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Boy S[1], Reitz A[1], Wirth B [1], Knapp P[1], Haferkamp A[2], Schurch B [1]
1. Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital , 2. Department of Urology, University of Heidelberg, Germany

NEUROMODULATIVE EFFECT OF DULOXETINE ON SPHINCTER MOTOR NEURONS – A FUNCTIONAL URODYNAMIC STUDY IN HEALTHY WOMEN

Hypothesis / aims of study
The aim of this functional urodynamic experiment in healthy females was to study the effect of the combined serotonin and norepinephrine (5-HT/NE) reuptake inhibitor duloxetine on the urethral pressure in healthy human females and to assess first the urethral resting pressure, second the excitability of pudendal motor neurons and third the urethral sphincter contractility.

Study design, materials and methods
After a positive vote from the local ethics committee 11 healthy female subjects gave their written informed consent and were included in the study. A microtip pressure transducer catheter was inserted into the bladder and three baseline urethral pressure profiles were obtained to study urethral resting pressure. Afterwards the individual motor threshold for urethral sphincter contraction in response to cortical magnetic stimulation was determined to study the excitability of pudendal motor neurons. Another three urethral pressure profiles were recorded while magnetic pulse stimulation of the sacral roots was performed above the individual motor threshold of the pelvic floor to evoke reproducible urethral contractions to study urethral sphincter contractility. Then the subjects received 40 mg of duloxetine and the entire protocol was repeated four hours after drug administration. Mean and maximal urethral pressure values calculated over the entire urethra, mean pressure values calculated over the proximal, middle and distal third of the urethra, motor thresholds for cortical magnetic stimulation and the pressure amplitudes in response to sacral magnetic stimulation at baseline were statistically compared to the follow-up measurements with duloxetine by ANOVA for repeated measures.

Results
Oral administration of duloxetine significantly lowered the motor threshold for urethral sphincter contraction in response to cortical magnetic stimulation ($P<0.014$). In addition duloxetine significantly increased pressure amplitudes in response to sacral magnetic stimulation ($P<0.0008$). Urethral resting pressures were not affected.

Interpretation of results
Clinical studies in women have shown that duloxetine effectively improves stress urinary incontinence and quality of life. As a combined serotonin and norepinephrine (5-HT/NE) reuptake inhibitor duloxetine temporally prolongates serotonin and norepinephrine in the synaptic cleft. It is thought to act facilitatory on pudendal motor neurons in the Onuf nucleus and thus increase urethral sphincter activity. Animal studies in cats have indicated that duloxetine significantly increases sphincteric muscle activity measured by Sphincter- EMG thus promoting the idea of improved continence by increased sphincter activity [1] . The results also showed that the effects of duloxetine on the sphincter were mediated centrally through both motor efferent and sensory afferent modulation.
Though a similar mechanism of action in humans can be suspected comparable studies in humans are still lacking. In our study the lowered motor threshold for urethral sphincter contraction in response to cortical magnetic stimulation indicates an increased excitability of pudendal sphincter motor neurons after administration of duloxetine. Additionally sphincter contractility was increased. It can be concluded that the effect of duloxetine is indeed achieved through a facilitatory neuromodulative effect on sphincter motor neurons in humans. Urethral resting pressures are not affected suggesting that duloxetine works mainly by amplifying existing continence reflexes.

Concluding message

This is the first functional, urodynamic controlled study to show that the combined 5-HT/NE reuptake inhibitor duloxetine has a significant effect on the excitability of pudendal motor neurons and on sphincter contractility in healthy females in vivo. There is no relevant effect of duloxetine on urethral resting tone. Our data confirm a facilitatory neuromodulative effect of duloxetine on sphincter motor neurons in the Onuf nucleus, which has been demonstrated in animal experiments but never in humans.