

TOLTERODINE INCREASES THE URGENCY-FREE TIME INTERVAL: A SENSORY AND MOTOR EFFECT?

Hypothesis / aims of study

The most bothersome symptom associated with overactive bladder (OAB) is urgency [1]—a sudden, compelling desire to pass urine that is difficult to defer [2]. For any OAB treatment to be beneficial, it must reduce the symptom of urgency to improve quality of life. One important goal of treatment is to increase the urgency-free time interval (UFI), which is the time between the last void and the onset of urgency. In this retrospective analysis, we evaluated the effects of tolterodine tartrate (TOL) versus placebo (PBO) on the UFI in patients who kept detailed charts of their urgency symptoms and voiding habits. Our hypothesis was that TOL would significantly increase the UFI relative to PBO.

Study design, materials and methods

In this multicentre, international study, patients with OAB were randomised to TOL extended release (ER; 4 mg once daily) or PBO for 12 weeks. Patients were asked to keep a voiding diary in which they recorded the times of their voids and symptoms of urgency and urge incontinence. For 7 days, patients were asked to time the interval between the onset of urgency and the time they voided using a stopwatch. The patients also completed the Patient Perception of Urgency Scale. Assessments were performed at baseline and weeks 1, 4, and 12. The mean UFI was approximated by subtracting from the total duration of diary collection the total time between any voids without urgency or from an urgency void to a nonurgency void and the total time from onset of urgency to void divided by the total number of urgency episodes. Between-group comparisons were performed using a van Elteren test adjusted for country.

Results

Of the 597 patients enrolled, 264 TOL and 256 PBO patients comprised the evaluable patient population, defined as randomised patients who were at least 80% compliant with study drug, did not violate any inclusion criteria, and had primary efficacy measures collected at baseline and week 12. 32% of patients reported that urgency was their most bothersome OAB symptom. By week 12, the UFI increased in both groups; however, the improvement in the TOL ER group was significantly greater than that in the PBO group ($P=0.009$). There was also a significantly greater decrease in the number of urgency episodes/24 h in the TOL ER group (median percent change, 43%) compared with the PBO group (median percent change, 34%; $P=0.041$). There was an overall increase in the intervoid interval, owing to a decline in urinary frequency in both treatment groups; however, the improvement in the TOL ER group was significantly greater than that in the PBO group ($P=0.018$). There were no significant treatment group differences in the time to void after experiencing an urgency symptom after 12 weeks of treatment (Table). Results on the Patient Perception of Urgency scale showed a greater improvement from baseline in the TOL ER group (52%) versus the PBO group (43%; odds ratio [95% CI], 1.5 [1.0–2.1]; $P=0.032$); however, the between-group difference was not statistically significant when adjusted as a coprimary endpoint (P value of 0.025).

Interpretation of results

These findings suggest that compared with PBO, treatment with TOL ER increases the UFI among patients with the bothersome symptom of urgency associated with OAB. As an efficacy variable, the time from onset of urgency to micturition has little relationship to the symptom of urgency; furthermore, treatment effects that increase the duration of this interval by several minutes have little clinical relevance. In contrast, treatment effects that prolong the filling phase and allow a shift from last void to a feeling of urgency, which is difficult to control, to a desire to void are more relevant to patients in terms of improving their quality of life.

Concluding message

Urgency is a difficult symptom to quantify; however, improvements associated with TOL ER treatment appear to be related to a lengthening of the UFI, which may be associated with a prolonged filling phase that ultimately leads to a reduction in urgency episodes. Additional studies are needed to determine the relative contribution of afferent and efferent factors as the mechanism(s) by which urgency is reduced.

Table. Summary of Results

Efficacy measure	PBO	TOL	P value*
IVI (all voids), min	17.5	25.5	0.018
median change (min, max)	(-138, 248)	(-51, 267)	
UFI, min	19.7	31.4	0.009
median change (min, max)	(-143, 411)	(-50, 289)	
Time to void after urgency, sec	5	5	0.795
median change (min, max)	(-293, 2850)	(-615, 2866)	

IVI=intervoid interval; UFI=urgency-free interval.

*van Elteren test.

References

1. The impact of urinary urgency and frequency on health-related quality of life in overactive bladder: results from a national community survey. Value Health 2004 (in press).
2. The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-178.

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