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Penile erections induced by vasoactive intestinal peptide and sodium nitroprusside

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Summary. The use of vasoactive intestinal peptide (VIP), sodium nitroprusside (SNP), and the reference combination of papaverine, prostaglandin E_1, and phentolamine was studied in 22 adult cats. The maximal erectile response (intracavernous pressure, penile length, and rigidity) was produced by intracavernous injection of a combination of 1.65 mg papaverine, 0.5 μg PGE_1, and 25 μg phentolamine. This combination was considered as "control" in order to compare the effect of other agents. VIP and SNP increased the intracavernous pressure and caused erection in a dose-dependent manner with a maximal response obtained with 5 μg VIP or 10 μg SNP. The duration of peak erection and the total duration of drug effect were significantly shorter with VIP and SNP than with the reference combination ($P < 0.01$). Epinephrine (30 μg) reversed the effects of SNP and significantly shortened the duration of peak action and total effect ($P < 0.05$). This study supports the use of an in vivo feline model for the evaluation of vasoactive agents and demonstrates that the intracavernous injection of either VIP or SNP can induce penile erection in the adult cat.

Key words: Nitroprusside – Penile erection, feline model – VIP

We have earlier reported on the use of the cat as an appropriate model for the evaluation of agents causing penile erection [7]. In that report potassium channel agonists were found to be effective. In the present study we extend these findings to include two additional agents: vasoactive intestinal peptide and sodium nitroprusside.

Clinical use is limited by concerns about fibrosis of the corpora cavernosa, priapism, and pain caused by agents injected intracavernosally. Novel, more potent, and safer vasoactive agents with the potential for alternative routes of administration need to be developed. Moreover, the physiology and pathophysiology of penile erection, its mechanism and regulation, are still not completely known. The present study was undertaken to extend and clarify the parameters of the erectile response in the adult cat.

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Materials and methods

The methods are the same as previously described [7]. Twenty-two mature male cats weighing 4.0–5.3 kg were sedated with ketamine hydrochloride (10–15 mg/kg intramuscularly) and anesthetized with sodium pentobarbital (30 mg/kg intravenously) by insertion of a polyethylene catheter into the left external jugular vein. Supplemental doses of pentobarbital were administered as needed. The trachea was cannulated. Systemic arterial pressure was measured with a polyethylene catheter in the carotid artery.

After the pubic area had been shaved, 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 midway into the left corpus for the measurement of intracavernous pressure. Both systemic arterial and intracavernous pressures were measured with Statham P23 transducers attached to a Grass Model-7 polygraph zeroed at the right atrial level. A 30-gauge needle was placed in the right corpus to permit administration of drugs into the penis.

Papaverine hydrochloride (Eli Lilly, Indianapolis, Ind.) prostaglandin E_1 (PGE_1; Upjohn, Kalamazoo, Mich.) and phentolamine (Ciba-Geigy, Summit, N.J.) were mixed in different doses and injected in a volume of 200 μl into the corporus cavernosum (i.c.). The catheter was flushed with 200 μl normal saline. Intracavernous pressures were recorded continuously before, during, and after the injections of the drugs. The penile length was measured before and after injection of the drugs.

Purified vasoactive intestinal peptide (VIP; Peptide Laboratories, Tulane University School of Medicine, New Orleans, La.), was injected (i.c.) in doses of 1 to 8 μg. Sodium nitroprusside (SNP; Sigma Chemical Co., St. Louis, Mo.) was injected (i.c.) in doses of 1 to 15 μg. In later studies, after the peak erectile response was obtained with SNP, an antagonist (30 μg epinephrine) was injected for comparison of the duration and intensity of changes in pressure. At the conclusion of each experiment the control mixture of papaverine, PGE_1, and phentolamine was administered to permit quantitative comparison with the "control".

All data were expressed as mean ± SEM and analyzed by Student's *t*-test for single-group comparisons and by one-way

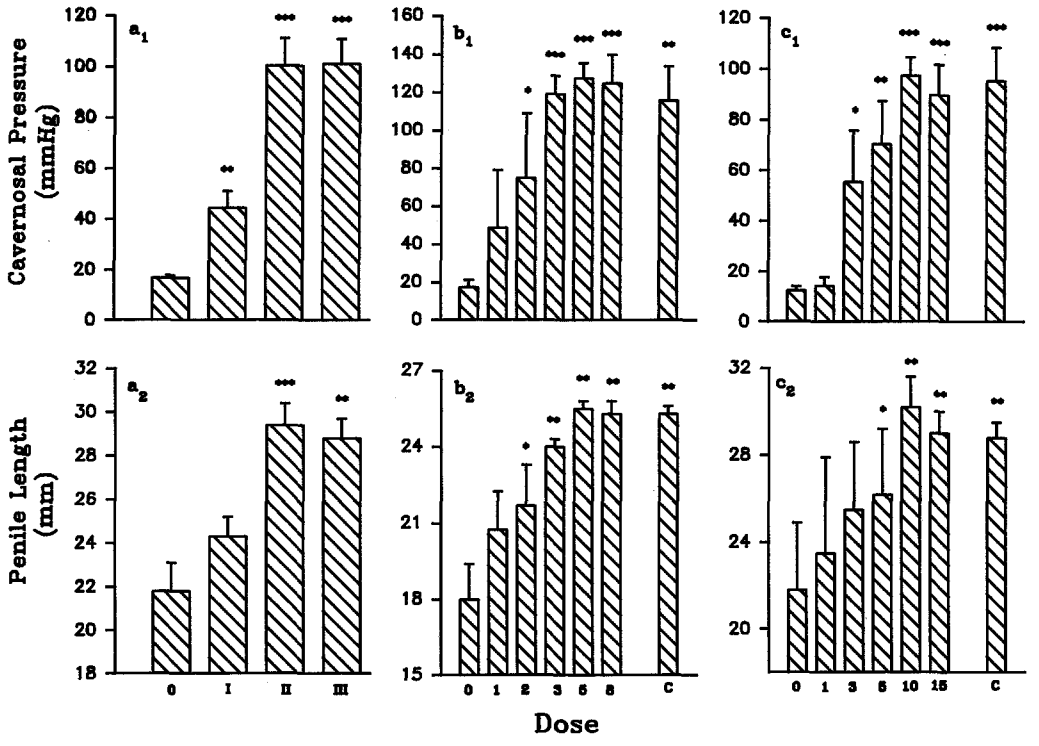

Fig. 1a–c. Dose-response effects of vasoactive agents on intracavernous pressure and on penile length. The triple drug combination was administered intracavernously as 200 µl injections (a_1, a_2, $n=10$). *O,* baseline; *I,* 0.825 mg papaverine, 12.5 µg phentolamine, and 0.25 µg PGE_1; *II,* 1.65 mg papaverine, 25 µg phentolamine, and 0.5 µg PGE_1; *III,* 6.6 mg papaverine, 100 µg phentolamine, and 2 µg PGE_1. Vasoactive intestinal peptide (VIP) and sodium nitroprusside (SNP) were injected in increasing doses from 1 to 8 µg for VIP (b_1, b_2, $n=6$) and from 1 to 15 µg for SNP (c_1, c_2, $n=6$). *C* denotes control combination (1.65 mg papaverine, 25 µg phentolamine, and 0.5 µg PGE_1) administered at the end of the experiment. *Asterisks* denote the level of significance compared with baseline (*O*). $*P<0.05$; $**P<0.01$; $***P<0.001$

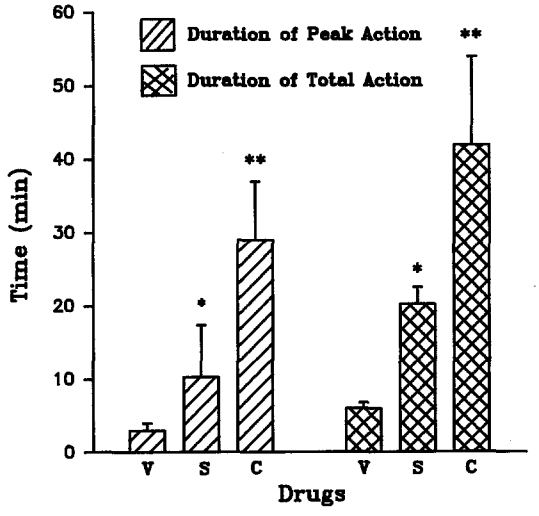

Fig. 2. Duration of peak effect and total action of different drugs on intracavernous pressure. *V,* vasoactive intestinal peptide (5 µg); *S,* sodium nitroprusside (10 µg); *C,* control combination (1.65 mg papaverine, 25 µg phentolamine, and 0.5 µg PGE_1). *Asterisks* denote level of significance: i.e., $*S$ compared with V ($P<0.05$); ** C compared with V ($P<0.01$) and S ($P<0.05$)

analysis of variance for multiple-group comparisons. The value of $P<0.05$ was considered to be statistically significant.

Results

Intracavernous injection of the combination of 0.825 mg papaverine, 0.25 µg PGE_1, and 12.5 µg phentolamine resulted in an increase in intracavernous pressure (mmHg) from the baseline value of 16.8 ± 1.0 to 44.4 ± 6.6 ($P<0.05$). This increase was maximal (100.5 ± 10.8) with the control combination of 1.65 mg papaverine, 0.5 µg PGE_1, and 25 µg phentolamine (Fig. 1 a_1). The penile length (mm) increased from 21.8 ± 1.3 to 29.4 ± 1.0 with this combination (Fig. 1 a_2). There were no further increases in pressure and penile length with increasing doses of the triple drug combination. The mean systemic arterial pressure (mmHg) decreased from 145.0 ± 6.1 to 115.0 ± 5.4 when the maximal response was obtained.

VIP caused a dose-dependent increase in cavernosal pressure (Fig. 1 b_1) and penile length (Fig. 1 b_2) with the maximal effect observed with a dose of 5 µg. The maximal effects on penile pressure (6-fold) and length (56%) were similar in intensity to those observed with the control combination or with 8 µg VIP.

SNP caused a dose-dependent effect on both cavernosal pressure (Fig. 1 c_1) and penile length (Fig. 1 c_2). A maximal 6-fold increase in penile pressure and a 38% increase in penile length were observed with 10 µg SNP. This peak response was similar in intensity to that observed with the control combination. The systemic arterial pressure decreased significantly from 143.0 ± 3.4 to 125.0 ± 8.4 mmHg with 10 µg SNP and from 146.0 ± 8.6 to 111.0 ± 7.8 mmHg with 5 µg VIP.

The duration (in minutes) of the peak erectile response and the total duration of action was longest with the control combination (Fig. 2), for which the values were 29 ± 8 min and 42 ± 12 min, respectively. With SNP the total duration of action was 20 ± 8 min with a peak erectile response of 10 ± 5 min, while for VIP the total duration was 6 ± 1 min with a peak erectile response of 3 ± 1 min. The peak erectile response with use of both SNP and VIP was approximately 50% of the total duration of action. With use of the triple combination, the peak time was 70% of the total duration. Epinephrine (30 µg) reversed the

effects of SNP and shortened both the duration of maximal pressure (from 12.1 ± 4.2 to 0.9 ± 0.2 min) and the total duration of drug action (from 22.2 ± 11.4 to 3.6 ± 1.2 min).

Discussion

Vasoactive agents have been helpful in the evaluation and treatment of impotence [2, 3, 16, 17]. A standard animal model could be useful in the development of new drugs for intracavernous injection and could also improve our understanding of the penile erectile mechanism. A feline model was the first animal model used in earlier studies on pharmacologically induced erections; however, those studies were conducted by use of intravenous routes [6]. The use of the cat model offers many advantages. Anatomically, both corpora of the cat penis are located ventrally with the corpus spongiosum running in a dorsal position and cradled by the os penis in the distal part of the organ [5]. Our study has shown that the adult cat is a useful and reliable model for exhibiting the penile erectile response to intracavernous injections of vasoactive agents.

The combined use of papaverine, PGE_1, and phentolamine has been shown to be beneficial in the diagnosis and treatment of impotence. Clinial experience from human studies demonstrated that the mixture of these three drugs was effective in 50% of previously non-responding patients [12]. The spasmolytic action of papaverine involves inhibition of oxidative phosphorylation, blocking of cyclic adenosine monophosphate (cAMP) phosphodiesterase, and interference with calcium exchange during muscular contraction [15]. It increases arterial blood flow, venous resistance, and relaxation of sinusoidal smooth muscle [11]. PGE_1 acts directly via a receptor-mediated increase in levels of cAMP to effect relaxation of the smooth muscle of the corpus cavernosum [13]. It has also been suggested that formation of prostaglandins is under muscarinic control, which would facilitate relaxation of the smooth muscle of the corpus cavernosum by reduction of adrenergically induced tone [13]. Phentolamine induces relaxation of smooth muscle by blocking the alpha-adrenergic receptors on cell membranes [15]. It increases the arterial blood flow into the penis but has a minimal direct effect on the venous outflow from the corpora cavernosa. Combining phentolamine with papaverine potentiates the smooth muscle relaxing effect of papaverine [11].

However, with the use of intracavernosal injections, priapism was reported in 1.6%–18.8% of patients [10]. Many patients develop fibrotic penile lesions and nodules after self-injecting for longer than 1 year [4]. Animal studies have shown hypertrophy of smooth muscle after prolonged use [1, 2]. Two percent of patients report orthostatic hypotension [15]. The introduction of intracavernosal PGE_1 was aimed at reducing these problems. Unfortunately, with this agent a significant number of patients develop penile pain [18]. The introduction of other agents, alone or in combination, could lessen some of these concerns. The standardized feline model has enabled us to assess a number of these agents.

VIP is in high concentration in the erectile tissue of both animals and man, and may either modulate or act as the neurotransmitter mediating the erectile response at the non-adrenergic, non-cholinergic, post-ganglionic terminals of the nerves innervating the penis [8, 9]. These higher concentrations of VIP were not found consistently during all pharmacologically induced erections [8, 9]. In human studies, the response to intracavernous injection of VIP alone has not been satisfactory, but its addition to the combination of papaverine and phentolamine has improved the erectile response [9]. Our study confirmed that the intracavernous injection of VIP alone induced penile erection in the cat and had the same maximal effect on penile pressure as observed with the control combination of papaverine, PGE_1, and phentolamine. This lends support to the concept that VIP may have importance in the erectile response [11].

SNP induces the relaxation of vascular smooth muscle by releasing nitric oxide which increases the cellular concentration of 3′,5′-cyclic guanosine monophosphate. In an in vitro study both SNP and papaverine caused relaxation of human corpus cavernosal tissue [14]. There are no published reports regarding use of intracavernous injections of SNP in man or in animal models. In the present study the increase in intracavernous pressure and the penile erection in the cat induced by SNP were similar in intensity to those observed with the control combination. This may indicate that SNP could be of use in man.

The duration of total and peak drug action on intracavernous pressure induced by SNP and VIP was significantly less than with the control combination. Use of VIP or SNP in combinations with other vasoactive agents may provide further advantages, such as reduced incidence of priapism, limited discomfort, or a decrease in the percentage patients with erectile dysfunction who do not respond to treatment.

Epinephrine, an adrenergic agonist, significantly reduced the duration of the penile response to SNP. This may help to reverse priapism when SNP is employed for pharmacological induction of erection.

All agents used in this study reduced the systemic arterial pressure in a dose-related manner. The use of a double rubber band at the penile base may have reduced the systemic absorption of the vasoactive agent combined with its vehicle and would be expected to diminish the hypotensive effect. The decrease in systemic pressure always returned to normal levels within 3 min after injection. In future trials, careful selection of doses and volumes of drugs administered may be critical in preventing or decreasing such systemic effects.

Intracavernous injection has improved our understanding of the physiology and pharmacology of penile erection. This study provides support for the use of an in vivo feline model to evaluate different vasoactive drugs for potential use in man.

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