

ORAL NITRIC OXIDE DONORS - A NEW PHARMACOLOGICAL APPROACH TO DETRUSOR-SPHINCTER DYSSYNERGIA IN SPINAL CORD INJURED PATIENTS?

Aims of Study

Patients with spinal cord injuries on suprasacral level often lose the coordination between bladder and urethral sphincter function. This phenomenon known as detrusor-sphincter dyssynergia (DSD) is a common cause of bladder outlet obstruction in these patients and leads to several complications which increase morbidity after SCI. Poor bladder emptying and high bladder pressures can cause recurrent urinary tract infections, structural bladder damage and vesicoureteric reflux, which if left untreated might cause hydronephrosis and at least renal failure. In this study, we hypothesized that the sublingual administration of a nitric oxide donor could be a novel pharmacological approach to DSD in humans with spinal cord injuries.

Methods

12 male spinal cord injured patients presenting with neurogenic detrusor overactivity and DSD were studied. 6 performed clean intermittent catheterisation and 6 used suprapubic tapping for bladder emptying. During cystometry and cardiovascular monitoring the bladder was filled until the first bladder contraction accompanied by DSD occurred while bladder and external urethral sphincter (EUS) pressures were continuously recorded. Then the bladder was emptied and the patients received 10 mg of isosorbide dinitrate sublingually. Resting pressures were recorded for 15 min and then cystometry was repeated. Mean values for bladder and EUS pressures were calculated within the resting period and in both fillings within time windows of 30 s, 60 s, 90 s and 120 s after the onset of a bladder contraction and statistically compared by analysis of variance for repeated measurements (level of significance $p < 0.05$).

Results

Cystometry and drug treatment were well tolerated in all patients. In 7 patients mild headache occurred. Nitric oxide lowered the resting blood pressure and increased heart rate for a period up to 30 min after administration without any clinical significance.

During baseline cystometry all studied patients showed a bladder contraction accompanied by DSD. The mean reflex volume was 345 ml (range 194 to 456 ml) and the mean voiding pressure was 65.8 cm H₂O (SD 23.0). Post-triggering residual urine volume in the group of 6 patients using suprapubic triggering for bladder emptying was 133 ml (SD 47).

Following sublingual administration of 10 mg isosorbide dinitrate the mean EUS resting pressure decreased significantly from 74.9 cm H₂O (SD 22.5) at baseline to 63.4 cm H₂O (SD 20.8, $p < 0.01$) calculated from 0-5 min, to 48.4 cm H₂O (SD 22.8, $p < 0.01$) calculated from 5-10 min and to 42.4 cm H₂O (SD 18.5, $p < 0.01$) calculated from 10-15 min. In the same period the mean resting bladder pressure remained almost unchanged (16.1 cm H₂O (SD 6.9) at baseline, 15.1 cm H₂O (SD 6.8) from 0-5 min, 17.8 cm H₂O (SD 9.5) from 5-10 min and 20.6 cm H₂O (SD 12.4) from 10-15 min.

Then cystometry was repeated and in all patients a bladder contraction occurred again. The mean reflex volume was 369 ml ranging from 201 ml to 458 ml (non significant vs. baseline reflex volume) and the mean voiding pressure was 62.4 cm H₂O (SD 21.9) which was non significant vs. baseline voiding pressure. In the six patients who used to empty the bladder by suprapubic triggering the post-triggering residual volume was with 73 ml (SD 35) significant lower than without isosorbide dinitrate ($p < 0.001$).

Mean value calculations within the analyzed time windows of 30 s, 60 s, 90 s and 120 s after the onset of a bladder contraction revealed significant differences for EUS pressures without vs. with nitric oxide ($p < 0.01$) and non significant changes for bladder pressures.

Conclusions

Oral administration of nitric oxide donors could significantly reduce DSD in all studied patients and improve bladder emptying in the patients with triggered voiding. These results in humans with spinal cord injury indicate that the inhibitory neurotransmitter nitric oxide is involved in urethral smooth and striated muscle regulation and that oral nitric oxide donors mediate a relaxation of the external urethral sphincter. This pharmacological approach could offer a new treatment option for DSD.