groups (ITT analysis).

Volume at first contraction. The volume at first contraction, which refers to the filling volume at the first pathological detrusor contraction (≥ 10 cmH_2O), increased with respect to mean values from baseline to week 4 in all of the treatment groups (mean change: 40, 67, and 89 ml in the placebo, tolterodine 1 mg b.i.d., and tolterodine 2 mg b.i.d. groups, respectively). The median change was greater in both of the tolterodine groups than in the placebo group (median change: 0 in the placebo group, 25 ml in the tolterodine 1 mg b.i.d. group, and 44 ml in the tolterodine 2 mg b.i.d. group; Table 4).

Analysis of the ranked data showed that the change from baseline to week 4 was statistically significant in both of the tolterodine groups but not in the placebo group (placebo, $p = 0.11$; tolterodine 1 mg b.i.d. $p < 0.001$; tolterodine 2 mg b.i.d., $p < 0.001$). Treatment with tolterodine at 2 mg b.i.d. resulted in a significantly greater increase from baseline to week 4 relative to placebo ($p = 0.030$). However, there was no statistically significant difference between the placebo group and the tolterodine 1 mg b.i.d. group ($p = 0.22$).

Maximal height of wave. The maximal height of wave, which refers to the maximal height of any pathological detrusor contraction (≥ 10 cmH_2O) during the filling phase, decreased with respect to mean values from baseline to week 4 in all of the treatment groups (mean change: -7, -6, and -15 cmH_2O in the placebo, tolterodine 1 mg b.i.d., and tolterodine 2 mg b.i.d. groups, respectively). The median change was greater in both of the tolterodine groups than in the placebo group (median change:

Table 4 Volume at first contraction expressed in ml

	Placebo	Tolterodine	
		1 mg b.i.d.	2 mg b.i.d.
Number (missing[a])	44 (0)	99 (0)	98 (1)
Baseline:			
Median	113	130	116
Mean (SD)	140 (86)	142 (102)	141 (102)
Range	30–370	5–490	0–521
Week 4:			
Median	140	162	192
Mean (SD)	181 (142)	210 (163)	230 (160)
Range	3–659	6–754	0–646
Change from baseline to week 4:			
Median	0	25	44
Mean (SD)	40 (134)	67 (144)	89 (144)
Range	−183–450	−365–559	−190–600

[a]Patients for whom data were not available for either visit

-2 cmH_2O in the placebo group, -4 cmH_2O in the tolterodine 1 mg b.i.d. group, and -7 cmH_2O in the tolterodine 2 mg b.i.d. group; Table 5).

Analysis of the ranked data showed that the change from baseline to week 4 was statistically significant in both of the tolterodine groups but not in the placebo group (placebo, $p = 0.053$; tolterodine 1 mg b.i.d., $p = 0.0071$; tolterodine 2 mg b.i.d., $p < 0.001$). There was no statistically significant difference between the active treatment and the placebo group with respect to the change from baseline to week 4 in the mean maximal height of wave (tolterodine 1 mg b.i.d. versus placebo, $p = 0.97$; tolterodine 2 mg b.i.d. versus placebo, $p = 0.17$).

Maximal cystometric capacity. The maximal cystometric capacity, which refers to the volume at which the patient feels he/she can no longer delay micturition, increased with respect to mean values from baseline to week 4 in all of the treatment groups (mean change: 4, 18, and 44 ml in the placebo, tolterodine 1 mg b.i.d., and tolterodine 2 mg b.i.d. groups, respectively). The median change was 0 in the placebo and tolterodine 1 mg b.i.d. groups and 40 ml in the telterodine 2 mg b.i.d. group (Table 6).

Analysis of the ranked data showed that the change from baseline to week 4 was statistically significant in the tolterodine 2 mg b.i.d. group ($p < 0.001$) but not in the tolterodine 1 mg b.i.d. group ($p = 0.36$) or the placebo group ($p = 0.80$). Treatment with tolterodine at 2 mg b.i.d. resulted in a significantly greater increase from baseline to week 4 relative to placebo ($p = 0.034$). However, there was no statistically significant difference between the placebo groups and the tolterodine 1 mg b.i.d. group with respect to the change from baseline to week 4 ($p = 0.43$).

Residual volume. The residual volume, which refers to the urine volume remaining in the bladder immediately following spontaneous micturition, increased with respect to mean values from baseline to week 4 in all of the treatment groups (mean change: 3, 10, and 18 ml in the placebo, tolterodine 1 mg b.i.d., and tolterodine 2 mg b.i.d. groups respectively). The median change was 0 in each of the treatment groups (Table 7).

Analysis of the ranked data showed that the change from baseline to week 4 was statistically significant in the tolterodine 2 mg b.i.d. group ($p = 0.0076$) but not in the tolterodine 1 mg b.i.d. group ($p = 0.063$) or the placebo group ($p = 0.99$). Treatment with tolterodine at 1 or 2 mg b.i.d. resulted in a significantly greater increase from baseline to week 4 relative to placebo (tolterodine 1 mg b.i.d. versus placebo, $p = 0.034$; tolterodine 2 mg b.i.d. versus placebo, $p = 0.042$).

Other urodynamic variables

Number of waves of contraction. There was a statistically significant decrease from baseline for all treatment groups. No dose-response relationship was seen.

Bladder compliance. There was a statistically significant increase in bladder compliance from baseline to 4 weeks for both tolterodine groups but not for the placebo group. No dose-response relationship was seen.

Volume at first sensation. There was a statistically significant increase in the volume at first sensation from baseline to 4 weeks for both tolterodine groups but not for placebo group. No dose-response relationship was seen.

Volume at normal desire to void. There was a statistically significant increase in the volume at normal desire to void from baseline to 4 weeks for all treatment groups. The volume at normal desire to void increased with

Table 5 Maximal height of wave expressed in cmH_2O

	Placebo	Tolterodine	
		1 mg b.i.d.	2 mg b.i.d.
Number (missing[a])	44 (0)	99 (0)	98 (1)
Baseline:			
Median	36	28	38
Mean (SD)	47 (34)	41 (34)	52 (43)
Range	10–140	10–220	0–224
Week 4:			
Median	27	20	25
Mean (SD)	40 (36)	35 (36)	37 (38)
Range	10–174	10–208	0–219
Change from baseline to week 4:			
Median	−2	−4	−7
Mean (SD)	−7 (27)	−6 (31)	−15 (36)
Range	−84–68	−190–125	−181–121

[a]Patients for whom data were not available for either visit

Table 6 Maximal cystometric expressed in ml

	Placebo	Tolterodine	
		1 mg b.i.d.	2 mg b.i.d.
Number (missing[a])	44 (0)	98 (1)	98 (1)
Baseline:			
Median	268	250	255
Mean (SD)	264 (116)	276 (142)	272 (136)
Range	37–540	30–682	52–687
Week 4:			
Median	272	262	305
Mean (SD)	268 (135)	294 (151)	316 (156)
Range	45–659	32–754	16–648
Change from baseline to week 4:			
Median	0	0	40
Mean (SD)	4 (104)	18 (117)	44 (116)
Range	−250–245	−330–427	−325–327

[a]Patients for whom data were not available for either visit

dose, but there was no statistically significant dose-response relationship.

Volume at strong desire to void. There was a statistically significant increase in the volume at strong desire to void from baseline to 4 weeks for both tolterodine groups but not for the placebo group. The volume at normal desire to void increased with dose, but there was no statistically significant dose-response relationship.

Urinary maximal flow. No effect on urinary maximal flow was observed in any treatment group.

Detrusor pressure at maximal flow. There was a statistically significant decrease in the detrusor pressure at maximal flow from baseline to 4 weeks for tolterodine at 2 mg b.i.d. The detrusor pressure at maximal flow decreased slightly with dose, but there was no statistically significant dose-response relationship.

Adverse events

Overall, 25 adverse events (AEs) were reported by 17 (39%) patients in the placebo group, 34 AEs were reported by 31 (32%) patients in the tolterodine 1 mg b.i.d. group, and 43 AEs were reported by 32 (32%) patients in the tolterodine 2 mg b.i.d. group. The number of patients reporting AEs is summarized by body system and treatment group in Table 8. For each patient, each type of AE was counted only once, irrespective of the number of times it was reported.

There was no statistically significant difference between the active treatment groups and the placebo group with respect to the number of patients reporting AEs (32% in the tolterodine 1 mg b.i.d. group versus 39% in the placebo group, $p = 0.42$; 32% in the tolterodine 2 mg b.i.d. group versus 39% in the placebo group, $p = 0.46$). There was no significant difference between the active treatment groups with respect to the number of patients reporting AEs ($p = 0.92$).

Table 7 Residual volume expressed in ml

	Placebo	Tolterodine	
		1 mg b.i.d.	2 mg b.i.d.
Number (missing[a])	44 (0)	99 (0)	98 (1)
Baseline:			
Median	28	0	0
Mean (SD)	38 (53)	25 (45)	28 (47)
Range	0–214	0–244	0–262
Week 4:			
Median	5	10	10
Mean (SD)	41 (62)	35 (52)	46 (70)
Range	0–184	0–272	0–300
Change from baseline to week 4:			
Median	0	0	0
Mean (SD)	3 (54)	10 (46)	18 (63)
Range	−150–150	−95–194	−162–214

[a]Patients for whom data were not available for either visit

Table 8 Number (%) of patients reporting adverse events as summarized by body system[a]: safety population

WHO body system	Number (%) of patients		
	Placebo (n = 44)	Tolterodine 1 mg b.i.d. (n = 98)	Tolterodine 2 mg b.i.d. (n = 99)
Total number (%) of patients with at least one adverse event	17 (39)	31 (31)	32 (32)
Total number of events[b]	25	34	43
Skin and appendages	2 (5)	1 (1)	1 (1)
Musculoskeletal	2 (5)	–	–
Central and peripheral nervous system	1 (2)	–	1 (1)
Autonomic nervous system	4 (9)	11 (11)	16 (16)
Psychiatric	–	1 (1)	1 (1)
Gastrointestinal	3 (7)	5 (5)	6 (6)
Liver and biliary	–	–	1 (1)
Cardiovascular	1 (2)	–	–
Extracardiac	–	1 (1)	–
Respiratory	–	1 (1)	3 (3)
Red blood cell	–	–	1 (1)
White blood cell	–	–	1 (1)
Urinary	5 (11)	6 (6)	5 (5)
Reproductive/male[c]	1 (9)	–	–
Reproductive/female[c]	1 (3)	–	–
General disorders	4 (9)	7 (7)	6 (6)
Resistance mechanism	–	–	1 (1)
Other events	1 (2)	1 (1)	–

[a]Patients with more than one adverse event in any body system were counted only once for that body system
[b]Total number of events by WHO included term; for each patient an event was counted only once, irrespective of the number of times it was reported during the study
[c]Reported as the percentage of male (1/11) or female patients (1/33) only

Generally, AEs were reported from the same body systems, irrespective of the treatment group. In both active treatment groups, disorders of the autonomic nervous system, particularly dry mouth, were most frequently reported [11 (11%)] patients in the tolterodine 1 mg group and 16 (16%) patients in the tolterodine 2 mg group]. In the placebo group, urinary disorders were most frequently reported [reported by 5 (11%) patients].

The five most commonly reported AEs are listed in Table 9. Dry mouth was the most commonly reported AE in each active treatment group (reported by 8% of patients in the tolterodine 1 mg b.i.d. group and by 10% of patients in the tolterodine 2 mg b.i.d. group), whereas in the placebo group, one (2%) patient reported dry mouth. However, there was no statistically significant difference between either of the tolterodine groups and the placebo group in the incidence of dry mouth (tolterodine 1 mg b.i.d. versus placebo, $p = 0.18$; tolterodine 2 mg b.i.d. versus placebo, $p = 0.10$). A total of 19 patients (1 in the placebo group, 8 in the tolterodine 1 mg b.i.d. group, and 10 in the tolterodine 2 mg b.i.d. group) had dry mouth during the study (Table 10). Only one patient in the tolterodine 2 mg b.i.d. group reported dry mouth of severe intensity (Table 10). No action was taken for any of the patients with dry mouth.

Ten patients [3 (7%) in the placebo group, 4 (4%) in the tolterodine 1 mg b.i.d. group, and 3 (3%) in the

Table 9 Most commonly reported adverse events

WHO body system	Adverse event (WHO-preferred term)	Number (%) of patients		
		Placebo (n = 44)	Tolterodine 1 mg b.i.d. (n = 98)	Tolterodine 2 mg b.i.d. (n = 99)
Autonomic nervous system	Dry mouth	1 (2)	8 (8)	10 (10)
Urinary	UTI	2 (5)	5 (5)	2 (2)
Autonomic nervous system	Accommodation abnormal	–	3 (3)	5 (5)
Gastrointestinal system	Constipation	2 (5)	2 (2)	3 (3)
General disorders	Headache	1 (2)	3 (3)	3 (3)

UTI, Urinary tract infection

Table 10 Maximal intensity of dry mouth per patient as expressed in *n* (%)[a]

Maximal intensity	Placebo (n = 44)	Tolterodine 1 mg b.i.d. (n = 98)	Tolterodine 2 mg b.i.d. (n = 99)
Mild	1 (2)	5 (5)	7 (7)
Moderate	0 (0)	3 (3)	2 (2)
Severe	0 (0)	0 (0)	1 (1)
Totals	1 (2)	8 (8)	10 (10)

[a]For each patient, only the event of maximal severity was included in this summary

tolterodine 2 mg b.i.d. group] were withdrawn due to AEs. One of these patients (placebo group) was withdrawn due to a serious AE. For four patients (three in the tolterodine 1 mg b.i.d. group and one in the tolterodine 2 mg b.i.d. group) the events were judged to be of severe intensity. None of the patients discontinued treatment because of dry mouth.

Discussion

Efficacy

Urodynamics is the most important investigation for the detection of disturbances of the lower urinary tract and quantification of the degree of the pathology [2, 4]. By means of urodynamics it is possible to assess objectively the efficacy of drug treatment. The urodynamic data obtained in this study confirmed the results of previous dose-finding studies. A significant effect on bladder function was found for tolterodine at 2 mg b.i.d. after 4 weeks of treatment as expressed by the volume at first contraction and the maximal cystometric capacity.

Safety

Tolterodine was safe and generally well tolerated. Altogether, ten patients withdrew due to AEs, no more frequently in the active treatment groups than in the placebo group (tolterodine 1 mg b.i.d., 4%; tolterodine 2 mg b.i.d., 3%; placebo, 7%). No patient reported dry mouth as a factor contributing to withdrawal.

Dry mouth was mostly mild to moderate. The incidence of dry mouth in this study was lower in the tolterodine groups (9%) than that reported for oxybutynin (50%) [8], the most common pharmaceutical treatment for this indication. Other AEs were few. There was a small but clinically insignificant increase in residual urine for both active treatment groups in comparison with the placebo group. One patient on tolterodine at 2 mg b.i.d. reported urinary retention (of mild intensity), which resolved 14 days after the AE onset (study drugs were stopped for a few days) and one patient on placebo developed complete loss of spontaneous micturition which recovered two days after treatment stop.

In conclusion, with regard to efficacy, the analysis of the ranked data from the urodynamics evaluation after 4 weeks of treatment showed a statistically significantly greater increase in the volume at first contraction (p = 0.030) and the maximal cystometric capacity (p = 0.034) in the tolterodine 2 mg b.i.d. group as compared with the placebo group. With regard to safety, tolterodine given at 1 and 2 mg b.i.d. was generally well tolerated in patients with unstable bladders. There was no significant difference between the tolterodine and placebo groups in the proportion of patients with AEs. The majority of AEs were of mild to moderate intensity. The incidence of withdrawal due to AEs was similar in each group. Although dry mouth was the AE most commonly reported by patients on tolterodine, the incidence remains low. There was no significant difference between either of the tolterodine groups and the placebo group in terms of the incidence of dry mouth, and no patient had to stop treatment due to dry mouth.

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