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Mehnert U[1], Reitz A[1], Mueller N[1], Knapp P A[1], Schurch B[1]
1. Neurourology, Spinal Cord Injury Center, Balgrist University Hospital

THE EFFECT OF ORAL TOLTERODINE EXTENDED RELEASE ON BLADDER FILLING SENSATIONS – A PLACEBO CONTROLLED DOUBLE BLIND STUDY WITH 4 AND 8 MG IN HEALTHY HUMAN SUBJECTS

Hypothesis / aims of study
There is evidence that anticholinergic drugs such as tolterodine not only have depressant influence on bladder muscle activity due to temporary blockage of cholinergic receptors, but also act on afferent pathways. The aim of this study was to assess bladder afferents on a physiological basis, using standard filling cystometry and to evaluate the effect of a single dose tolterodine extended release (ER) 4 and 8 mg on bladder sensations.

Study design, materials and methods
30 healthy female subjects (mean age: 23.7±2.3 years, mean BMI: 20.5±1.7 kg/m^2) were included and randomly assigned to 3 groups (n=10/group): A) placebo, B) tolterodine ER 4 mg and C) tolterodine ER 8 mg in a double blind manner.
The investigation consisted of 2 measurements: baseline and 4 hours post medication. Each measurement was performed identically in each group according to the following protocol: 1) Filling cystometry with 25ml/min and volunteers lying comfortably on an urodynamic examination table with ear plugs to avoid possible distraction. Subjects had to indicate first sensation of bladder filling (FSF), first desire to void (FDV) and strong desire to void (SDV) by pressing a pushbutton. Corresponding volumes were recorded. 2) Uroflowmetry and ultrasound control for residual urine.
The differences of measured values before and after medication are presented as change in percent. Statistical analysis was performed with the non-parametric Kruskal-Wallis and Mann-Whitney tests.

Results
At FSF no significant difference in change of bladder volumes between groups was found (p = 0.847) and no significant difference was found between groups A and B at any filling sensation.
At FDV group C showed a clear tendency to have a higher increase of bladder volumes post medication than group A and B, although there was no significant difference between groups (p = 0.088). Direct comparison of group A and C however showed significant difference (p = 0.035).
At SDV group C showed significantly higher bladder volumes post medication regarding to pre medication than group A (p = 0.001).
No significant difference between groups was found for change in bladder compliance (p = 0.272), change in $Flow_{max}$ (p = 0.697), change in $Flow_{ave}$ (p = 0.546) and change in post voiding residual volume (p = 0.381). The post voiding residual volume remained unchanged at 1 ml (median) in group A, increased from 1 ml to 3 ml in group B and increased from 3 ml to 12.5 ml in group C. The maximum post void residual volume after the treatment was measured in group C with 54 ml.
Only minor side effects (e.g. tiredness, slight headache) were reported in single cases from all groups.

	Group A		**Group B**		**Group C**	
	Mean [ml]	SD [ml]	Mean [ml]	SD [ml]	Mean [ml]	SD [ml]
FSF	147.80	90.58	172.19	78.02	135.95	101.88
FDV	298.41	119.51	354.67	156.39	274.04	149.02
SDV	628.70	141.18	686.50	228.48	625.30	216.50

Table1: Mean and standard deviation (SD) values of bladder filling sensations at baseline in all groups with FSF = first sensation of bladder filling, FDV = first desire to void and SDV = strong desire to void.

	Group A		**Group B**		**Group C**	
	Mean [ml]	SD [ml]	Mean [ml]	SD [ml]	Mean [ml]	SD [ml]
FSF	120.95	41.99	173.78	107.46	162.63	120.11
FDV	236.77	60.84	314.39	136.42	331.18	147.80
SDV	414.30	76.35	583.50	239.31	576.90	153.73

Table2: Mean and standard deviation (SD) values of bladder filling sensations post treatment in all groups with FSF = first sensation of bladder filling, FDV = first desire to void and SDV = strong desire to void.

Interpretation of results

At baseline the filling volumes at FSF and FDV of all 30 subjects are very well in accordance to the values found in previous studies from other investigators [1]. Only at SDV the subjects of this study reached slightly higher filling levels, which might be due to a high motivation at the beginning of the investigation. A deceasing motivation towards the end of the measurement or a sensitization of the bladder towards high volumes might explain why subjects in the placebo group indicated FDV and SDV much earlier in the post medication cystometry compared to baseline (Table 1 + 2). This could be observed in the tolterodine 4 mg group as well, but less pronounced.

Although tolterodine ER was only given as a single dose, the results of this study show that 8 mg of this M2/M3 - selective antimuscarinic drug could significantly delay physiological bladder sensation compared to placebo. Additionally to this finding, no significant effect on voiding function could be observed. This result affirms the hypothesis that anticholinergics like tolterodine in a certain does range act at least to some extend on bladder afferents without causing urinary retention. At higher doses the affect on the afferents might be even higher, but at the same time, the risk of urinary retention will probably increase. Tolterodine ER 4 mg, which did not show significant changes compared to placebo but a tendency to delay sensations, might perform differently when applied for a longer time period.

Concluding message

This prospective urodynamic study shows that a single dose tolterodine extended release 8 mg but not 4 mg could significantly elevate bladder volumes at FDV and SDV compared to placebo. Delayed occurrence of filling sensations to volume suggests an effect of tolterodine on the afferent pathway. There was no significant influence of a single dose tolterodine ER 4 or 8 mg on voiding function.

References

1 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, J Eur Urol (2002) 42; 34 -38

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HUMAN SUBJECTS: This study was approved by the Kantonale Ethikkommission Zürich and followed the Declaration of Helsinki Informed consent was obtained from the patients.