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Feline penile erection induced by transurethral administration of sodium nitroprusside

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Abstract Nitric oxide (NO) is an important mediator in the relaxation of cavernosal smooth muscle. The aim of this study was to investigate the in vivo feline erectile response after transurethral administration of sodium nitroprusside (SNP), a NO donor drug. Erectile responses after administration of transurethral SNP were compared with those elicited by an intracavernosal control triple-drug combination (1.65 mg papaverine, 25 μg phentolamine, and 0.5 μg prostaglandin E_1). SNP was administered via a 20-gauge Jelco intravenous catheter in a volume of 200 μl and changes in intracavernosal pressure, penile length, and systemic blood pressure were monitored. The control triple-drug combination was administered via a 30-gauge needle at the end of each experiment to serve as a control reference. Transurethral administration of SNP (1–4 mg) induced penile erection in a dose-dependent manner with minimal changes in systemic blood pressure. The maximum increase in intracavernosal pressure and penile length after transurethral administration of SNP (4 mg) was significantly less than after the intracavernosal injection of the control triple-drug combination ($P < 0.01$). These data suggest that transurethral administration of SNP can induce an erectile response in cats with minimal side effects.

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Introduction

Penile erection is a neurovascular event involving a complex interplay of neuroregulatory control mechanisms which cause relaxation of cavernous smooth muscle [1, 2]. In the genitourinary tract, nitric oxide (NO) is the physiological mediator of penile erection, and a number of studies have characterized its involvement in both neurogenically mediated and endothelium-dependent relaxation of the vascular and trabecular smooth muscle of the penis [5, 6, 13]. The primary role of NO is to bind to the heme moiety of guanylate cyclase, which subsequently increases intracellular 3′,5′-cyclic guanosine monophosphate (cGMP) thus causing smooth muscle relaxation [14]. These observations encouraged further experiments in which NO donor drugs were injected into cavernosal tissues to cause penile erection. Stief and colleagues [18] demonstrated the therapeutic efficacy of NO in the management of erectile dysfunction by intracavernosal administration of linsidomine chlorhydrate (SIN-1). This pharmacological agent releases NO nonenzymatically and, when injected intracavernosally in 63 patients, induced a dose-related erectile response, with 46% of men experiencing full tumescence [18]. However, in another study employing intracavernosal sodium nitroprusside (SNP), severe hypotension with only minimal tumescence was exhibited [4]. Recently, intracavernosal administration of SNP and papaverine were compared in 32 patients. Duplex Doppler sonography after administration of either SNP or papaverine demonstrated no differences in peak flow velocities. However, the increase in diameter and end-diastolic velocities were higher after intracavernosal SNP compared with intracavernosal papaverine [19].

Intracavernosal injection of vasoactive agents has gained global acceptance for the pharmacological treatment of erectile dysfunction, notwithstanding the

known side effects of pain, hematoma, priapism, and penile nodules [7, 11, 12]. Unfortunately, a sizable number of men on intracavernosal injection therapy report low satisfaction and efficacy leading to low long-term compliance and a high dropout rate [11]. Alternative methods, such as the medicated urethral system of delivery (MUSE) for the transurethral administration of prostaglandin E_1 (Alprostadil) and the oral administration of sildenafil (Viagra), a type 5 phosphodiesterase inhibitor, may offer effective, but less invasive means for introducing vasoactive agents for the purpose of treating erectile dysfunction [9, 16]. Our laboratory has established a reliable and reproducible feline model for the investigation of novel vasoactive agents to induce penile erection. Our previous work has demonstrated the erection-producing effect of intracavernosal injection of SNP in both the feline and primate models [10, 20].

Although the effects of SNP on smooth muscle relaxation and blood flow have been investigated in several in vitro and in vivo organ systems, little is known about its effect on penile erection when administered transurethrally. This study explores the effects of transurethral delivery of SNP on erectile function in an in vivo cat model.

Materials and methods

Adult male cats (3.5–4.6 kg) obtained from a USDA class B animal supplier were used in this study. The animals were sedated with ketamine hydrochloride (10–15 mg/kg intramuscularly) and anesthetized with pentobarbital sodium (30 mg/kg intravenously). Supplemental doses of sodium pentobarbital were administered as needed to maintain a uniform level of anesthesia. The animals were maintained at 37°C with a heating blanket. The trachea of each animal was cannulated, and animals either spontaneously respired room air or were ventilated with a Harvard model 607 respirator at a tidal volume of 40–60 ml at a rate of 15–22 breaths/min. Catheters were inserted into the external jugular for intravenous administration of drugs and into the carotid artery for the measurement of systemic arterial (aortic) pressure. A vertical, circumcision-like incision was made to expose the two ventral corpora cavernosa and the dorsal corpus spongiosum. A 25-gauge needle was placed into the left corpus for the measurement of intracavernosal pressure. Systemic arterial and intracavernosal pressures were measured with Statham P23 transducers connected to a Grass model-7 polygraph, and mean pressures were obtained by electronic averaging. Techniques for the exposure of cavernosal tissue and recording of mean arterial and intracavernosal pressure were based on previously published articles [3, 8]. Penile length was measured with a ruler. All procedures were approved by the Tulane University Animal Care and Use Committee.

In the experiments in which the transurethral administration of SNP was employed, drugs were introduced into the urethra via a 20-gauge Jelco intravenous catheter (Critikon, Tampa, Fla.) in a volume of 200 µl. Incremental doses of SNP were administered after 100 µl of normal saline (25°C) had been delivered transurethrally in order to moisten the urethral mucosa to improve absorption. Transurethral administration of SNP was made when the basal intracorporal pressure was at a resting baseline value. When basal intracorporal pressure was achieved, a single injection of incremental doses of SNP was administered transurethrally. The change in intracavernosal pressure and penile length were monitored with each dose of SNP. The next randomized injection was made at least 10–15 min after the previous intracavernosal response had returned to a stable baseline. When the dose-response curve for SNP was achieved transurethrally, a 30-gauge needle was placed into the right corpus to permit administration of the control triple-drug combination into the penis.

Sodium nitroprusside (Sigma Chemical, St. Louis, Mo.) was dissolved in 0.9% NaCl. The control triple-drug combination comprised of prostaglandin E_1 (0.5 µg) (Upjohn Pharmaceuticals, Kalamazoo, Mich.), papaverine (1.65 mg), and phentolamine (25 µg) (Sigma Chemical, St. Louis, Mo.) was prepared and injected intracavernosally at the end of each experiment to serve as a control comparison, as previously described [3, 8].

The data were expressed as means ± standard error of the mean (SEM) and analyzed by one-way analysis of variance (ANOVA) and Dunnett's test for multiple-group comparisons and by Student's *t*-test for comparison between groups. The value of $P < 0.05$ was established as the criterion for statistical significance.

Results

Erectile response to transurethral delivery of SNP

Given the favorable erectile profile of SNP when administered intracavernosally, SNP was administered transurethrally in the cat, and the effects on cavernosal pressure and penile length are shown in Figs. 1 and 2. When administered transurethrally, SNP (1–4 mg) induced dose-related increases in cavernosal pressure and penile length (Figs. 1, 2). The maximal effect on intracavernosal pressure was obtained by the transurethral delivery of 4 mg of SNP (Fig. 1). The maximal effect on intracavernosal pressure was approximately three-fold higher than the baseline and about 50% of the result obtained by the intracavernosal injection of the control triple-drug combination ($P < 0.01$) (Fig. 1). The maxi-

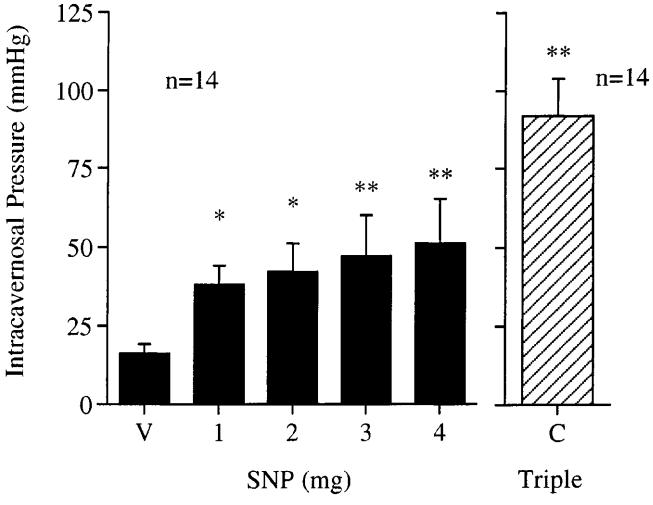

Fig. 1 Dose-dependent increase in intracavernosal pressure induced by transurethral application of sodium nitroprusside (*SNP*). SNP was administered in incremental doses from 1 to 4 mg. *V* vehicle, *C* control triple-drug combination (1.65 mg papaverine, 25 µg phentolamine, and 0.5 µg prostaglandin E_1) administered intracavernosally at the completion of each experiment, *n* the number of animals. *One asterisk* indicates that the response is significantly different from the baseline with a *P* value less than 0.05 ($*P < 0.05$); *two asterisks* indicate that the *P* value was less than 0.01 ($**P < 0.01$)

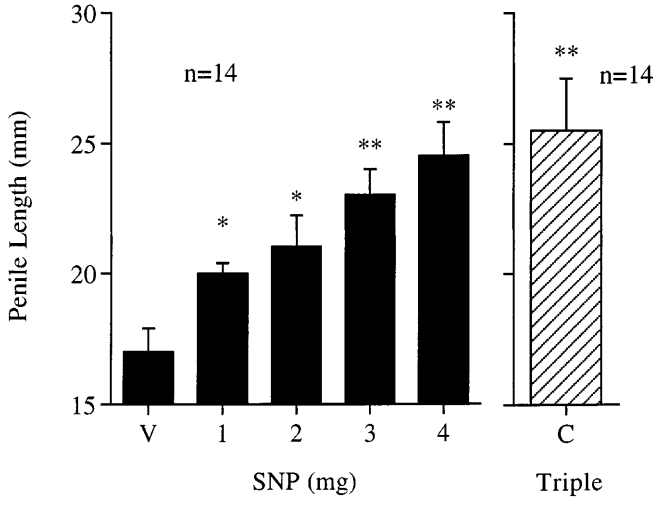

Fig. 2 Dose-dependent increase in intracavernosal pressure induced by transurethral application of sodium nitroprusside (*SNP*). SNP was administered in incremental doses from 1 to 4 mg. *V* vehicle, *C* control triple-drug combination (1.65 mg papaverine, 25 μg phentolamine, and 0.5 μg prostaglandin E_1) administered intracavernosally at the completion of each experiment, *n* the number of animals. *One asterisk* indicates that the response is significantly different from the baseline with a *P* value less than 0.05 (*$P < 0.05$); *two asterisks* indicate that the *P* value was less than 0.01 (**$P < 0.01$)

mum increase in penile length induced by the transurethral administration of 4 mg of SNP was approximately 33% greater than the baseline and was comparable to that caused by the intracavernosal injection of the control triple-drug combination (Fig. 2).

The duration of the erectile response, as determined by the duration of the peak response and the total duration of erectile response, induced by the transurethral injection of SNP (4 mg) was significantly less than that produced by the control triple-drug combination ($P < 0.01$). SNP (4 mg), when administered transurethrally, exhibited a duration of peak response of 7 ± 3 min and a total duration of erectile response of 14 ± 4 min. The control triple-drug combination, when administered intracavernosally, exhibited a duration of peak response of 30 ± 8 min and a total duration of erectile response of 42 ± 12 min. When the peak durations of the erectile response and the total duration of erectile response exhibited by SNP were compared with those of the control triple-drug combination, the peak duration and total erectile response exhibited by the control triple-drug combination were significantly longer ($P < 0.01$).

Decreases in systemic arterial pressure in response to transurethral administration of SNP are summarized in Table 1. Transurethral administration of 3 and 4 mg SNP significantly decreased systemic blood pressure by 9 ± 4 and 15 ± 2 mmHg ($P < 0.05$), respectively, while the triple-drug control combination induced significant decreases in systemic blood pressure by 32 ± 14 mmHg ($P < 0.01$) when compared with the pre-injection baseline values (Table 1).

Table 1 Decrease in mean systemic arterial pressure (*SAP*; mmHg) in response to transurethral administration of sodium nitroprusside and intracavernosal injection of the control triple-drug combination in the feline erection model (Values are mean ± SEM; $n = 14$)

	ΔSAP (mmHg)
Sodium nitroprusside	
1 mg	−4 ± 5
2 mg	−7 ± 3
3 mg	−9 ± 4*
4 mg	−15 ± 2*
Triple-drug combination	−32 ± 14**

*$P < 0.05$; **$P < 0.01$

Discussion

Penile erection is a neurovascular event that depends on the complete relaxation of intracavernosal smooth muscle [1]. SNP induces smooth muscle relaxation by releasing NO, which in turn increases the cellular concentration of cGMP [14]. In vitro studies have confirmed that SNP causes relaxation of human corpus cavernosal tissue, and in vivo studies have also demonstrated that intracavernosal injection of SNP can cause penile erection in a dose-dependent manner in both feline and primate models [10, 17, 20]. On the basis of these findings, it has been postulated that the administration of exogenous NO may be worthwhile in the management of male erectile dysfunction. Though SNP has been studied in basic research settings to measure its influence on cavernosal smooth muscle relaxation, it has not been used clinically to treat erectile dysfunction for fear of inducing systemic hypotension in patients after intracavernosal injection [4].

This study showed that SNP can induce penile erections in cats by the transurethral delivery route. In this manner, SNP was administered locally to the urethral mucosa with subsequent absorption and action on the cavernosal smooth muscle to induce penile erection. These data provide evidence that, like prostaglandin E_1, SNP can induce an erectile response when administered transurethrally. A distinct advantage of this approach is the potential for reduced systemic side effects as witnessed by the minimal change in systemic blood pressure. Transurethral administration of as much as 4 mg of SNP decreased systemic blood pressure by only 15 mmHg. Our early studies in the cat reported that intracavernous injection of as little as 10 μg of SNP decreased systemic blood pressure by 20 mmHg, and studies in humans found severe hypotension in men who injected SNP intracavernosally [4, 20]. The difference in the results of these earlier studies and those of the present study could be attributed to the vasodilatory effects of SNP in the immediate vicinity of the corpora cavernosa, causing less of a systemic hemodynamic effect in the cat. This may also limit the erectile response; however, it may reduce the risk of priapism as is

observed with triple-drug therapy. Another apparent advantage of the transurethral route of drug delivery over the intracavernosal route may be better patient compliance because of the absence of needles and minimal patient discomfort during delivery of the drug. The oral type 5 cGMP phosphodiesterase inhibitor, Viagra, has gained worldwide acceptance as the leading oral medication for erectile dysfunction. However, the use of local vasoactive agents administered transurethrally may be appealing to many patients who do not respond to Viagra, cannot tolerate the systemic side effects, or in whom Viagra is contraindicated.

The fact that transurethral SNP produced only 50% of the intracavernosal pressure effect compared with the triple-drug combination may be of some concern with regard to penile rigidity. One can postulate that the diminished effect of transurethral SNP may be due to the premature release of NO before arrival at its active site in the corpora cavernosum. Furthermore, saline may not be the appropriate vehicle for SNP via the transurethral approach. However, the maximum increase in penile length induced by transurethral SNP was 94% of that induced by the triple-drug combination. Our previous studies in cats and primates demonstrated that SNP was a potent erectogenic agent when administered by the intracavernosal route [10, 20]. Rigidity and release of SNP to the corpus cavernosum may be subsequently improved by further refinements in the transurethral delivery of SNP or possibly by combining SNP with other vasoactive agents, such as a specific cGMP phosphodiesterase inhibitor.

Transurethral delivery of pharmacological agents offers a viable alternative for many anxious patients concerned about needle injections. This study clearly demonstrates that the erectile response caused by transurethral SNP is comparable, in terms of intracavernosal pressure and penile length, to the intracavernosal injection of the control triple-drug combination. Additionally, there were no major significant systemic side effects as measured by changes in systemic blood pressure after transurethral delivery of SNP. There was a significant decrease in systemic blood pressure after intracavernosal administration of the control triple-drug combination in the cat which could be attributed to the very large amount of prostaglandin E_1 (0.5 μg), papaverine (1.65 mg), and phentolamine (25 μg) used in order to achieve a consistent full erection in the cat. Moreover, there were no episodes of priapism in any of the cats that received transurethral SNP. These findings support the further investigation of transurethral SNP as an effective and safer means of delivery of vasoactive agents to the penis.

In summary, this study confirms the efficacy of the transurethral administration of SNP in inducing penile erection in the cat. The results provide clear evidence that SNP can induce dose-dependent increases in cavernosal pressure and penile length in the cat when administered transurethrally. The increases in cavernosal pressure and penile length were less than those observed with the intracavernosal triple-drug combination. The maximum increase in cavernosal pressure in response to transurethral SNP was associated with a minimal decline in systemic arterial pressure. In contrast, the decreases in systemic arterial pressure in response to intracavernosal injection of the triple-drug combination were significantly greater. Further quantitative studies which measure the amount of NO delivered to the cavernosal tissues after transurethral administration of SNP will help delineate the mechanism of absorption and transfer of NO into the cavernosal tissue responsible for inducing penile erection.

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