203

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

DOES TOLTERODINE EXTENDED RELEASE AFFECT THE BLADDER ELECTRICAL PERCEPTION THRESHOLD? – A PLACEBO CONTROLLED DOUBLE BLIND STUDY WITH 4 AND 8 MG IN HEALTHY VOLUNTEERS

Hypothesis / aims of study

Clinical observations of reduced urgency, animal studies observing a selective desensitizing effect of anticholinergics like tolterodine on bladder afferent C-fibers and immunohistological studies finding M2 and M3 receptors on afferent nerve endings and the urothelium, provide strong 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. Endovesical electro stimulation (EVES) is a useful method to assess bladder afferents, especially when using different neuroselective frequencies to distinguish between different fiber types. It was therefore the aim of this study to investigate the effect of a single dose tolterodine extended release (ER) 4 and 8 mg on human bladder afferents using EVES with different potentially neuroselective stimulation frequencies.

Study design, materials and methods

30 healthy female subjects (mean age: 23.9 ±2.2 years, range: 20-28 years, mean BMI: 20.5 ±1.7 kg/m2, range: 17-25 kg/m2) 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) Transurethral placement of an 8 Ch fill and stimulation catheter (Fig. 1) at empty bladder 2) Bladder filling with 100 ml 0.9% saline including contrast medium 3) Placement of stimulation electrodes 3 mm above bladder neck under fluoroscopic control (Fig. 2) 4) Determination of EPTs with subjects lying comfortably on a urodynamic examination table in a quiet ambience. Subjects had to indicate sensations by pressing a push button. Bipolar stimulation was performed using 3 different square wave stimuli (2.5, 5 and 250 Hz with pulse width 0.2 ms each), starting at 1 mA and using 0.5 mA increments. Thresholds were determined using method of levels.

Differences of EPT values before and after medication were statistically analysed and compared between groups using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparison of age, BMI and baseline EPTs between groups, the one-way ANOVA was used. In regard to the relevant literature and pilot experiments, the sample size was calculated with an estimated change of EPTs of 40% in the tolterodine groups. The standard deviation was estimated at 20% for all groups. The alpha level was set at 1% and the power at 80%. This calculation resulted in a necessary group size of n = 10.

Results

All subjects completed the study and tolerated the treatment well. No significant difference between groups could be found regarding age [F (2,27) = 1.387; p = 0.267], BMI [F (2,27) = 0.41; p = 0.960] and baseline electrical thresholds at 2.5 Hz [F (2,27) = 0.005; p = 0.995], 5 Hz [F (2,27) = 0.129; p = 0.880] and 250 Hz [F (2,27) = 0.949; p = 0.399] stimulation (table 1).

	Group A		**Group B**		**Group C**	
	Mean [mA]	SD [mA]	Mean [mA]	SD [mA]	Mean [mA]	SD [mA]
2.5Hz	3.15	1.45	3.10	1.43	3.15	1.16
5Hz	3.00	1.22	2.75	1.03	2.80	1.23
250Hz	1.75	0.75	1.35	0.71	1.55	0.44

Table1: Mean and standard deviation (SD) values of bladder EPTs at baseline in all groups for all 3 stimulation frequencies

After treatment EPTs raised in all groups at all frequencies and no significant difference could be found in change of EPTs after medication between groups at 2.5 Hz (p = 0.178), 5 Hz (p = 0.817) and 250 Hz (p = 0.365)(table 2). There was only a slight tendency in the tolterodine groups to elevate EPTs at 250 Hz (4 mg < 8 mg).

	Group A		**Group B**		**Group C**	
	Mean [mA]	SD [mA]	Mean [mA]	SD [mA]	Mean [mA]	SD [mA]
2.5Hz	4.25	2.32	3.25	1.36	3.9	2.37
5Hz	3.6	1.68	3.2	1.14	3.45	2.07
250Hz	1.85	0.58	1.9	0.97	2.1	0.74

Table2: Mean and standard deviation (SD) values of bladder EPTs post medication in all groups and for all 3 stimulation frequencies

In most cases, electrical stimulation with 2.5 Hz and 5 Hz was described as slight twinging, tickling or desire to void. Stimulation with 250 Hz was indicated as most uncomfortable and described as strong distinct twinge or burning “like urinary tract infection”.

Interpretation of results

The EPT values at baseline correspond very well with the literature and the range of age, BMI and EPTs are very similar in each group, which indicates proper randomisation and reliable measurement of EPTs.

Due to our hypothesis we would have expected a rise of EPTs after treatment in the tolterodine groups, especially at 5 Hz stimulation, which is supposed to selectively stimulate C-fibers. Instead we found a slight rise of thresholds in every group, which is most probably due to normal variability and secondary to minor adaption.

One reason for this non significant finding might be the pharmacokinetic property of the extended release form, which has lower plasma level fluctuation but a quite low Cmax in comparison to the immediate release form, which showed significant changes in bladder EPTs in a previous study.

Another explanation for the results might be that the healthy population has intact and stable afferents, which can not be further desensitized with this dosage and formulation of tolterodine. Moreover there is evidence, that afferent C-fiber properties are altered in patients with overactive bladder. Therefore similar investigations in patients with idiopathic overactive bladder and neurogenic overactive bladder are necessary. Concerning the neuroselective stimulation it has to be further clarified, if this approach is transferable to the LUT to gain reasonable results.

Concluding message

In this prospective study tolterodine ER 4 and 8 mg did not significantly affect the bladder EPT of healthy volunteers compared to placebo. Tolterodine ER seems not to have significant selective influence on a specific stimulation frequency.

References

FUNDING: Pfizer Detrol Grant

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