

Oral Nitric Oxide Donors: A New Pharmacological Approach to Detrusor-Sphincter Dyssynergia in Spinal Cord Injured Patients?

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Abstract

Purpose: Detrusor-sphincter dyssynergia is a common cause of bladder outlet obstruction in spinal cord injured patients and leads to poor bladder emptying and high bladder pressures, which if left untreated might cause renal failure. In this study, we tested the recently published hypothesis that oral administration of a nitric oxide donor could be a new pharmacological approach to treat detrusor-sphincter dyssynergia in humans with spinal cord injury.

Methods: 12 male spinal cord injured patients presenting with neurogenic detrusor overactivity and detrusor-sphincter dyssynergia were studied. 6 performed clean intermittent catheterisation and 6 used suprapubic tapping for bladder emptying. During cystometry the bladder was filled until the first overactive bladder contraction accompanied by detrusor-sphincter dyssynergia occurred while bladder and external urethral sphincter pressures were continuously recorded. Then the bladder was emptied and the patients received 10 mg of isosorbide dinitrate sublingually. Resting pressures were recorded and cystometry was repeated starting 15 min after drug administration. Maximal and mean values for bladder and external urethral sphincter pressures were calculated in both fillings and statistically compared by analysis of variance for repeated measurements (level of significance $p < 0.05$).

Results: Nitric oxide significantly reduced external urethral sphincter pressures at rest ($p < 0.05$) and during dyssynergic contraction ($p < 0.05$) while bladder pressures at rest and during contraction as well as the reflex volume remained unchanged. In the patients who used suprapubic tapping for bladder emptying the mean post triggering residual volume was significantly reduced ($p < 0.05$).

Conclusions: Oral administration of nitric oxide donors significantly reduced bladder outlet obstruction due to detrusor-sphincter dyssynergia suggesting a role for nitric oxide in inhibitory neurotransmission to the urethral sphincter. This new approach could offer a potential pharmacological option to treat detrusor-sphincter dyssynergia in spinal cord injured patients.

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1. Introduction

Patients with spinal cord injuries (SCI) on suprasacral level often lose the coordination between bladder

and urethral sphincter function. This phenomenon known as detrusor-sphincter dyssynergia (DSD) is defined as the presence of an involuntary contraction of the external urethral sphincter during an involuntary detrusor contraction [1]. DSD is a common cause of bladder outlet obstruction in this patient population and leads to several complications which increase

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morbidity after SCI. Poor bladder emptying and high bladder pressures can cause recurrent urinary tract infections, structural bladder damage and vesicoureteric reflux, which ultimately may lead to hydronephrosis and renal failure.

Treatment options include reversible interventions such as the injection of botulinum toxin into the external urethral sphincter, balloon dilatation of the sphincter, implantation of urethral stents or the external sphincterotomy. Basically, all these procedures are more or less effective but have considerable side effects. Urethral stents are prone to encrustation and stone formation. The botulinum toxin injections need to be repeated within intervals of 2–4 months. Also the results of surgical sphincterotomy are not fully convincing. Prospective studies showed that in 15–40% repeated sphincterotomy is required and raised residual urine volumes and recurrent urinary tract infections persisted in 20–35% and 20–25% respectively [2,3]. Reflux failed to resolve in 10–60% and hydronephrosis remained in around 30%. In patients with cervical and higher thoracic lesions bladder filling associated autonomic dysregulation persisted in 5–10% after sphincterotomy [2,3]. Although severe surgical complications are rare, urethral strictures in 5–10% and erectile dysfunction in 3–7% needs to be considered. Furthermore, the main goal of the procedure, to decrease high intravesical pressures as a potential risk factor for renal damage, can not be achieved in a considerable number of patients and around one third of the patients develop upper urinary tract complications. To sum up it can be said that effective, reversible and well-tolerated treatment strategies for DSD in SCI men are currently not available.

Since alpha-blockers are often not effective in detrusor-sphincter dyssynergia [4,5], a short and locally acting pharmacological agent such as a nitric oxide donor could be the solution in this group of patients. Recently Mamas et al. hypothesized that nitric oxide donors could be a potential new treatment option for detrusor-external urethral sphincter-dyssynergia [6]. Animal and human studies suggested that the inhibitory neurotransmitter nitric oxide plays an important regulatory role in urethral sphincter relaxation [7–9]. In this study, we hypothesized that the oral administration of nitric oxide donors *first* could lower the resting external urethral sphincter pressure; *second* could lower the sphincter pressure during dyssynergic sphincter contraction, and *third* could reduce the maximal bladder pressure during voiding. Within an acute urodynamic study the effect of the oral nitric oxide donor isosorbide nitrate on dyssynergic external urethral sphincter activity and voiding pressure was assessed in 12 males with

suprasacral SCI. Furthermore, the post-triggering residual volume in 6 patients using suprapubic tapping for bladder emptying were compared with vs. without nitric oxide.

2. Patients and methods

12 male patients (mean age 32 years, range 29–36) with chronic suprasacral spinal cord injury were studied. All patients presented with upper motor neuron lesion, neurogenic detrusor overactivity and DSD. Medication known to influence the vesicourethral function was discontinued within 48 h before the test and none of the patients had used sildenafil for treatment of erectile dysfunction during that period. Patients with higher thoracic or cervical lesions and known severe hypotonia were excluded.

Patients underwent detailed neurological examination to confirm the segmental level of SCI. 6 patients performed clean intermittent catheterisation and 6 used triggered voiding for bladder emptying. During standard cystometry with saline solution of room temperature the pressures within the bladder and the external urethral sphincter (EUS) were continuously recorded using an 8 French three channel pressure transducer catheter (Unisensor, Switzerland). Correct placement of the pressure transducers within the bladder and the EUS was ensured radiologically using fluoroscopy. The abdominal pressure was measured using an 8 F single channel pressure transducer catheter placed in the rectum.

During baseline cystometry the bladder was filled with 10 ml per second until the first bladder contraction accompanied by DSD occurred. The volume infused is defined as reflex volume. Patients who used triggered voiding as standard bladder management then emptied their bladder by repeated suprapubic triggering until the urine flow stopped. Afterwards, the bladder was emptied by catheterisation and the residual urine was measured.

All patients received 10 mg of isosorbide nitrate sublingually while heart rate and blood pressure were monitored continuously. To study the drug effect on the resting bladder and EUS activity both pressures were continuously recorded five minutes before and within the first 15 minutes after drug delivery. For that period bladder and EUS pressures were analyzed and mean values were calculated within four time windows (baseline, 0–5 min, 5–10 min, 10–15 min).

Afterwards standard cystometry was repeated starting 15 min after drug delivery up to the point, when the first bladder contraction accompanied by DSD occurred. In patients on triggered voiding the post-triggering residual volume was measured again by catheterisation. The obtained pressure curves for both fillings were recorded with a 1000 Hz sampling rate and further analyzed using the SoleasyTM-software package (ALEASolutions, Switzerland). Mean values for bladder and EUS pressures at baseline before bladder contraction and within time frames of 30, 60, 90 and 120 sec after onset of an uninhibited bladder contraction were calculated in both fillings and compared by analysis of variance for repeated measures (level of significance $p < 0.05$).

3. Results

Cystometry and drug treatment were well tolerated in all patients. In 7 patients mild headache occurred.

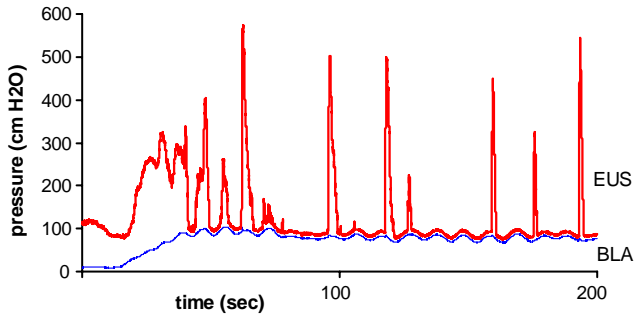


Fig. 1. Neurogenic detrusor overactivity accompanied by DSD in a patient with traumatic SCI on T6 level (EUS: external urethral sphincter, BLA: bladder).

Nitric oxide lowered the mean blood pressure from 124/85 mmHg to 102/68 mmHg and increased heart rate from 72 beats per min to 96 beats per minute. This cardiovascular effect lasted for a period up to 30 min and was without any clinical significance.

During baseline cystometry all patients studied showed an uninhibited bladder contraction accompanied by DSD (Fig. 1). The mean reflex volume was 345 ml (range 194–456 ml) and the mean voiding pressure was 65.8 cmH₂O (S.D. 23.0). Post-triggering residual urine volume in the group of 6 patients using suprapubic triggering for bladder emptying was 133 ml (S.D. 47).

Following sublingual administration of 10 mg isosorbide dinitrate the EUS pressure decreased in all individuals studied. The mean EUS resting pressure decreased significantly from 74.9 cmH₂O (S.D. 22.5) at baseline to 63.4 cmH₂O (S.D. 20.8, $p < 0.05$) calculated from 0 to 5 min, to 48.4 cmH₂O (S.D. 22.8, $p < 0.05$) calculated from 5 to 10 min and to 42.4 cmH₂O (S.D. 18.5, $p < 0.05$) calculated from 10 to 15 min (Fig. 2). In the same period the mean resting bladder pressure remained almost unchanged (16.1 cmH₂O (S.D. 6.9) at baseline, 15.1 cmH₂O (S.D. 6.8) from 0 to 5 min, 17.8 cmH₂O (S.D. 9.5) from 5 to

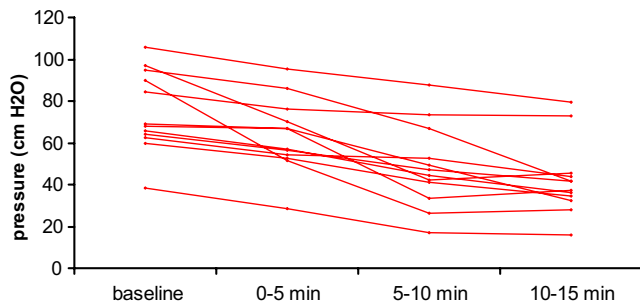


Fig. 2. Resting external urethral sphincter pressures separately calculated as mean value for every single patient within the time frames of 5 min duration before and after sublingual administration of 10 mg isosorbide dinitrate.

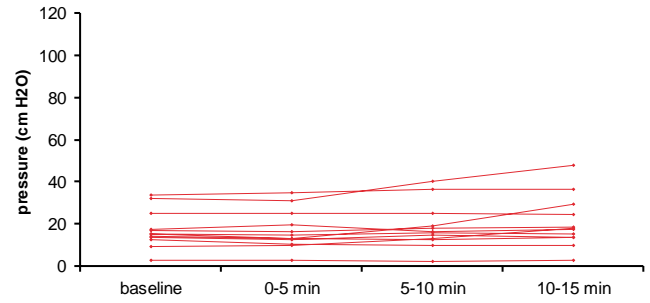


Fig. 3. Resting bladder pressures separately calculated as mean value for every single patient within the time frames of 5 min duration before and after sublingual administration of 10 mg isosorbide dinitrate.

10 min and 20.6 cmH₂O (S.D. 12.4) from 10 to 15 min. For details see Fig. 3.

Then cystometry was repeated and in all patients an uninhibited detrusor contraction occurred again (Fig. 4). 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 cmH₂O (S.D. 21.9) which was non significant from the baseline voiding pressure. In the six patients who used to empty their bladder by suprapubic triggering the post-triggering residual volume was with 73 ml

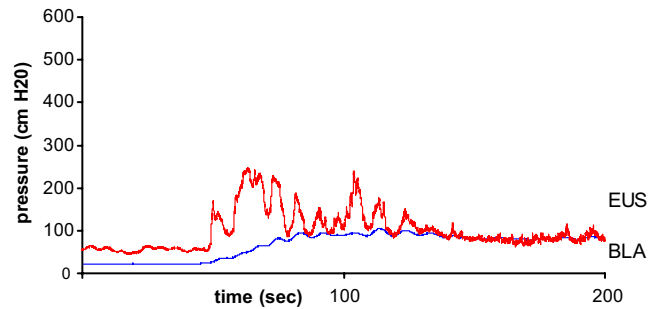


Fig. 4. Neurogenic detrusor overactivity accompanied by DSD in the same patient as shown in Fig. 1, 20 min after sublingual administration of 10 mg isosorbide dinitrate.

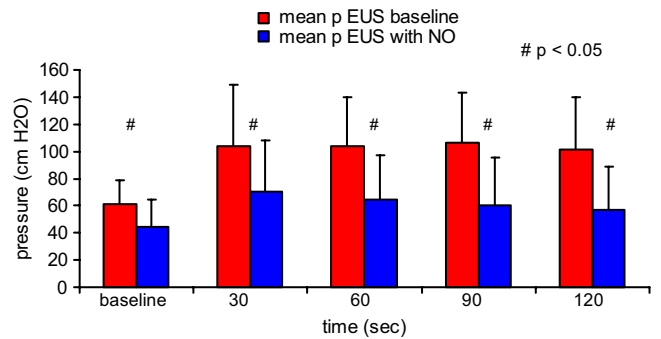


Fig. 5. Mean external urethral sphincter pressures (mean ± S.D.) during dyssynergic external sphincter contractions before and after sublingual administration of 10 mg isosorbide dinitrate ($n = 12$).

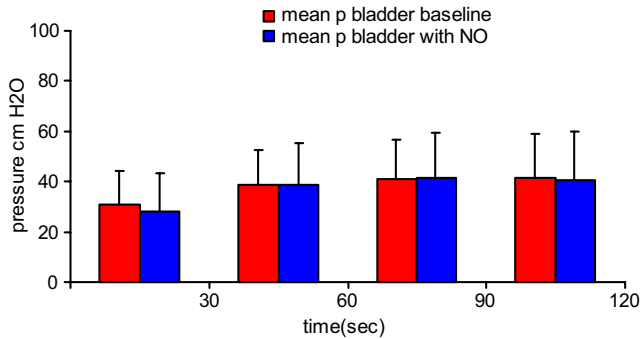


Fig. 6. Mean bladder pressures (mean \pm S.D.) during neurogenic detrusor overactivity and dyssynergic external sphincter contractions before and after sublingual administration of 10 mg isosorbide dinitrate ($n = 12$).

(S.D. 35) significantly lower than without isosorbide dinitrate ($p < 0.05$).

Mean value calculations within the analyzed time windows of 30 s, 60 s, 90 s and 120 s after the onset of an uninhibited bladder contraction revealed that the nitric oxide donor significantly decreased the EUS pressure ($p < 0.05$) without having a significant effect in bladder pressure (Figs. 5 and 6).

4. Discussion

To our knowledge, this is the first study using an oral nitric oxide donor as a pharmacological approach to DSD in spinal cord injured patients. In this urodynamic controlled study the oral administration of 10 mg isosorbide dinitrate significantly reduced EUS pressure at rest and also during dyssynergic sphincter contraction. Furthermore, the drug treatment improved bladder emptying in patients who used to empty their bladder by suprapubic tapping and reduced the post-void residual volume significantly.

Nitric oxide has been suggested as an important inhibitory neurotransmitter in the lower urinary tract. Nerves with the capacity to synthesize nitric oxide supply the urethra and the urinary bladder [10–13], and those nerves seem to be predominant in the parasympathetic innervation of the urethra [14]. Nitric oxide also seems to be important for the relaxation of the striated external urethral sphincter [15].

After spinal cord injury on a suprasacral level the coordination between detrusor and sphincter is frequently absent because the inhibitory pathways from the brain stem to the sacral spinal cord and the urethral sphincter structures are disrupted. The lack of supraspinal coordination of bladder and sphincter function causes poor bladder emptying because when the bladder contracts the sphincter does not relax or even also

contracts. This leads to high bladder pressures and elevated residual urine, structural bladder damage and vesicoureteral reflux, and when combined with recurrent infections to renal failure. To date, treatment options for detrusor-sphincter dyssynergia are limited and in many patients ineffective. Therefore, new approaches to this unsolved problem are necessary.

In the present acute urodynamic study we found that sublingual nitric oxide donors lower the EUS pressure at rest and during contraction. After sublingual administration isosorbide dinitrate reaches maximal plasma concentrations after 10–15 min and the duration of the effect is estimated to be 1–2 hours (half-life 30–40 min). The EUS is considered to have a rich blood supply. Therefore, after sublingual administration the drug should reach the sphincteric area within a few minutes. This consideration corresponds with our findings during the first 15 min after drug administration when we observed the resting EUS pressure. Already after 5 min there was a significant decrease of the resting sphincter pressure which decreased further after 10 and 15 minutes. These findings suggest that sublingually administered nitric oxide donors can lower the resting pressure of the EUS significantly within a short period of time and maintain this reduction for at least more than 15 min.

Also the contractile ability of the EUS seems to be influenced by the drug. Mean EUS pressures calculated within time frames of 30, 60, 90 and 120 s after onset of a overactive bladder contraction were significantly lower with isosorbide dinitrate than without. This suggests that sublingual administration of isosorbide dinitrate results in a significant reduction of the contractile strength of the EUS during a dyssynergic contraction. Since high volumes of residual urine might increase the risk of urinary tract infections and bladder stones, a more or less complete bladder emptying is crucial in patients using suprapubic tapping for voiding. Our results show that the post-triggering residual volume in these patients is significantly lower with nitric oxide indicating an improved bladder emptying by a reduction of the bladder outlet obstruction caused by DSD.

Concerning our third hypothesis, the drug did not influence the resting bladder pressure and it did not significantly reduce the mean bladder pressure during contraction. This supports earlier findings that nitrergic innervation within the bladder is sparse. However, the main goal of a new treatment option would be a reduction of high voiding pressures which cause the unfavourable consequences such as bladder wall damage, reflux and renal failure. A possible explanation for the persisting high bladder pressure during voiding despite considerable reduced outlet resistance

is an adaptation of the detrusor muscle on a certain contractile strength which cannot be changed during an acute experiment, but might improve after chronic administration. However, in patients using suprapubic tapping for bladder emptying a sufficient bladder contractility should be maintained to ensure voiding with tolerable residual urine volumes.

Since nitric oxide donors can cause hypotonia and tachycardia, cardiovascular monitoring is recommended especially in patients with spinal cord injury on the level T6 and higher because they are known to have hypotonia frequently at rest. Autonomic dysregulation in response to bladder filling or contraction is also common in these patients and nitric oxide donors could provide in addition to the sphincter relaxation a beneficial cardiovascular effect and avoid excessive blood pressure rise and bradycardia.

Because of the risk of severe hypotension the parallel intake of sildenafil must be avoided and a careful history is necessary prior to treatment since many of spinal cord injured men take sildenafil for erectile dysfunction. In 7 of the 12 studied patients headache has been observed after drug administration, which is a typical side effect of nitric oxide donors but known to

disappear when the drug is used for longer times. Further studies are required to evaluate the efficacy and safety of a chronic administration of oral nitric oxide donors to treat DSD in SCI patients.

5. Conclusion

Oral administration of nitric oxide donors significantly reduced bladder outlet obstruction due to DSD in the spinal cord injured patients studied, and improved bladder emptying in the patients with triggered voiding. These results are consistent with a role for nitric oxide in inhibitory neurotransmission to the urethral sphincter. This pharmacological approach could offer a potential new treatment option for bladder outlet obstruction due to DSD.

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References

- [1] Blaivas JG, Sinha HP, Zayed AA, Labib KB. Detrusor-external sphincter dyssynergia. *J Urol* 1981;125(4):542–4.
- [2] Fontaine E, Hajri M, Rhein F, Fakacs C, Le Mouel MA, Beurton D. Reappraisal of endoscopic sphincterotomy for post-traumatic neurogenic bladder: a prospective study. *J Urol* 1996;155(1):277–80.
- [3] Catz A, Luttwak ZP, Agranov E, Ronen J, Shpaser R, Paz A, et al. The role of external sphincterotomy for patients with a spinal cord lesion. *Spinal Cord* 1997;35(1):48–52.
- [4] Perkash I. Efficacy and safety of terazosin to improve voiding in spinal cord injury patients. *J Spinal Cord Med* 1995;18(4):236–9.
- [5] Chancellor MB, Erhard MJ, Rivas DA. Clinical effect of alpha-1 antagonism by terazosin on external and internal urinary sphincter function. *J Am Paraplegia Soc* 1993;16(4):207–14.
- [6] Mamas MA, Reynard JM, Brading AF. Augmentation of nitric oxide to treat detrusor-external sphincter dyssynergia in spinal cord injury. *Lancet* 2001;357(9272):1964–7.
- [7] Thornbury KD, Hollywood MA, McHale NG. Mediation by nitric oxide of neurogenic relaxation of the urinary bladder neck muscle in sheep. *J Physiol* 1992;451:133–44.
- [8] Andersson KE, Garcia Pascual A, Persson K, Forman A, Tottrup A. Electrically-induced, nerve-mediated relaxation of rabbit urethra involves nitric oxide. *J Urol* 1992;147(1):253–9.
- [9] Persson K, Andersson KE. Non-adrenergic, non-cholinergic relaxation and levels of cyclic nucleotides in rabbit lower urinary tract. *Eur J Pharmacol* 1994;268(2):159–67.
- [10] McNeill DL, Traugh Jr NE, Vaidya AM, Hua HT, Papka RE. Origin and distribution of NADPH-diaphorase-positive neurons and fibers innervating the urinary bladder of the rat. *Neurosci Lett* 1992;147(1):33–6.
- [11] Saffrey MJ, Hassall CJ, Moules EW, Burnstock G. NADPH diaphorase and nitric oxide synthase are expressed by the majority of intramural neurons in the neonatal guinea pig urinary bladder. *J Anat* 1994;185(Pt 3):487–95.
- [12] Smet PJ, Edyvane KA, Jonavicius J, Marshall VR. Colocalization of nitric oxide synthase with vasoactive intestinal peptide, neuropeptide Y, and tyrosine hydroxylase in nerves supplying the human ureter. *J Urol* 1994;152(4):1292–6.
- [13] Smet PJ, Edyvane KA, Jonavicius J, Marshall VR. Distribution of NADPH-diaphorase-positive nerves supplying the human urinary bladder. *J Auton Nerv Syst* 1994;47(1–2):109–13.
- [14] Vizzard MA, Erdman SL, Forstermann U, de Groat WC. Differential distribution of nitric oxide synthase in neural pathways to the urogenital organs (urethra, penis, urinary bladder) of the rat. *Brain Res* 1994;646(2):279–91.
- [15] Ho KM, McMurray G, Brading AF, Noble JG, Ny L, Andersson KE. Nitric oxide synthase in the heterogeneous population of intramural striated muscle fibres of the human membranous urethral sphincter. *J Urol* 1998;159(3):1091–6.