THE EFFECTS OF TOLTERODINE AND 5-HYDROXYMETHYL TOLTERODINE (5HMT) ON CARBACHOL-INDUCED CONTRACTION IN HUMAN BLADDER SMOOTH MUSCLES IN NORMAL STATE AND IN DETRUSOR OVERACTIVITY ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA

Hypothesis / aims of study
Tolterodine is an antimuscarinic drug and is converted to 5-HMT by the cytochrome P450 (CYP) 2D6 enzyme system. Fesoterodine acts functionally as a prodrug [1]. Thus 5-hydroxymethyl tolterodine (5-HMT) is the active metabolite of both tolterodine and fesoterodine, and this active metabolite has been reported to be responsible for the antimuscarinic activity. The aim of this study is to investigate whether the antagonist effect of tolterodine and 5-hydroxymethyl tolterodine (5HMT), an active metabolite of tolterodine and fesoterodine on carbachol-induced contraction, differed between normal human detrusor muscle and detrusor overactivity (DO) in patients with benign prostatic obstruction (BPO).

Study design, materials and methods
Tissue samples of human bladder muscles were obtained from patients undergoing total cystectomy due to bladder cancer without lower urinary tract symptoms (normal bladder, n=14), and those undergoing prostatectomy due to benign prostatic hyperplasia (BPH/DO, n=10). All of the patients with BPH/DO had detrusor overactivity in video-urodynamic studies or ambulatory urodynamics before the surgery. Tissues were mounted in 5 ml organ baths containing Krebs solution, and concentration-response curves (CRCs) to carbachol were obtained. After incubation for 30 minutes, a second CRC to carbachol was constructed in the continued presence of antagonist or vehicle. In this way, 4 CRCs to carbachol were obtained from the same strip, three in the presence of increasing concentrations of tolterodine or 5HMT (3, 10, 30nM) or in the presence of vehicle. The study has been conducted in accord with the Helsinki Declaration. The procedures have been approved by the local ethics committee, and written informed consent was obtained from each patient before entry into the study.

Results
Carbachol produced concentration-dependent contraction with mean pEC50 values and maximum responses of 6.56±0.18 and 9.55±0.72g, respectively, in the normal bladder. Carbachol also produced concentration-dependent contraction of the human urinary bladder with BPH/DO with mean pEC50 values and maximum responses of 5.75±0.04 and 9.79±1.7g, respectively. Tolterodine produced parallel, rightward displacement of the CRCs to carbachol without affecting maximum responses. On Schild plot Mean (±SEM) pA2 values for tolterodine in normal bladder and BPH/DO were 8.63±0.17 and 8.74±0.16 respectively. 5HMT also produced parallel, rightward displacement of the CRCs to carbachol without affecting maximum responses. On Schild plot Mean pA2 values in normal bladder and BPH/DO were 8.89±0.14 and 8.85±0.08 respectively.

Interpretation of results
Both tolterodine and 5HMT are subtype non-selective muscarinic receptor antagonists. These drugs antagonized CRCs to carbachol with high affinities. Antagonist affinities of these drugs did not change in bladder smooth muscle with BPH/DO.

Concluding message
Tolterodine and 5HMT inhibited bladder smooth muscle contraction induced by muscarinic receptor stimulation with high affinity both in the normal state and in overactive bladder associated with BPH. Antagonist affinities of these drugs did not change in bladder smooth muscle with BPH/DO.

References