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Title: TOLTERODINE TREATMENT IS SAFE IN MEN WITH BLADDER OUTLET OBSTRUCTION (BOO) AND SYMPTOMATIC DETRUSOR OVERACTIVITY (DO)

Aims of Study:

Patients with bladder outlet obstruction often have concurrent involuntary detrusor contractions and associated overactive bladder symptoms. It has been reported that these symptoms effect over 50% of men with BOO[1]. Using the validated ICS male questionnaire in both community[2] and hospital[3] populations of older men, it has been shown that storage symptoms suggestive of detrusor overactivity such as urgency, urge incontinence, and frequency (Overactive Bladder)[4] are more bothersome than voiding symptoms such as slow stream and hesitancy. Even though this is the case, these patients are often not treated with muscarinic receptor antagonists due to concern that they will experience acute urinary retention.

Tolterodine is a potent and pure muscarinic receptor antagonist that was developed specifically for the treatment of overactive bladder. Tolterodine has been shown to be effective, safe and well tolerated in adult overactive bladder patients including elderly men.

This study is the first to be designed to assess the safety and tolerability of an antimuscarinic medication in men with both BOO and DO.

Methods:

In a multinational, multicentre, double-blind study, men aged ≥40 years with urodynamically verified overactive bladder and mild [Abrams/Griffith (AG) score 20-40], moderate (AG 40-60) or severe BOO (AG >60) were randomised (2:1) to oral therapy with either tolterodine 2 mg twice daily (bid) or placebo for 12 weeks, following which pressure-flow and other urodynamic variables were re-assessed. Concurrent treatment with 5α-reductase inhibitors or α-andrenergic antagonists was not allowed. Patients were also excluded if they had a baseline post void residual (PVR) $\geq$ 40% maximum cystometric capacity or prior prostate or bladder surgery.

In the study, safety was assessed by comparing the changes in Qmax, pdetQmax, detrusor contractility [bladder contractility index (BCI) = pdetQmax + 5Qmax], PVR, voiding efficiency, and adverse events. The International Prostatic Symptom Score (IPSS) was also recorded at baseline and study end. Tolerability was evaluated from adverse event reports and withdrawal rates, with special attention paid to the reporting of clinically significant voiding difficulties.

Results:

A total of 221 (149 randomized to tolterodine and 72 to placebo) men were randomized into the study and 193 (87%) completed the 12-weeks of treatment. A total of 16 (11%) tolterodine and 12 (17%) placebo patients discontinued prematurely primarily due to adverse events or withdraw of consent. Over half of enrolled patients had moderate or severe BOO, and were well balanced between the tolterodine and placebo treatment groups.

No changes in urodynamic parameters suggestive of safety concern were noted (Table 1). Overall, changes from baseline in maximum flow rate (Qmax) and detrusor pressure at maximum flow (PdetQmax) for tolterodine recipients were statistically equivalent to placebo (estimated differences in median change: Qmax, –0.7 ml/s; PdetQmax, –7 cm H_2O). Median increase in residual volume was significantly higher in the tolterodine group (+25 ml) compared to placebo (0 ml), however, this change and the other minor changes were not accompanied by higher urinary system adverse events and therefore, not considered to be clinically significant. The effects of tolterodine on urodynamic variables related to efficacy were consistent with other tolterodine studies. Tolterodine significantly increased volume at first contraction and maximum cystometric capacity compared to placebo.

	Placebo		**Tolterodine 2 mg bid**	
	Baseline	Week 12	Baseline	Week 12
Qmax (ml/sec)	8.0	8.5	8.8	8.5
PdetQmax (cm H_2O)	60	60	68	60
AG number	43	43	49	40
PVR ml	27	27	22	47
BCI	105	108	112	106
BE %	90	90	91	84
VFC (ml)	209	178	163	217
MCC (ml)	293	285	260	320

Tolterodine was safe and well tolerated as measured with adverse events and treatment withdrawals. A total of 51% of placebo and 58% of tolterodine patients reported at least one adverse event. Acute urinary retention was reported by one patient in each treatment group and urinary adverse events occurred with similar rates in the tolterodine (12.8%) and placebo groups (12.5%). Dry mouth (any severity) was the most common adverse event (24% of patients) but did not result in any cases of treatment discontinuation. Rates of withdrawal due to adverse events were comparable for the two groups (tolterodine, 6.0%; placebo, 6.9%), as were rates of increased urinary residual volume (tolterodine, 3.4%; placebo, 2.8%).

Conclusions: At the recommended dosage of 2 mg bid, treatment with tolterodine in men with overactive bladder and concomitant BOO is not associated with urinary safety concerns. These results justify the use of tolterodine in this population.

References:

1) Urology 1999, 53:1-6
2) BJU 1994, 74: 551-555
3) J Urol 1997, 157: 1295-1300
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