146

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NIGHTTIME DOSING OF TOLTERODINE REDUCES OVERACTIVE BLADDER–RELATED NOCTURNAL FREQUENCY IN PATIENTS WITH OVERACTIVE BLADDER AND NOCTURIA

Hypothesis / aims of study

Tolterodine is indicated for overactive bladder (OAB), which is defined as urinary urgency with or without urgency urinary incontinence, usually with frequency and nocturia [1]. Nocturia can negatively affect quality of life by interrupting sleep, which in turn, can lead to daytime fatigue. We evaluated the efficacy and safety of nighttime dosing of tolterodine on nocturnal urinary urgency and frequency in patients with OAB and nocturia.

Study design, materials and methods

We analyzed data from a 12-week, double-blind, placebo-controlled study of nighttime dosing (≤4 h before bed) of tolterodine extended release (ER; 4 mg QD) in patients with OAB (≥8 micturitions/24 h) and nocturia (mean ≥2.5 episodes/night). The primary endpoint, change in mean number of nighttime micturitions, was assessed using a 7-day diary. At the time of each micturition, patients rated the degree of urgency using a 5-point urgency rating scale: 1 = "I felt no need to empty my bladder but did so for other reasons," 2 = "I could postpone voiding as long as necessary without fear of wetting myself," 3 = "I could postpone voiding for a short time without fear of wetting myself," 4 = "I could not postpone voiding but had to rush to the toilet in order not to wet myself," and 5 = "I leaked before arriving at the toilet" [2]. Micturitions associated with an urgency rating of 1–2 were considered non-urgency, micturitions associated with a rating of 3 were borderline urgency (were or were not associated with urgency depending on how the patient interpreted "a short time"), and micturitions associated with ratings of 4–5 were clearly associated with urgency. A rating of 5 was counted as an urgency incontinence episode and a micturition. Individual micturitions were analyzed post hoc by urgency rating category: total micturitions (1–5), non-OAB micturitions (1–2), OAB micturitions (3–5), and severe OAB micturitions (4–5).

Results

850 patients (mean age, 59 y) were randomized to tolterodine ER (n=421) or placebo (n=429). Treatment groups were comparable at baseline; 49% of patients were men, and 77% were continent (<5 incontinence episodes/wk). Compared with placebo, tolterodine ER significantly reduced mean urgency rating (P<0.01), as well as OAB and severe OAB nighttime, daytime, and 24-hour micturitions **(Table)**. Tolterodine ER had no effect on normal micturitions (1–2). At week 12, significantly more patients taking tolterodine ER compared with placebo reported a benefit of treatment (62% vs 51%; P=0.0013) and a willingness to continue treatment (60% vs 49%; P=0.008). Adverse events associated with tolterodine ER versus placebo were low (dry mouth, 9% vs 2%; constipation, 3% vs 2%; headache, 2% vs 1%). Withdrawals due to adverse events (1% vs 4%) also were low.

Interpretation of results

Daytime efficacy of tolterodine ER was not compromised in this nighttime dosing study. Although a significant reduction in the total number of nighttime micturitions was not observed, significantly greater decreases in nighttime, daytime, and 24-hour micturition frequency for OAB micturitions (3–5) and severe OAB micturitions (4–5) were achieved with tolterodine ER compared with placebo. Nighttime dosing of tolterodine ER resulted in fewer adverse events and withdrawals due to adverse events compared with placebo.

Concluding message

These results suggest that: (1) tolterodine ER reduced OAB nighttime micturitions; (2) patients who have effectively managed their OAB symptoms with daytime tolterodine ER dosing might consider a nighttime regimen to further reduce the potential occurrence of

adverse events; and (3) OAB micturition should be considered a meaningful clinical endpoint for efficacy monitoring.

Table. Summary of Results

	Placebo (n=429)			Tolterodine ER (n=421)		
	Mean Micturition Frequency/Wk		Median % Change	Mean Micturition Frequency/Wk		Median % Change
	Baseline	Change		Baseline	Change	
Nighttime						
Total	24.6	–5.1	–18.5	24.6	–5.5	–23.1
OAB	17.2	–3.5	–21.7	16.6	–4.6*	–30.0**
Severe OAB	7.2	–1.7	–42.5	6.7	–2.6**	–58.6*
Daytime						
Total	68.6	–5.1	–8.3	68.5	–9.1***	–11.5**
OAB	42.5	–3.4	–8.3	41.1	–7.0**	–16.7**
Severe OAB	16.9	–2.5	–30.0	14.8	–5.6***	–51.7*
24-hour						
Total	93.4	–10.2	–9.4	93.1	–14.7**	–14.7**
OAB	59.6	–6.9	–11.5	57.7	–11.5**	–18.1**
Severe OAB	24.2	–4.1	–30.2	21.6	–8.2***	–50.0*
	Mean Change in Urgency Rating					
Nighttime	0.00			–0.11***		
Daytime	0.00			–0.10**		
24-hour	–0.01				–0.12**	

OAB=overactive bladder.
*P<0.05; **P<0.01; ***P<0.001.

References

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2. European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products. *Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence.* CPMP/EWP/18/01; London; December 2002.

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