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Proof of Principle: The Effect of Antimuscarinics on Bladder Filling Sensations in Healthy Subjects—A Placebo Controlled Double Blind Investigation Using 4 and 8 mg Tolterodine Extended Release

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Aims: There is evidence that antimuscarinic drugs have depressant influence not only on bladder muscle activity, but also on bladder sensations. The aim of this study was to evaluate the effect of a single dose tolterodine extended release (ER) 4 and 8 mg on bladder sensations during filling cystometry. **Methods:** After approval of the local ethics committee, 30 healthy female subjects (23.7 ± 2.3 years) were included and randomly assigned to three groups: (A) placebo, (B) tolterodine ER 4 mg, and (C) tolterodine ER 8 mg in a double blind manner. Measurements were performed at baseline and 4 hr postmedication in each group, consisting of: (1) Filling cystometry with 25 ml/min at which subjects had to indicate first sensation of filling (FSF), first desire to void (FDV), and strong desire to void (SDV). (2) Uroflowmetry and ultrasound control for residual urine. **Results:** In the placebo group, filling volumes at FDV and SDV decreased significantly posttreatment. This effect could not be observed for the tolterodine 8 mg group and only at SDV in the 4 mg group. No significant difference between groups was found regarding uroflowmetry parameters and postvoid residual volume. **Conclusions:** No increase of filling volumes in healthy subjects could be observed with tolterodine. However, the results suggest that tolterodine is able to alleviate irritation caused by repeated catheterization and cystometry. There was no significant influence of tolterodine ER 4 or 8 mg on voiding function. *Neurourol. Urodynam. 29:464–469, 2010.* © 2009 Wiley-Liss, Inc.

Key words: bladder afferents; bladder filling sensations; filling cystometry; lower urinary tract; tolterodine ER

INTRODUCTION

The main characteristics of the overactive bladder (OAB) are urgency with or without incontinence and frequency.[1] Urgency as the most bothersome symptom is described as a sudden, compelling desire to void, which is difficult to defer and often forces the patients to rush to the rest room. If urgency is associated with incontinence, because the patient cannot reach the toilette in time, the problem becomes even more bothersome and the quality of life is severely reduced.[2]

There are several antimuscarinic drugs on the market to treat this condition. The well known mechanism of action of these drugs is to competitively block the acetylcholine (ACh) receptors (M2, M3) on the detrusor muscle and therefore reduce detrusor overactivity (DO).[3] However, not all patients suffering from OAB show a DO in urodynamics. Nevertheless, those patients experience a benefit from antimuscarinic treatment, by means of reduced urgency and reduced frequency.[4] Especially the warning time, defined as the time from the first sensation of urgency to voluntary micturition or incontinence, is significantly increased in OAB patients taking antimuscarinics.[5] This clinical observation raises the possibility that there might be additional mechanisms of action of antimuscarinics. Antimuscarinics are usually competitive antagonists and act mainly during the storage phase, when only little or no parasympathetic outflow to the detrusor exists.[3] Recent immunohistological studies showed that the muscarinic receptors M2 and M3 could be found not only on detrusor muscle cells, but also on bladder afferent nerve endings, the interstitial cells and the urothelium itself and animal studies revealed a depressant influence of antimuscarinics like tolterodine on bladder afferent nerves.[3,6–10] Summarizing these findings, an effect of antimuscarinic drugs on the afferent pathways can be strongly assumed.

However, it is not clear, if this effect on the afferent pathway is mediated by a reversal or alleviation of pathophysiological mechanisms, as some studies might suggest, or simply on an effect on the normal sensory pathways.

Therefore, we investigated in healthy subjects the effect of 4 and 8 mg tolterodine on bladder filling sensations. Our hypothesis was that tolterodine extended release (ER) has an effect on the normal sensory pathway and will, in contrast to placebo, elevate the perception threshold for the different filling sensations, which means higher bladder volumes at first sensation of filling (FSF), first desire to void (FDV), and strong desire to void (SDV). We expected a more pronounced effect for the 8 mg group compared to the 4 mg group.

SUBJECTS AND METHODS

After approval of the local ethics committee, a volunteer sample of healthy female subjects was recruited.

Conflicts of interest: Dr. Mehnert-Trial consultant-Pfizer. Dr. Schurch-Consultant-Allergan, Astellas, Pfizer, Trial participant-Pfizer; Research grant-Pfizer.
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Inclusion criteria: Healthy female subjects aged 18–30 years. *Exclusion criteria*: Any known past or current illness of the upper and lower urinary tract (LUT) or the female genital tract (including OAB and any form of incontinence or other LUT symptoms), pregnant or breastfeeding subjects, any current general medical treatment or intervention (except seasonal allergies, routine medical examinations or check-ups and preventive consultations—but examinations or check-ups should be performed not shorter than 3 days before the assigned study day), any regular medication (except oral contraceptives, low-dose antiallergic drugs for the treatment of seasonal allergies, any occasionally taken low dose non-steroidal anti-inflammatory drugs (NSAIDs) or other over the counter pain killers are allowed but not on the examination day), any medical condition that interferes or is a contraindication for the use of tolterodine (e.g., glaucoma, myasthenia gravis, liver or renal insufficiency, allergy against anticholinergics), any neurological or psychiatric condition, any condition that suggests that the subject does not feel well or will not be able to complete the study examinations.

After written informed consent was obtained, all subjects were randomly assigned to three groups: (A) placebo, (B) tolterodine ER 4 mg, and (C) tolterodine ER 8 mg in a double blind manner. Each subject was assigned to a specific test date, on which the subject was not allowed to drink before the study investigation (except a small glass of water). Prior to the investigation each subject was checked for pregnancy and urinary tract infection (UTI), using urine dipstick tests.

The investigation consisted of a measurement at baseline and 4 hr postmedication, when maximum plasma concentrations can be expected.[11] Each measurement was performed identically in each group according to the following protocol: (1) Subjects were positioned comfortably and supine on an urodynamic examination table, wearing ear plugs to avoid possible distraction. (2) An 8 Fr transurethral microtip filling catheter (UniTip, Unisensor AG, Attikon, Switzerland) was inserted and correct positioning of the catheter was controlled by urethral pressure and fluoroscopy. Filling cystometry using body warm saline was performed with 25 ml/min and subjects had to indicate FSF, FDV, and SDV by pressing a push button. All three filling sensations were defined according to the ICS terminology and all definitions were explained comprehensibly to the subjects before the measurement.[1] The corresponding intravesical pressures and filling volumes were recorded. There was no interaction between subjects and investigator during the filling cystometry. The filling was stopped shortly after subjects indicated SDV. (3) Following cystometry, subjects were allowed to empty their bladder in an uroflowmetry-toilette, where maximum flow rate (Q_{max}), average flow rate (Q_{ave}) and voided volume were recorded. Finally, ultrasound control for postvoid residual volume (PVRV) was performed.

During the break between the baseline and postmedication measurement, the transurethral catheter was removed and subjects were allowed to dress and spend their break in the cafeteria, the relaxation room, or the hospital park.

A telephone follow up was performed 2–3 days after the investigation to check for any side effects.

All bladder volumes are presented as corrected volumes according to the following formula: (voided volume + PVRV)/cystometric capacity at SDV. The resulting factor was multiplied with the cystometric volumes at FSF, FDV, and SDV.

A sample size calculation was performed based on the few, available literature references and own pilot investigations.[12–14] The alpha level was set at 5% and the power at 80%. A pairwise double-sided analysis within one group with an expected change for FDV of 50 ml in the tolterodine 4 mg group and a standard deviation of 140 ml would require a sample size of five subjects. However, to compare between groups with an estimated difference of 20% between placebo and tolterodine 4 mg and a standard deviation of 14%, a sample size of at least nine subjects would be necessary (http://www.quantitativeskills.com/sisa/).

A statistical analysis of outcome parameters before and after treatment within each group was performed using the Wilcoxon signed ranks test in SPSS 14.0 (SPSS, Inc., Chicago, IL).

Differences in outcome parameters between groups before and after treatment were statistically analyzed using the Kruskal–Wallis test and Mann–Whitney *U* test (2-tailed) in SPSS 14.0.

RESULTS

Thirty healthy female subjects (mean age: 23.7 ± 2.3 years, mean BMI: 20.5 ± 1.7 kg/m^2) were included and equally randomized among the three groups (Table I).

As per our exclusion criteria, none of the subjects had OAB symptoms or incontinence. All subjects tolerated the measurements well and completed the whole investigation and follow up. However, catheterization and the SDV sensation were reported as rather uncomfortable but still easily tolerable. None of the subjects showed DO in the cystometries.

Only minor side effects (e.g., tiredness, slight headache) were reported in single cases from all groups.

At baseline, no significant difference between the three groups regarding age and BMI as well as for FSF, FDV, SDV, bladder compliance, Q_{max}, Q_{ave}, and PVRV could be observed (Table I). Summarizing all 30 baseline measurements, subjects showed a mean (±SD) bladder volume of 152 ml (±88.8), 309 ml (±141.8), and 646.8 ml (±194.3) at FSF, FDV, and SDV, respectively (Fig. 1).

Comparing the bladder volumes before and after treatment in each group for each filling sensation, no changes in filling volume could be observed at FSF in any group (Table I, Fig. 2).

At FDV, a significant decrease in filling volumes was found in group A, comparing pre- with post-treatment cystometry. Groups B and C showed no significant change in filling volumes at FDV, although a tendency towards elevated filling volumes after treatment could be observed in group C (Table I, Fig. 3). Nevertheless, no significant differences between groups posttreatment could be found at FDV.

At SDV, group A showed again a significant decrease in filling volumes, comparing pre- with post-treatment cystometry (Table I, Fig. 4). This time, the decrease was even more pronounced as compared to at FDV. In group B, a significant decrease in filling volumes at SDV could be found as well. Group C showed no significant change in filling volumes at SDV (Table I, Fig. 4). The comparison between groups posttreatment showed significant lower bladder volumes at SDV in group A compared to group C (Fig. 4).

The intravesical pressure decreased significantly in the placebo group at FDV and SDV. No significant changes in intravesical pressure could be observed for the tolterodine groups. Regarding the comparison of intravesical pressure between groups, no significant difference could be found before or after treatment (Table I).

For bladder compliance, Q_{max}, Q_{ave}, and PVRV no significant differences were found before and after treatment within each group or between groups (Table I).

TABLE I. Mean Values ± Standard Deviation (SD) of Age, Body Mass Index (BMI), Bladder Volumes and Intravesical Pressure at First Sensation of Filling (FSF), First Desire to Void (FDV), and Strong Desire to Void (SDV), Bladder Compliance, Maximum Flow Rate During Micturition ($FLOW_{max}$), Average Flow Rate During Micturition ($FLOW_{ave}$), and Postvoid Residual Volume (PVRV) for All Groups at Baseline (BL), and Posttreatment (PT)

	Group A n = 10 subjects		Group B n = 10 subjects		Group C n = 10 subjects	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	23.3	2.1	24.6	2.7	23.2	2.1
BMI (kg/m^2)	20.5	1.0	20.4	2.5	20.6	1.4
Bladder volume at FSF (ml)						
BL	147.80	90.58	172.19	78.02	135.95	101.88
PT	120.95	41.99	173.78	107.46	162.63	120.11
Asymp. Sig. (2-tailed)	None		None		None	
Bladder volume at FDV (ml)						
BL	298.41	119.51	354.67	156.39	274.04	149.02
PT	236.77	60.84	314.39	136.42	331.18	147.80
Asymp. Sig. (2-tailed)	$P = 0.028$		None		None	
Bladder volume at SDV (ml)						
BL	628.70	141.18	686.50	228.48	625.30	216.50
PT	414.30	76.35	583.50	239.31	576.90	153.73
Asymp. Sig. (2-tailed)	$P = 0.005$		$P = 0.047$		None	
Intravesical pressure at FSF ($cm\ H_2O$)						
BL	3.85	3.07	3.67	4.52	6.18	8.33
PT	3.76	2.96	3.85	2.44	4.54	2.47
Asymp. Sig. (2-tailed)	None		None		None	
Intravesical pressure at FDV ($cm\ H_2O$)						
BL	6.20	3.39	6.48	5.12	9.01	10.47
PT	5.12	3.06	5.55	2.87	7.10	3.44
Asymp. Sig. (2-tailed)	$P = 0.047$		None		None	
Intravesical pressure at SDV ($cm\ H_2O$)						
BL	12.12	3.19	9.11	6.09	17.92	20.64
PT	7.70	3.59	9.04	3.15	11.11	5.50
Asymp. Sig. (2-tailed)	$P = 0.005$		None		None	
Compliance ($ml/cm\ H_2O$)						
BL	55.9	22.2	123.7	132.5	71.0	72.0
PT	69.8	39.3	67.7	29.9	60.1	20.5
Asymp. Sig. (2-tailed)	None		None		None	
$Flow_{max}$ (ml/s)						
BL	34.10	15.07	42.50	16.67	41.40	19.29
PT	33.90	21.55	37.00	17.49	40.22	21.79
Asymp. Sig. (2-tailed)	None		None		None	
$Flow_{ave}$ (ml/s)						
BL	16.40	7.21	22.50	12.34	21.80	12.60
PT	14.80	9.38	18.10	8.35	19.60	11.08
Asymp. Sig. (2-tailed)	None		None		None	
PVRV (ml)						
BL	4.10	4.25	4.80	8.01	9.80	19.04
PT	3.70	4.35	29.10	61.33	18.00	19.17
Asymp. Sig. (2-tailed)	None		None		None	

DISCUSSION

Our hypothesis was that a single dose of 4 and 8 mg tolterodine ER will elevate the perception threshold for bladder filling sensations. This effect was expected to be more pronounced with 8 mg compared to 4 mg.

Our results showed that all groups had equal or similar baseline values in all measured parameters. Comparing at first the baseline filling volumes of all groups (Fig. 1) with the literature, a great similarity with the results of the study from Wyndaele et al. can be observed.[15] This accordance demonstrates quite a good reproducibility of urodynamically measured filling sensations, bearing in mind that Wyndaele et al. investigated two different subject populations with an interval of 5 years and our results are even coming from a different site.

Regarding the effect of tolterodine on the filling sensation, our hypothesis seems not correct and has to be rejected based on these data.

Although there was no elevation of filling volumes due to tolterodine, despite the tendency in group C at FDV, there was a significant decrease in filling volumes in group A at FDV and SDV, which was not observed in group C. Group B ranged in an intermediate position with a decrease of filling volumes at SDV only.

The remarkable decrease of filling volumes at SDV in the placebo group resulted in a highly significant difference between the placebo group and the tolterodine 8 mg group, in which filling volumes remained on the same level pre- and post-treatment (Fig. 4). Likewise, the pVes showed a significant reduction in the placebo group at FDV and SDV. However, this effect on the pVes was not pronounced enough to show significant differences between groups.

A possible explanation for the decreased filling volumes and pVes values in the placebo group during the second cystometry might be a sensitization of the LUT in our female study population due to the repeated catheterization and bladder filling, which led to an increased sensibility. Bladder

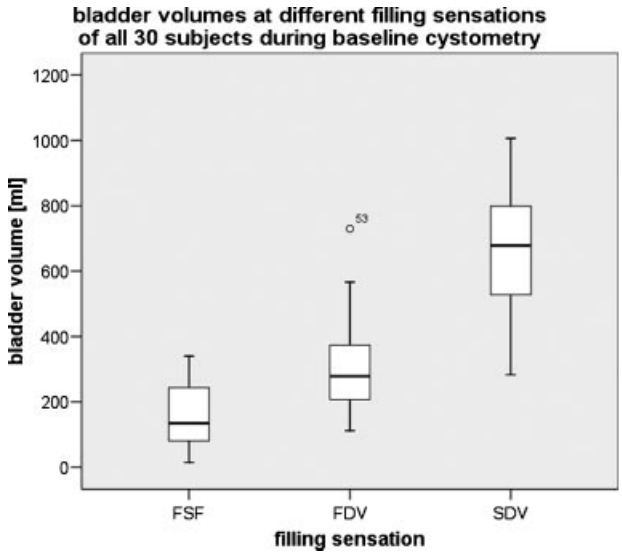

Fig. 1. Bladder volumes of all 30 subjects at first sensation of filling (FSF), first desire to void (FDV), and strong desire to void (SDV) during the baseline cystometry. The boxplots include minimum, 25% percentile, median, 75% percentile, and maximum.

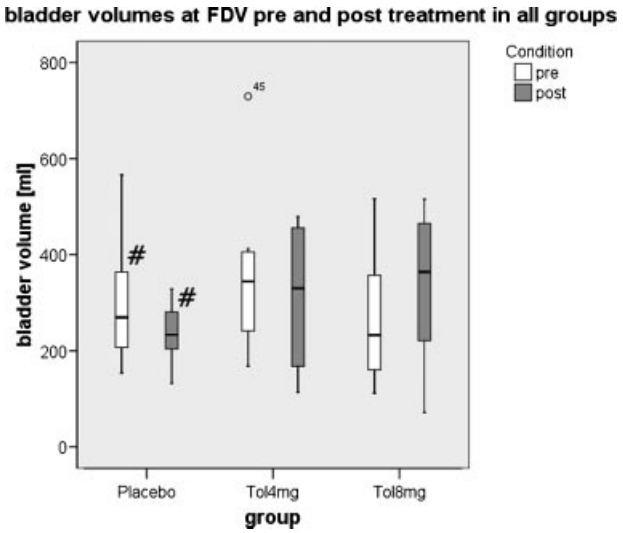

Fig. 3. The diagram shows the bladder volumes at first desire to void (FDV) in each group before (white boxplots) and after (gray boxplots) treatment. The boxplots include minimum, 25% percentile, median, 75% percentile, and maximum. $^{\#}P = 0.028$

afferent firing and subsequently most likely also the perception of filling sensations is strongly related to the intravesical pressure,[16] which in turn is mainly affected by the intravesical volume in healthy non-OAB subjects. If there is sensitization or irritation of the LUT, less intravesical pressure and therefore less volume is probably necessary to cause afferent activity of Aδ-fibers and thus the sensation of FDV and SDV. During the second cystometry, subjects in the placebo group indicated sensations earlier, before pVes reached the threshold at which the subjects had indicated sensations during the baseline cystometry, that is, the pressure threshold for perceiving filling sensations was lowered. As both, filling volume and pVes decreased, compliance remained more or less unchanged.

In group B and even more in group C, although both groups were not significantly different, the sensitization seems to be alleviated by tolterodine, as pVes and filling volumes remained constant in both tolterodine groups. From this point of view, we of course cannot argue that the LUT in the female subjects was still "normal" as it was in fact sensitized or irritated by the repeated catheterization and filling.

The few studies investigating the effect of repeated filling cystometries in healthy females reported conflicting results.[17–20] In the study of Mortensen et al.,[19] bladder volumes at FDV and SDV were significantly lower in the second compared to the first cystometry. In an older study from Sorensen et al.,[20] bladder volumes at FDV and SDV were

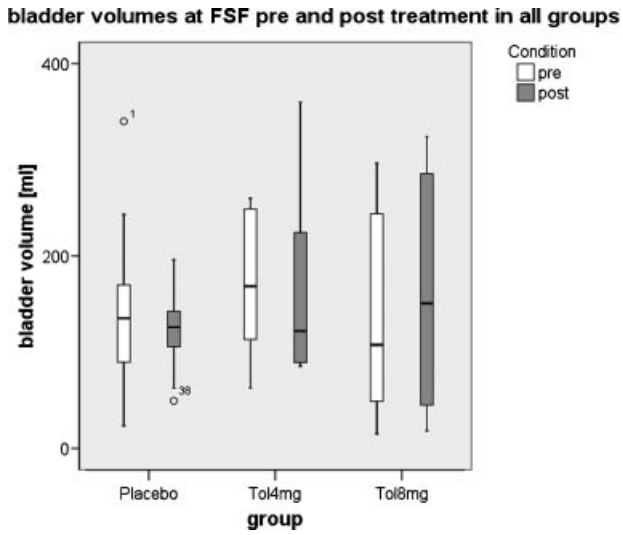

Fig. 2. The diagram shows the bladder volumes at first sensation of filling (FSF) in each group before (white boxplots) and after (gray boxplots) treatment. The boxplots include minimum, 25% percentile, median, 75% percentile, and maximum.

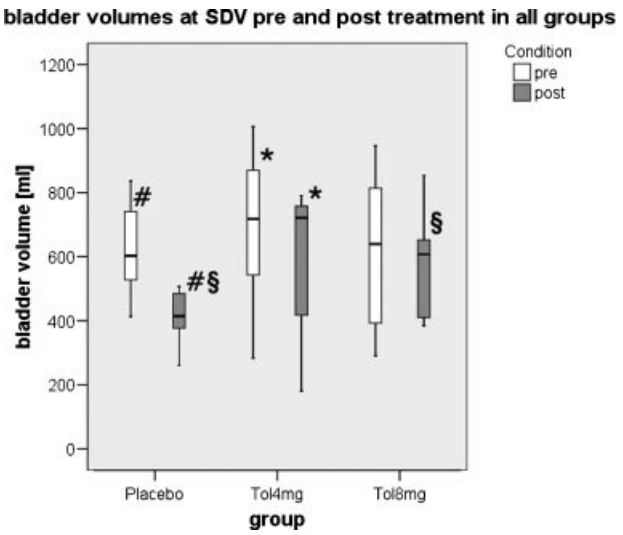

Fig. 4. The diagram shows the bladder volumes at strong desire to void (SDV) in each group before (white boxplots) and after (gray boxplots) treatment. The boxplots include minimum, 25% percentile, median, 75% percentile, and maximum. $^{\#}P = 0.005$, $^{*}P = 0.047$, $^{\S}P = 0.019$.

as well lower in the second cystometry. However, for SDV the finding was not significant. In contrast, the study of Brostrom et al.[17] showed elevated bladder volumes at FDV in the second cystometry and constant volumes at SDV. A newer study by Gupta et al.[18] showed a significant increase in FSF, FDV, and voided volumes in the second compared to the first cystometry. Nevertheless, there are two main differences between those studies and this study. First, all four previously mentioned studies performed consecutive cystometries immediately succeeding each other, leaving the transurethral catheter in place. In our study, the catheter was removed after the first cystometry and reinserted after 4 hr. A repeated catheterization probably causes irritation of the LUT. Secondly, the age range in the previously mentioned studies was very broad, ranging from 14 to 74 years, resulting in an inhomogeneous population of females previous to childbirth, after one or more pregnancies, and postmenopausal. In our study a homogeneous population of young females (20–28 years) without previous pregnancy was investigated. Age however has a considerable influence on LUT sensibility, which decreases with age.[21–23] Young women without previous childbirth have a more sensible urethra compared to elderly women or women with previous childbirth.

We therefore strongly assume that the reduced volumes and pVes values at FDV and SDV during the second cystometry observed in the placebo group are related to LUT sensitization or irritation due to the repeated catheterization and filling cystometry. As this could not be observed in the tolterodine 8 mg group, tolterodine seems to be able to reduce or prevent irritative sensations from the LUT.

However, these findings do not suggest that a single dose tolterodine ER 4 or 8 mg has an influence on unaffected healthy bladder filling sensations or that it can significantly elevate the filling perception threshold beyond baseline in health subjects.

There are only two open label, non-randomized, non-controlled single dose studies available, investigating the urodynamic effect of tolterodine in healthy subjects.[14,24] The first study by Stahl et al. was performed in 12 healthy males, who were in the same age range (21–29 years) as our female sample. Despite this, the major difference to our study was that 6.4 mg of the immediate release (IR) preparation were used. The results of this study showed that tolterodine significantly increased the volumes necessary to induce FSF and normal desire to void sensations but also significantly increased the PVRV and significantly decreased Q_{max}.[14] The most plausible reason for the different findings in our and the study of Stahl et al. are the different pharmacokinetic properties of the two formulations IR and ER.[14] The once daily ER formulation of tolterodine 4 mg has indeed a similar area under the serum concentration–time curve from 0 to 24 hr (AUC_{24}) as the 2 mg twice daily IR formulation, but maximum serum concentration (C_{max}) is significantly lower for ER, which might explain the lower rate of side effects like dry mouth or urinary retention, but also the lesser development of effects on the LUT at single dosing.[11] 6.4 mg tolterodine IR is quite a high dose, which was specifically selected to secure an effect on the bladder.[14] However, this same effect on filling sensations could not be shown in our study even with 8 mg ER.

The other study by Boy et al.[24] showed no difference in filling volumes 2 hr after oral administration of 4 mg tolterodine IR in seven healthy females. Instead, a significant increase in bladder electrical perception threshold (EPT) was observed.[24] However, bladder EPTs and filling sensations are neither related to nor are they correlated with each other and are therefore hardly comparable.[25,26] If the difference in findings between the study of Stahl et al. and Boy et al. is mainly related to the different dosage used (6.4 mg vs. 4 mg, respectively), or if the time points of urodynamic measurement also play a crucial role (1 and 5 hr postdose vs. 2 hr postdose, respectively), remains unclear. It is however surprising, that the significant increase in filling volumes at normal desire to void in the study of Stahl et al.[14] could be only detected in the 5 hr postdose cystometry but not during the cystometry 1 hr postdose, although the plasma level evaluation clearly indicated a mean C_{max} at 1 hr postdose.

In OAB, the storage phase is disturbed with urgency and frequency. The underlying pathomechanism might be neurogenic, myogenic, and/or a resulting dysbalance/dysfunction of the biochemical interaction between the urothelium, neural pathways, interstitial cells, and smooth muscle cells, which is still not completely understood. Nevertheless, dysregulation of ACh-release and muscarinic receptor expression, not only from and on the presynaptic nerve fibers, but also from and on the urothelium seems to play an important role in the pathogenesis of OAB.[3,6,27,28] Antimuscarinics have shown to be beneficial in the therapy of OAB symptoms, most probably due to their influence on ACh-release and ACh-receptor binding.[6,27] Although it is known that the main muscarinic input to the bladder occurs during the micturition phase, there is also ACh-release and ACh-receptor expression during the storage phase, which might be abnormal in the case of OAB and would explain why OAB symptoms are susceptible to antimuscarinic treatment.[3,27] In our experiment, repeated catheterization and filling cystometry probably irritated the LUT of the subjects and might have temporarily altered the ACh-release or ACh-sensitivity in the LUT. Tolterodine might have antagonized this irritation and thereby kept the filling sensations on a steady level at FDV in group B and C and at SDV in group C.

The ACh-release in the unaffected LUT of a healthy person during storage, which is supposed to be quite low, might not be affected by antimuscarinic drugs below a certain dosage. High dosage antimuscarinic treatment as used in the study of Stahl et al.[14] might cause further depression of ACh-interactions in the LUT of healthy subjects, but usually with the disadvantage of impaired bladder emptying.

As our results of the uroflow parameters and PVRV show, tolterodine ER 4 and 8 mg have little to no effect on bladder emptying in the healthy subjects, although a slight tendency towards higher PVRVs in the tolterodine groups (more with 8 than 4 mg) could be observed (Table I). This finding is probably due to the inability of the used tolterodine dosage and formulation to block the strong parasympathetic output to the detrusor in healthy subjects. Higher doses of tolterodine ER (>12.8 mg) would be more likely to result in urinary retention.[29]

In general, we cannot completely exclude that some subjects might have metabolized tolterodine differently to other subjects and did not reach the maximum plasma level around the assumed 4 hr and therefore might have influenced our findings. However, only a minor proportion of the population (e.g., 7% of Caucasians) lack CYP2D6, which is the liver enzyme mainly metabolizing tolterodine.[11] In these "poor metabolizers" serum concentrations of tolterodine are higher than in those who possess the enzyme ("extensive metabolizers"). Nevertheless, despite differences in tolterodine pharmacokinetics, exposure to the pharmacologically active moiety in extensive (sum of unbound tolterodine and 5-HM) and poor (unbound tolterodine) metabolizers is comparable regardless of metabolic phenotype. This is explained

by the 10-fold difference in the extent of tolterodine and 5-HM binding to serum proteins (unbound fractions of 3.7% and 36%, respectively).[11] In addition, the study from Olsson and Szamosi demonstrated that both, extensive and poor metabolizers show a median t_{max} of 4 hr (2–6 hr in extensive metabolizers, 3–6 hr in poor metabolizers). Due to its quite stable C_{max} over time compared to the IR form, the ER form has lower fluctuation index values.[30] Furthermore, due to the randomization, a possible influence of extensive or poor metabolism should have been minimized.

Although we worked as sterile as possible during catheterization, we did not control the urine prior to the second measurement and we cannot completely exclude a contamination of the bladder with bacteria. It might be possible that in some subjects infection was introduced at the first catheterization and that with a mean doubling time of 50 min for common bacteria an infection could have been present subclinical, which might have added to the sensitization or irritation. However, in the follow-up interview 2–3 days later, none of the subjects reported about symptoms suggesting UTI, like burning sensation during micturition, frequency, or hematuria. Thus, if a UTI occurred, it was subclinical and self-limited.

CONCLUSION

This prospective urodynamic study shows that a single dose tolterodine ER 4 and 8 mg does not increase the filling perception threshold in healthy female subjects. However, tolterodine seems to alleviate irritating symptoms caused by the repeated catheterization and filling cystometry, resulting in almost unchanged filling volumes in the 8 mg group compared to the placebo group, which showed a significant decrease in filling volumes at FDV and SDV during repeated cystometry. Tolterodine 4 mg showed a lesser and only insignificant effect compared to 8 mg. These effects of tolterodine occurred in the absence of a significant change in voiding function.

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REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37–49.
2. Starkman JS, Dmochowski RR. Urgency assessment in the evaluation of overactive bladder (OAB). Neurourol Urodyn 2008;27:13–21.
3. Andersson KE, Yoshida M. Antimuscarinics and the overactive detrusor—Which is the main mechanism of action? Eur Urol 2003;43:1–5.
4. Nabi G, Cody JD, Ellis G, et al. 2006. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane database of systematic reviews (Online)(4):CD003781.
5. Cardozo L, Dixon A. Increased warning time with darifenacin: A new concept in the management of urinary urgency. J Urol 2005;173:1214–8.
6. Abrams P, Andersson KE, Buccafusco JJ, et al. Muscarinic receptors: Their distribution and function in body systems, and the implications for treating overactive bladder. Br J Pharmacol 2006;148:565–78.
7. De Laet K, De Wachter S, Wyndaele JJ. Systemic oxybutynin decreases afferent activity of the pelvic nerve of the rat: New insights into the working mechanism of antimuscarinics. Neurourol Urodyn 2006;25:156–61.
8. Hedlund P, Streng T, Lee T, et al. Effects of tolterodine on afferent neurotransmission in normal and resiniferatoxin treated conscious rats. J Urol 2007;178:326–31.
9. Kim Y, Yoshimura N, Masuda H, et al. Antimuscarinic agents exhibit local inhibitory effects on muscarinic receptors in bladder-afferent pathways. Urology 2005;65:238–42.
10. Yokoyama O, Yusup A, Miwa Y, et al. Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol 2005;174:2032–6.
11. Olsson B, Szamosi J. Multiple dose pharmacokinetics of a new once daily extended release tolterodine formulation versus immediate release tolterodine. Clin Pharmacokinet 2001b;40:227–35.
12. Jonas U, Hofner K, Madersbacher H, et al. 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. The International Study Group. World J Urol 1997;15:144–51.
13. Rentzhog L, Stanton SL, Cardozo L, et al. Efficacy and safety of tolterodine in patients with detrusor instability: A dose-ranging study. Br J Urol 1998;81:42–8.
14. Stahl MM, Ekstrom B, Sparf B, et al. Urodynamic and other effects of tolterodine: A novel antimuscarinic drug for the treatment of detrusor overactivity. Neurourol Urodyn 1995;14:647–55.
15. Wyndaele JJ, De Wachter S. Cystometrical sensory data from a normal population: Comparison of two groups of young healthy volunteers examined with 5 years interval. Eur Urol 2002;42:34–8.
16. Habler HJ, Janig W, Koltzenburg M. Myelinated primary afferents of the sacral spinal cord responding to slow filling and distension of the cat urinary bladder. J Physiol 1993;463:449–60.
17. Brostrom S, Jennum P, Lose G. Short-term reproducibility of cystometry and pressure-flow micturition studies in healthy women. Neurourol Urodyn 2002;21:457–60.
18. Gupta A, Defreitas G, Lemack GE. The reproducibility of urodynamic findings in healthy female volunteers: Results of repeated studies in the same setting and after short-term follow-up. Neurourol Urodyn 2004;23:311–6.
19. Mortensen S, Lose G, Thyssen H. Repeatability of cystometry and pressure-flow parameters in female patients. Int Urogynecol J Pelvic Floor Dysfunct 2002;13:72–5.
20. Sorensen S, Gregersen H, Sorensen SM. Long term reproducibility of urodynamic investigations in healthy fertile females. Scand J Urol Nephrol 1988;114:35–41.
21. Kenton K, Lowenstein L, Simmons J, et al. Aging and overactive bladder may be associated with loss of urethral sensation in women. Neurourol Urodyn 2007a;26:981–4.
22. Kenton K, Simmons J, FitzGerald MP, et al. Urethral and bladder current perception thresholds: Normative data in women. J Urol 2007b;178:189–92. discussion 192.
23. Kinn AC, Nilsson BY. Urethral sensitivity in incontinent women. Eur Urol 2005;48:116–20.
24. Boy S, Schurch B, Mehnert U, et al. The effects of tolterodine on bladder-filling sensations and perception thresholds to intravesical electrical stimulation: Method and initial results. BJU Int 2007;100:574–8.
25. De Laet K, De Wachter S, Wyndaele JJ. Current perception thresholds in the lower urinary tract: Sine- and square-wave currents studied in young healthy volunteers. Neurourol Urodyn 2005;24:261–6.
26. De Wachter S, Wyndaele JJ. Can the sensory threshold toward electrical stimulation be used to quantify the subjective perception of bladder filling? A study in young healthy volunteers. Urology 2001;57:655–8. discussion 658-659.
27. Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol 2004;3:46–53.
28. de Groat WC. Integrative control of the lower urinary tract: Preclinical perspective. Br J Pharmacol 2006;147:S25–40.
29. Brynne N, Stahl MM, Hallen B, et al. Pharmacokinetics and pharmacodynamics of tolterodine in man: A new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther 1997;35:287–95.
30. Olsson B, Szamosi J. Food does not influence the pharmacokinetics of a new extended release formulation of tolterodine for once daily treatment of patients with overactive bladder. Clin Pharmacokinet 2001a;40:135–143.