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Fatih Tarhan · Erkan Erbay · Bilal Eryıldırım
Gökhan Faydacı · Uður Kuyumcuoğlu

The effect of intravesical sodium nitroprusside on idiopathic detrusor overactivity

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Abstract Although nitric oxide (NO) plays an important role in the urethra and outlet region of the bladder, the role of this inhibitory neurotransmitter in the human detrusor remains unclear. We conducted a prospective, randomised, open study on 31 patients with urodynamically proven idiopathic detrusor overactivity in order to examine the effects of intravesical administration of the NO donor sodium nitroprusside (SNP) on detrusor overactivity. Thirty-one consecutive patients (14 male, 17 female; mean age 53.0 ± 2.7 years) with idiopathic detrusor overactivity diagnosed by pressure-flow analysis were included in this study. The patients were randomised into two groups. Cystometries were performed with normal saline in the control group ($n = 10$) and with 7.2 mM SNP solution (2.16 mg/ml) in the study group ($n = 21$). We urodynamically investigated sensation, maximal cystometric capacity, compliance, instability index, amplitude and frequency of involuntary contractions. No statistically significant differences was found between the first (pressure-flow) and second (saline or SNP cystometry) urodynamic values in the control and study groups ($P > 0.05$). We have demonstrated that SNP does not have any effect on uninhibited bladder contractions. These results suggest that the intravesical administration of SNP is not an effective treatment for detrusor overactivity.

Keywords Urine bladder · Detrusor overactivity · Nitric oxide · Sodium nitroprusside

F. Tarhan (✉) · E. Erbay · B. Eryıldırım · G. Faydacı
U. Kuyumcuoğlu
Urology Clinic, Kartal Training and Research Hospital,
Istanbul, Turkey
E-mail: tarhanf@yahoo.com
Tel.: +90-216-3263180
Fax: +90-216-3833193

F. Tarhan
Genç Sokak 10/7, 81010 Acıbadem-Kadıköy,
Istanbul, Turkey

Introduction

Detrusor overactivity is defined as an urodynamic process characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked [1]. The precise pathological mechanisms giving rise to detrusor overactivity are poorly understood. Most ideas on its etiology can be considered under two broad categories: myogenic and neurogenic [1]. The treatment of detrusor overactivity consists of lifestyle interventions, drugs or surgery.

Recent studies have provided evidence that nitric oxide (NO) plays an important role in the function of the smooth muscles of the lower urinary tract [2, 3]. NO is also thought to play a role in detrusor overactivity [4]. Inactivation of the cGMP-dependent protein kinase 1 (cGKI) gene in mice causes bladder hyperactivity, suggesting that bladder overactivity may be associated with impaired NO/cGKI signalling [5]. The pathology of the L-arginine-NO-cyclic guanosine monophosphate (cGMP) pathway may lead to impaired relaxation of the urethral outflow region, increased bladder afferent activity, and bladder overactivity [4, 6]. It has been suggested that involuntary detrusor contractions may be initiated from the bladder outlet region rather than from the detrusor itself [6]. The inhibition of NO production by the systemic administration of nitric oxide synthase (NOS) inhibitor inhibits urethral smooth muscle relaxation during micturition [7]. Another experimental study has demonstrated capsaicin-induced NO-dependent relaxation in the isolated dog urethra [8].

NO can be produced by and released from urothelium [9], and may be involved in the regulation of afferent nerve activity. In support of such a view, oxyhaemoglobin, a scavenger of NO which does not penetrate the urothelium, was found to induce bladder overactivity in unanaesthetized rats when given intravesically, probably by interfering with NO generated in the urothelium or suburothelially [10]. Chung et al. found that rat detrusor muscle is capable of responding to NO, and concluded

that these findings might lead to the treatment of bladder overactivity by intravesical instillation of NO donors [11]. In agreement with this, Ozawa et al. found that the intravesical administration of NO-donors suppresses bladder overactivity in rats. They suggested that this action may be due to an inhibitory effect of NO on bladder afferent pathways [12]. Theobald showed that the inhibition of endothelial NO synthase (eNOS) and neuronal NO synthase (nNOS] produce opposing effects on cat bladder, and concluded that eNOS inhibition could promote or enhance spontaneous activity, possibly to the point of converting such activity to detrusor overactivity [13].

Although there is good evidence to suggest that NO promotes relaxation of the urethra and outlet region, there is conflicting evidence for its role in the detrusor [2, 3]. Furthermore, the majority of experimental work has been performed on animal models. Evidence exists supporting an inhibitory role for NO in animal detrusor, yet the situation in humans is less clear. The nitrergic nerves observed in the human detrusor [14, 15] and, particularly, within and beneath the urothelium [14, 15], may be afferent terminals. Furthermore, improvement of the symptoms of obstructive benign prostatic hyperplasia was found in humans using the NO donor glyceryl trinitrate [16]. James et al. [17] investigated human detrusor in vitro and concluded that relaxation was sensitive to L-NOARG, suggesting the involvement of a NO-mediated inhibitory pathway. In a study by Moon [18], pre-contracted normal and unstable human detrusor displayed a mixed response to SNP and db-cGMP: relaxation, contraction or a transient relaxation followed by a contraction. Although these studies show that the role of NO in human detrusor is complex, they suggest that NO does contribute to detrusor function.

Therefore, we designed a study to evaluate the use of NO for the treatment of detrusor overactivity. However, since NO is a very labile molecule, only NO donors can be used pharmacologically [19, 20]. Sodium nitroprusside (SNP) is an inorganic nitroso compound which releases NO spontaneously and is an antihypertensive drug [19].

We studied 31 patients with urodynamically diagnosed detrusor overactivity to investigate the effects of the intravesical administration of SNP with special emphasis on its therapeutic potential for idiopathic detrusor overactivity.

Materials and methods

Thirty-one consecutive patients (14 male, 17 female; mean age 53.0 ± 2.7 years) with idiopathic detrusor overactivity (phasic) diagnosed by pressure-flow analysis were included in this study. The diagnosis of detrusor overactivity was made on the basis of an involuntary rise in detrusor pressure (phasic uninhibited contraction) without increasing abdominal pressure during the filling phase, spontaneously or by provocation.

None of these patients had hypertension, bladder outlet obstruction, bladder stone, cancer, diabetes mellitus or any evidence of neurological disease. Patients who had had surgery of the bladder and/or urethra were excluded.

A detailed medical history was taken and routine physical examination, blood and urine biochemical studies, electrocardiography and x-ray of the chest were performed for all patients. Approval was obtained from our Training Hospital's Ethics Committee. Written informed consent was obtained from all patients. Patients were randomised into two groups, the control group ($n = 10$), and the study group ($n = 21$).

For the urodynamic investigation, a MMS UD-2000 system was used. Following the measurement of the urinary free flow rate, all patients underwent cystometry at the physiological filling rate via a 7 F catheter. The methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically defined [21].

Cystometry was performed with normal saline in the control group and with 7.2 mM SNP solution (2.16 mg/ml) in the study group. Infused solutions during cystometries were at body temperature. SNP solution (Nipruss, Schwarz Pharma, Germany) was freshly prepared in 0.9% saline immediately before each cystometry. The container was wrapped in aluminium foil to protect it from light. In the SNP group, immediately before cystometry, 50 ml SNP (7.2 mM) was administered into the bladder which was drained after 30 min. The same procedure was performed using 50 ml 0.9% saline in the control group.

Patients' blood pressures and heart rates were measured during the urodynamic study. We evaluated first desire, normal desire and strong desire, maximal cystometric capacity, compliance, instability index [22] (instability index = sum of wave heights/bladder volume), amplitude, and frequency of the uninhibited contractions in both groups.

Results were calculated as means ± SEM. Statistical analyses were performed with the Wilcoxon test by using Prizm 2.01 (GraphPad Software).

Results

The mean ages of patients in the two groups did not differ ($P = 0.93$).

The doses of SNP administered varied between 185.8–1,023.8 mg (mean = 668 ± 76.2 mg) depending on the patient's maximum cystometric capacity.

Urodynamic findings, instability index, amplitude and frequency of the uninhibited contractions are given in Tables 1 and 2.

No significant differences was found between the first (pressure-flow) and second (saline or SNP cystometry) urodynamic values in either the control and study groups ($P > 0.05$). The amplitude and frequency of involuntary contractions and the instability index were also not significantly different between the first and second urodynamic studies in either groups ($P > 0.05$).

The mean systolic blood pressure in the study groups was 132 ± 5.7 mm Hg and 134 ± 4.4 mm Hg before and after SNP administration, respectively. The administration of SNP did not cause a significant change in systolic blood pressure ($P = 0.78$).

Discussion

NOS and guanylate cyclase activities have been identified in the urothelium, smooth muscle, blood vessels and the nerves of the human bladder [14, 15, 23, 24]. However, these activities were found to be significantly higher in the urethra compared to the detrusor in human tissue [24].

Table 1 Urodynamic findings for the control and SNP groups

	Control group		*P*	SNP group		*P*
	Pressure-flow cystometry			Pressure-flow cystometry		
First desire (ml)	154.1 ± 15.4	118.7 ± 11.0	0.109	113.5 ± 11.9	124.1 ± 12.3	0.700
Normal desire (ml)	218.6 ± 29.6	170.0 ± 32.4	0.375	190.8 ± 13.0	212.3 ± 24.1	0.376
Strong desire (ml)	344.5 ± 42.7	254.8 ± 38.7	0.156	282.5 ± 23.9	285.1 ± 27.0	0.831
Maximal cystometric capacity (ml)	402.4 ± 50.7	312.1 ± 39.2	0.461	300.6 ± 32.0	309.4 ± 35.3	0.916
Compliance (ml/cm H_2O)	47.2 ± 7.8	38.3 ± 8.6	0.065	45.9 ± 12.3	34.4 ± 8.3	0.577

Table 2 Amplitude, frequency, and instability index of involuntary contractions of the patients

	Control group		*P*	SNP group		*P*
	Pressure-flow cystometry			Pressure-flow cystometry		
Amplitude (cm H_2O)	14.4 ± 2.2	16.2 ± 2.3	0.375	69.9 ± 8.2	57.6 ± 11.4	0.083
Frequency (contractions/min)	0.5 ± 0.1	0.7 ± 0.2	0.139	0.4 ± 0.1	0.5 ± 0.1	0.716
Instability index	0.3 ± 0.1	0.3 ± 0.1	0.695	1.9 ± 0.5	1.4 ± 0.5	0.063

There is good evidence to suggest that NO promotes the relaxation of the urethra and outlet region during bladder emptying [2, 3]. The exact role of NO in detrusor physiology is unclear. In vitro human studies showed that the inhibition of NOS decreased relaxation of human detrusor strips in response to electrical field stimulation [17, 25]. Moon reported that NO donors and db-cGMP evoked a complex response (relaxing, contractile or biphasic) on isolated human detrusor muscle preparations [18]. Recent studies provide new insights into the role of NO on detrusor smooth muscle. The mechanisms suggested are that neuronally mediated NO might have an effect via interstitial cells rather than the detrusor smooth muscle cell itself [14], that urothelium-derived NO may play an important role in the regulation of detrusor muscle function [9, 13], and detrusor smooth muscle may be another source of NO in the human bladder [15]. Additionally, NO derived from neurones may modulate the effects of other neurotransmitters/mediators which are co-localized with NOS, and in this way may contribute to bladder relaxation during filling [23].

Our study is the first to report the effects of intravesical SNP administration on detrusor overactivity in human beings. In this study on a relatively small number of patients with idiopathic detrusor overactivity, the results suggest that the NO donor SNP does not have any effect on involuntary bladder contractions.

The maximum dose of SNP is 10 μg/kg/min by systemic administration [19]. Ozawa et al. reported that intravesical administration of SNP (1 mM) in rats has a suppressive effect on detrusor overactivity and does not decrease arterial blood pressure [12]. We did not observe any effect of SNP on detrusor overactivity, although we administered a seven times greater concentration of SNP compared to Ozawa et al. However, the results of animal studies can not always be extrapolated to humans. Higher intravesical doses of SNP would be inappropriate without further safety studies evaluating systemic effects.

SNP is not absorbed through the bladder mucosa since it does not penetrate cell membranes easily. Contact of the sulfuhydryl groups with the cell walls immediately initiates the breakdown of the molecule [19, 20]. This is the likely explanation for the absence of change in arterial blood pressure, despite the fact that the dose is higher than those used systemically.

SNP has a very short half-life. Its onset of action is 30 s, the peak effect occurs within 2 min, and the effect disappears within 3 min [19]. The detrusor has a low sensitivity to NO and agents acting via the cGMP system, which makes it less likely that NO plays a role as a relaxant neurotransmitter in this tissue [14, 26]. In fact, bladder relaxation was shown to be related more to the cyclic adenosine monophosphate than to the cGMP system [27]. The short half-life of SNP and the low sensitivity of the detrusor muscle to NO are the likely explanation of the ineffectiveness of the drug in our study.

Different NO donors do not have an equal effect on detrusor smooth muscle cells [6, 28]. The route of transformation to NO and the pharmacology are also different [29]. Therefore our results should not be generalized to all NO donors.

Our study suggests that the intravesical administration of SNP at the given doses is not an effective drug for the treatment of detrusor overactivity. However, intraurethral or intravesical administration of other NO donors, cGMP or agents acting via the cGMP pathway alone, or donors combined with other drugs, may prove to be useful in detrusor overactivity.

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