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Ocular side-effects of tolterodine and oxybutynin, a single-blind prospective randomized trial

R. Altan-Yaycioglu,[1,2] O. Yaycioglu,[2,3] Y. Aydin Akova,[1] S. Guvel[2,3] & H. Ozkardes[3]

[1]*Department of Ophthalmology, Baskent University Faculty of Medicine, Ankara, Turkey,* [2]*Adana Teaching and Medical Research Center, Adana, Turkey,* [3]*Department of Urology, Baskent University Faculty of Medicine, Ankara, Turkey*

Correspondence
Rana Altan-Yaycioglu, M.D., Baskent University Adana Teaching & Medical Research Center, Department of Ophthalmology, Dadaloglu Mah. 39 Sok. No: 6, 01250 Yuregir, Adana, Turkey.
Email: raltanya@yahoo.com

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Aim
To evaluate the effects of tolterodine and oxybutynin on visual accommodation, pupillary diameter, intraocular pressure and tear secretion in women with overactive bladder.

Methods
One hundred and four eyes from 52 consecutive female patients (age range: 22–60 years) with a urodynamic diagnosis of overactive bladder were prospectively investigated. Patients with a history of ocular disease or surgery were excluded. The subjects were randomly assigned to one of two groups: Group I received 2 mg tolterodine bid and Group II received 5 mg oxybutynin tid. All patients were evaluated at baseline (day 0) and after 1 month of treatment (day 28) by an ophthalmologist who was blinded to the medication. At each time point, a complete ophthalmic examination was performed and accommodation amplitude (AA), and pupillary diameter (PD) in dim and bright light were recorded. As well, tear secretion was assessed based on tear film break-up time and Schirmer *I*-test results. Statistical comparisons were made using the chi-square test, Student's *t*-test and Mann–Whitney *U*-test, as appropriate.

Results
Twenty-eight patients (56 eyes) received tolterodine and 24 patients (48 eyes) received oxybutynin. The mean ages of the two groups were similar ($P = 0.523$). After 4 weeks of treatment, AA was significantly lower in the oxybutynin treated group ($P = 0.003$, 95% CI 0.15, 0.62) whereas there was no significant change in AA in the tolterodine treated group ($P = 0.155$, 95% CI –0.042, 0.86). At day 28, PD in dim light was significantly larger in the tolterodine treated group ($P = 0.031$, 95% CI –0.82, –0.06), whereas no significant change in PD in dim light was noted in the oxybutynin treated group ($P = 0.330$, 95% CI –0.38, 0.18)). Neither group showed a significant change in PD in bright light values on day 28 ($P > 0.05$ for both). In each group, the differences from day 0 to day 28 for intraocular pressure, and Schirmer-*I* results were insignificant ($P > 0.05$ for all). Both groups had significantly shorter tear film break-up time after 1 month of therapy ($P = 0.014$ (95% CI 0.47, 3.81) and $P = 0.02$ (95% CI 1.14, 4.61) for the tolterodine and oxybutynin treated groups, respectively).

Conclusion
Four weeks of standard-dose oxybutynin treatment in women with overactive bladder decreases AA significantly, whereas the same duration of standard-dose tolterodine does not have this effect. However, tolterodine seemed to affect PD in dim light. One month of treatment with either of these anticholinergic drugs shortens tear film break-up time significantly. Concerning ocular side-effects, tolterodine seems to offer an

advantage over oxybutynin because it does not affect AA, however, the shorter tear film break-up time with both agents suggests potential problems for patients who already have dry eye.

Introduction

Overactive bladder is a condition with symptoms of frequency, urgency and urge incontinence. It is caused by inappropriate contractions of the detrusor muscle during the filling phase of the micturition cycle. Muscarinic receptor antagonists, such as oxybutynin and tolterodine, are the main treatments for this condition [1]. Compared with oxybutynin, tolterodine is reported to have similar efficacy but cause fewer side-effects in cases of overactive bladder [2, 3]. Recently, Chapple and Nilvebrant tested these two drugs in a group of healthy subjects, and found that a single super-therapeutic 5-mg dose of tolterodine has the same effect on visual accommodation as a single standard 5-mg dose of oxybutynin [4]. In this study, we investigated the ocular side-effects of tolterodine and oxybutynin in patients with overactive bladder who were treated with standard doses of these anticholinergic medications.

Methods

The study was conducted in accordance with the Declaration of Helsinki. Local ethics committee approval was obtained. All patients read and signed an informed consent form before participating.

The subjects were female patients who were diagnosed with urodynamically proven detrusor overactivity at our centre between December 2002 and August 2003. Each of the women was screened with an initial ophthalmic examination. Those with dry eyes, ocular surface disorders, glaucoma, or issues that could affect visual acuity or accommodation (such as cataract, macular degeneration, or history of ocular surgery) were excluded from the study.

One hundred and four eyes of 52 consecutive female patients who agreed to participate were studied. Patient age ranged from 22 to 60 years. The subjects were randomly assigned to groups that received either tolterodine 2 mg bid (Group I) or oxybutynin 5 mg tid (Group II).

In each case, a comprehensive ophthalmic evaluation was performed 24 h before (day 0, baseline) and 4 weeks after the medication was started (day 28). Visual accommodation, pupillary diameter (PD) in dim and bright light, and tear secretion were also evaluated at each of these time points. All these assessments were done by one clinician (R.A-Y) who was blinded to the type of anticholinergic medication the subject was taking. Patients were also asked whether they experienced adverse symptoms, including dry mouth, burning in the eyes, and foreign-body sensation in the eyes, during the 4 weeks of treatment. Dry mouth was classified as none, mild, moderate, or severe.

Visual accommodation was evaluated as follows: The refractive power of the eyes was determined and best-corrected visual acuity (BCVA) values were recorded for Snellen chart reading at 6 m. Additional minus spheres were added until the eye was unable to overcome the minus power by accommodation, and was unable to read letters smaller than 20/25 on the chart. This was recorded as the accommodation amplitude (AA). Pupillary diameter was measured in a darkened room under dim light, and in a bright room with the brightest light of the slit-lamp using the ruler of the slit-lamp (Topcon SL-7F, Tokyo, Japan).

Intraocular pressure was measured with a noncontact tonometer (Canon Tonometer TX-10, Canon Inc., Japan).

Aqueous tear production was evaluated with the Schirmer *I*-test using Whitman filter papers and topical anaesthesia. Tear film stability was measured according to invasive tear film break-up time (TBUT) [5]. A fluorescein-impregnated strip wetted with nonpreservative saline solution was placed in the lower conjunctival sac. After one blink, the time to appearance of the first non-stained spot in the stained tear film was recorded.

The frequencies of subjective complaints between the two treatment groups were compared with Fisher's exact test. The pre- and post-treatment comparisons within each group were performed with Student's *t*-test, and the differences between groups were compared using Mann–Whitney *U*-test. The level of significance was set at $P < 0.05$.

Results

Twenty-eight patients (56 eyes) received tolterodine and 24 patients (48 eyes) received oxybutynin. All patients in both groups completed 4 weeks of treatment. The mean (±SD) ages in the tolterodine and oxybutynin treated groups were similar, at 40.2 ± 10.7 years and 42.2 ± 11 years, respectively ($P = 0.523$, *t*-test).

The complaints reported by patients after 4 weeks of treatment are shown in Table 1. Fifty per cent of the

Table 1
The patients' subjective complaints after 4 weeks of treatment. Group results were compared using the Fisher's exact test

	Tolterodine treated group ($n = 28$)		Oxybutynin treated group ($n = 24$)			
	n	%	*n*	%	χ^2	*P*
Dry mouth						
Overall	14	50.0	20	83.3	6.34	0.012*
Mild	6	21.4	0	0	5.81	0.016*
Moderate or severe	8	28.5	20	83.3	15.59	<0.001*
Burning Sensation in eyes	12	42.9	14	58.3	1.24	0.266
Foreign-body sensation in eyes	6	21.4	6	25.0	0.09	0.761
Ocular dryness	4	14.3	4	16.7	0.06	0.812

**Statistically significant. Significance was accepted as <0.05.*

Table 2
Results for the functional measurements and tests in the two groups before (day 0) and after 4 weeks of treatment (day 28). Data are expressed as mean. Comparisons of findings at the two time points were made using the Student *t*-test. Probability of <0.05 was accepted as significant

	Tolterodine treated group				Oxybutynin treated group			
	Day 0	Day 28	*P*	95% CI	Day 0	Day 28	*P*	95% CI
BCVA	0.97	0.96	0.326	–0.0075, 0.022	0.96	0.95	0.083	–0.002, 0.03
AA (D)	2.06	1.65	0.073	–0.042, 0.86	2.18	1.80	0.003*	0.15, 0.62
TBUT (s)	11.96	9.82	0.014*	0.47, 3.81	10.83	7.96	0.002*	1.14, 4.61
Sch I (mm)	12.82	12.32	0.698	–2.84, 3.83	16.21	14.83	0.375	–2.51, 5.26
IOP (mmHg)	16.86	15.96	0.054	0.02, 1.76	15.58	15.33	0.497	–0.49, 0.99
PD-dim (mm)	3.72	4.16	0.025*	–0.82, –0.06	3.69	3.79	0.468	–0.38, 0.18
PD-bright (mm)	1.94	2.02	0.174	–0.20, 0.04	2.07	2.08	0.953	–0.15, 0.14

*BCVA: Best corrected visual acuity; AA: Accommodation amplitude; D: Diopters; TBUT: Tear film break-up time; Sch I: Schirmer I-test; IOP: Intraocular pressure; PD-dim: Pupillary diameter in dim light; PD-bright: Pupillary diameter in bright light; *Statistically significant.*

patients (14 cases) in the tolterodine treated group had some degree of dry mouth, whereas the corresponding rate in the oxybutynin treated group was significantly higher, at 83.3% (20 cases) ($P = 0.012$). The two groups reported significantly different severities of dry mouth ($P = 0.002$ for frequency of mild or moderate/severe dry mouth in the tolterodine treated group *vs.* the oxybutynin treated group, Fisher's exact test). The frequencies of different subjective ocular complaints in the two groups are listed in Table 1. There were no significant differences with respect to incidence rates for burning eyes, foreign-body sensation, and ocular dryness.

The group results for the various functional measurements and tests at baseline and after 28 days of treatment are shown in Table 2. Within each group, there was no significant difference between the mean BCVA at baseline and the mean BCVA at 4 weeks ($P = 0.326$ and $P = 0.083$ in the tolterodine and oxybutynin treated groups, respectively). The change in BCVA from baseline to 4 weeks was calculated and compared between groups, and the differences from pretreatment were similar ($P = 0.609$, Mann–Whitney *U*-test).

In the tolterodine treated group, there was no significant change in AA from baseline to day 28 of tolterodine administration ($P = 0.073$). However, the

oxybutynin treated group showed a significant decrease in AA during the first 4 weeks of oxybutynin treatment ($P = 0.003$). However, the changes in AA for the tolterodine and oxybutynin treated groups were similar ($P = 0.163$). Accommodation amplitude decreased more than 1 D in three patients in the tolterodine treated group and in five patients in the oxybutynin treated group.

In the tolterodine treated group, the mean PD in dim light was significantly larger after 4 weeks of treatment ($P = 0.025$), whereas the oxybutynin treated group showed no significant change in PD in dim light from baseline to 4 weeks ($P = 0.468$). The changes in PD in dim light for the two groups were not different ($P = 0.195$).

For PD in bright light, there was no significant difference after 4 weeks of treatment in either group ($P = 0.174$ and 0.953 for the tolterodine and oxybutynin groups, respectively), and comparison of the changes in PD in bright light for the two groups also revealed no significant difference ($P = 0.308$).

There were no significant differences between the baseline findings and the day 28 findings for IOP measurements or Schirmer *I*-values in either group ($P > 0.05$ for all). Additionally, intergroup comparison of the results for these parameters at each time point revealed no significant differences ($P > 0.05$ for all).

Concerning tear secretion, both groups had significantly shorter mean TBUT after 28 days of treatment ($P = 0.014$ for the tolterodine treated group and $P = 0.002$ for the oxybutynin treated group).

Discussion

Tolterodine and oxybutynin are muscarinic receptor antagonists that are frequently used to treat overactive bladder. The clinical value of anticholinergic agents for overactive bladder is limited by the adverse systemic effects of these drugs. Dry mouth is the most common and bothersome adverse effect of anticholinergics. In our comparative study of these two drugs, the oxybutynin group had a significantly higher frequency of dry mouth with significantly greater severity of this side-effect. Similar findings have been reported by others as well [2, 3, 6].

For the side-effect of burning sensation in the eyes, we observed frequencies of 42.9% and 58.3% in the tolterodine treated group (2 mg bid) and the oxybutynin treated group (5 mg tid), respectively. Several factors may have contributed to these unusually high incidences of ocular complaints. First, the women might have been more sensitized to ocular complaints because of the detailed ophthalmic evaluation they had undergone. It is also possible that dry eye has been under-reported in previous studies because patients were not specifically asked about this symptom. Our findings of significantly reduced TBUT (approximately 2 s) in both groups were in line with the high frequencies of burning eyes. Tear film break-up time is a test that evaluates the profile of the tear film [7]. Lacrimal glands have M_3-subtype muscarinic receptors [8] and therefore dry eye or abnormal tear secretion is fairly common in patients who are taking anticholinergic medication. In our study, neither group showed a significant change in Schirmer *I*-values after 4 weeks of therapy; however, this test is also affected by reflex tear secretion caused by stimulation of eyelids and eyelashes [9]. Dry eye is a condition that is easily overlooked. We stress that physicians and urologists who treat cases of overactive bladder should be cognisant of this entity and warn patients about this potential side-effect when prescribing antimuscarinic agents.

Abrams and colleagues reported abnormal accommodation in 3% of tolterodine- and 7% of oxybutynin-treated patients [3]. Chapple and Nilvebrant compared visual accommodation in healthy subjects who received a single super-therapeutic dose of 5 mg tolterodine or single 2.5-mg, 5-mg, or 7.5-mg doses of oxybutynin [4]. The area under the curve for accommodation values for 5 mg tolterodine was similar to the values for 5 mg and 7.5 mg oxybutynin. The authors measured the maximum change from baseline accommodation, and observed a linear increase with oxybutynin dose (13, 20 and 29% for 2.5, 5, and 7.5 mg doses, respectively). The maximum change with 5 mg tolterodine was 20%, matching the value for 5 mg oxybutynin. We investigated AA, and PD after 4 weeks of treatment with standard doses of both these agents. The accommodation data revealed lower AA in both groups at the 28-day stage, but only the subjects who received oxybutynin showed a significant difference from baseline to 4 weeks. This suggests that oxybutynin has a negative effect on accommodation and may result in blurred vision more frequently than tolterodine.

In one canine study, animals that were placed under general anaesthesia and received anticholinergic medication showed no significant rise in IOP, and the IOP values were similar to those in a group of dogs who received intravenous saline [10]. However, findings in humans with closed-angle glaucoma indicate that anticholinergics may increase IOP [11, 12]. In our study of women with overactive bladder, we observed no changes in IOP from baseline to after 4 weeks of treatment with either tolterodine or oxybutynin. This suggests that neither of these agents affects IOP in patients without glaucoma. However, since anticholinergics are

contraindicated in glaucoma, we feel that tolterodine and oxybutynin should be avoided in patients with this condition.

Some research has demonstrated that anticholinergic medication does not alter PD in dogs [10], whereas other work has shown that these agents cause mydriasis in men [11]. In our study, we evaluated PD under the bright and dim light of the slit-lamp. In both groups, after 4 weeks of treatment we found that PD in bright light had not changed significantly from baseline. Similarly, we observed no significant change in PD in dim light in the oxybutynin-treated group. In contrast, the tolterodine-treated patients showed significantly larger PD in dim light at 28 days (from 3.72 mm at baseline to 4.16 mm at 4 weeks). This is an unexpected finding since we would anticipate a greater change in PD in bright light rather than PD in dim light and a larger difference in the oxybutynin treated group since oxybutynin showed a greater effect on AA. However, the difference for the change with treatment was insignificant when both groups were compared. Thus, we believe that this measure should be further evaluated with larger patient numbers. This finding also suggests that patients who are prescribed tolterodine should be warned about glare during night driving.

Our investigation compared ocular side-effects and subjective complaints in women with overactive bladder who received 4 weeks of standard-dose anticholinergic treatment. In summary, the most important findings were that oxybutynin decreased AA significantly, and both oxybutynin and tolterodine reduced aqueous tear secretion markedly. We stress that patients who are prescribed these medications for overactive bladder should be warned and asked about dry eye. If an individual already has this condition, an ophthalmologist should be consulted before prescribing any anticholinergic, or else alternative treatment modalities should be considered. It is also important to note that this study investigated the ocular effects of tolterodine 2 mg bid and oxybutynin 5 mg tid, whereas extended-release once-daily forms of both these agents are now available. The ocular side-effects of these forms and newly released anticholinergic agents should also be investigated to determine whether our findings also apply in these treatment settings.

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