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Intracavernous Injection of Vasoactive Drugs in the Rabbit

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Summary. To investigate the erectile response and side effects of intracavernous injection of vasoactive agents, 7 groups of 5 rabbits each underwent injection of either isotonic saline or 1 of 6 drugs. Phentolamine most consistently produced full erection with few inflammatory reactions, while phenoxybenzamine produced erection but also severe inflammation and sclerosis of the corpus cavernosum. With prostaglandin E1, neither erection nor inflammation was observed.

Key words: Impotence – Intracavernous injection – Alpha-blockers – Prostaglandin – Rabbit

Introduction

The intracavernous injection of vasoactive agents in animal models and human volunteers has advanced the understanding of erectile physiology and the approach to the diagnosis and treatment of impotence [8]. Various agents have been used, including papaverine [13], phenoxybenzamine [3, 10], thymoxamine [6] prostaglandin E1 [11], or a combination of papaverine and phentolamine [14]. However, their repeated injection in humans and monkeys reportedly induces severe side effects such as fibrosis of the corpus cavernosum and angulation of the tunica albuginea [12]. Accordingly, we investigated the local response, especially the risk of inflammation, to intracavernous injection of different vasoactive agents in the rabbit.

Materials and Methods

Domestic rabbits weighing 1.7 to 2.2 kg were used. In a pilot study, 3 rabbits underwent cavernosography under general anesthesia to ensure that the tip of the needle was placed properly in the cavernous tissue.

Thirty-five rabbits were divided into 7 groups of 5 animals each. Each group received 5 injections of a different drug (see Table 1) over a 6- to 12-week period.

For intracavernous injection, the animals were not anesthetized. Each rabbit was held tightly by two investigators; another investigator protruded the penis with the left thumb and index finger and injected the agent via a 26-gauge needle into the right corpus cavernosum, dorsomedially, on the mid portion of the penis close to the attachment of the foreskin. The animal was then returned to its cage and observed for 3 hours. Special emphasis was placed on the erectile response, the reaction at the puncture site, and systemic reactions.

The quality of erection was expressed as a percentage of full erection. During the injection of 1 ml of fluid, the rabbit penis protrudes completely – this length was defined as 100% erection. During the 3-hour observation period, the erection was classified as 0% if the penis was not visible, 25% if the glans was visible, 50% if the penis protruded to half the length of full erection, and 75% when the length was between 50 and 100%. Systemic reactions were observable as changes (or lack thereof) in respiratory frequency and behavior. The latter was expressed by subjective grading scale: normal; agitated; and excited. The reaction at the puncture site was described individually.

One week after the 5th injection the animals were sacrificed, the penis was excised and fixed in formalin, sectioned and stained with hematoxylin-eosin. Special attention was given to the area of injection. The degree of inflammation seen on the stain was expressed as none, mild, or severe.

Table 1. Agents delivered via intracavernous injection to seven groups of five rabbits

Group	Agent	Dosage
1	Isotonic saline	1 ml
2	Phenoxybenzamine	5 mg/ml
3	Papaverine	20 mg/ml
4	Urapidil	5 mg/ml
5	Labetalol	5 mg/ml
6	Phentolamine	5 mg/ml
7	Prostaglandin E1	20 μg/ml

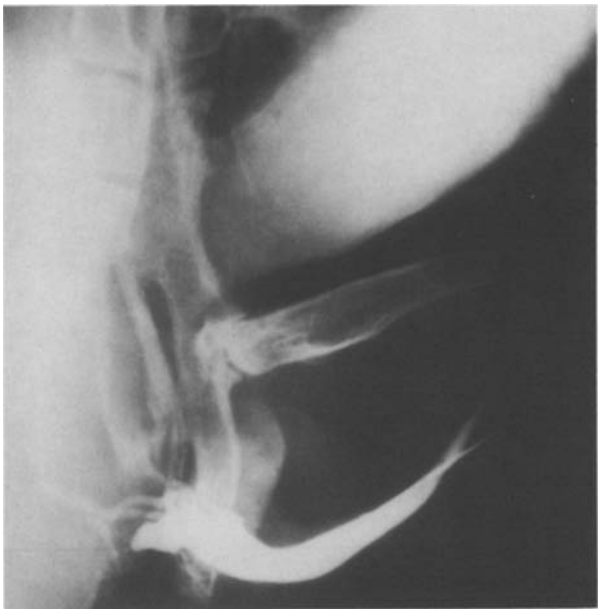

Fig. 1. Cavernosogram showing exact placement of the tip of the needle, opacification of the corpus cavernosum and subsequent drainage through the pelvic veins

Table 2. Erectile response to 25 intracavernous injections of isotonic saline

Hours	Percentage of full erection				
	100	75	50	25	0
0.5	–	–	–	4	21
1	–	–	–	–	25
2	–	–	–	–	25
3	–	–	–	–	25

Table 3. Erectile response to 18 intracavernous injections of phenoxybenzamine

Hours	Percentage of full erection				
	100	75	50	25	0
0.5	12	4	2	–	–
1	11	5	2	–	–
2	2	12	4	–	–
3	–	10	–	4	–

Table 4. Erectile response to 25 intracavernous injections of papaverine

Hours	Percentage of full erection				
	100	75	50	25	0
0.5	5	12	4	4	–
1	3	12	5	5	–
2	2	10	4	5	4
3	1	6	5	5	8

Table 5. Erectile response to 25 intracavernous injections of urapidil

Hours	Percentage of full erection				
	100	75	50	25	0
0.5	–	5	5	10	5
1	–	2	5	9	9
2	–	1	1	7	16
3	–	–	–	5	20

Table 6. Erectile response to 25 intracavernous injections of labetalol

Hours	Percentage of full erection				
	100	75	50	25	0
0.5	–	–	2	5	18
1	–	–	–	5	20
2	–	–	–	2	23
3	–	–	–	–	25

Table 7. Erectile response to 25 intracavernous injections of phentolamine

Hours	Percentage of full erection				
	100	75	50	25	0
0.5	20	3	2	–	–
1	19	3	3	–	–
2	15	4	4	2	–
3	12	4	4	5	–

Results

In the pilot study, cavernosography in 3 rabbits showed proper placement of the tip of the needle in the corpus cavernosum and subsequent drainage of the contrast medium via the pelvic veins (Fig. 1).

Systemic Reactions

All animals tolerated the injection without signs of pain. In the phenoxybenzamine group all animals were excited during the observation period, but each behaved normally on the day after injection. Two of the rabbits in the papaver-

Table 8. Erectile response to 25 intracavernous injections of prostaglandin E1

Hours	Percentage of full erection				
	100	75	50	25	0
0.5	–	–	–	7	18
1	–	–	–	5	20
2	–	–	–	2	23
3	–	–	–	–	25

Table 9. Inflammatory reactions

	Severe	Moderate	None
Isotonic saline	–	–	5[a]
Phenoxybenzamine	5	–	–
Papaverine	1	2	2
Urapidil	–	2	3
Labetalol	–	1	4
Phentolamine	–	2	3
Prostaglandin E_1	–	1	4

[a] Number of penises

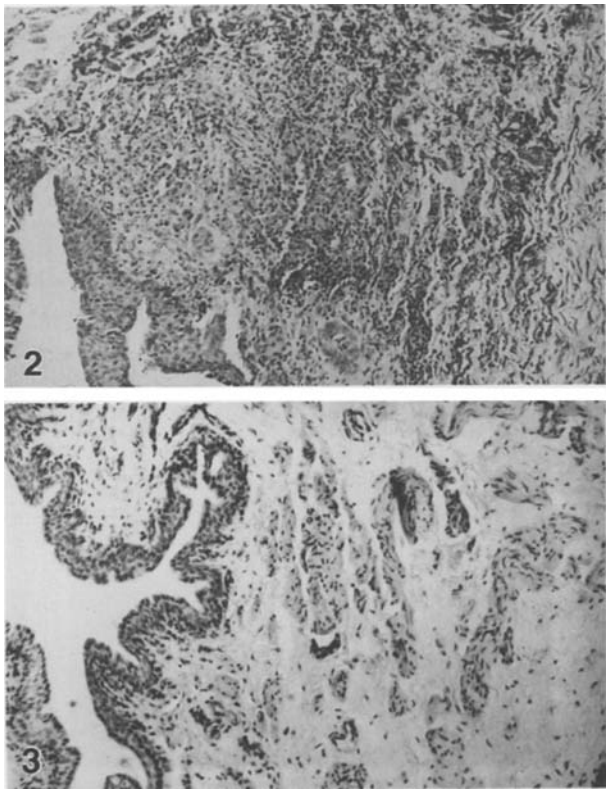

Fig. 2. Severe inflammation after 3 injections of 5 mg phenoxybenzamine (hematoxylin-eosin stain; magnification x250 before reduction)

Fig. 3. Corpus cavernosum with urethra of the rabbit after 5 injections of 1 ml isotonic saline; no signs of inflammation (hematoxylin-eosin stain; magnification x250 before reduction)

ine group were agitated after injection. The respiratory frequency did not change in any animal.

Erectile Response and Local Reactions

The responses to the injections are listed in Tables 2–8. In the phenoxybenzamine group (Table 3), only 18 injections could be delivered: 2 rabbits received 5, 2 received 3, and 1 received 2 injections. This last rabbit developed a severe necrotising inflammation of the penile skin after the second injection, and 2 other rabbits developed severe sclerosis of the cavernous tissue after 3 injections (Fig. 2). Three rabbits in the papaverine group developed edema of the penile skin for 2–3 days. In each group, subcutaneous hematomas developed immediately after the injecion on 5 to 9 occasions, but they subsided spontaneously without sequelae.

The inflammatory reactions are shown in Table 9. Figure 3 shows the corpus cavernosum with the urethra after 5 injections of 1 ml isotonic saline.

Discussion

The intracavernous injection of vasoactive drugs has become increasingly popular for the diagnosis and treatment of impotence. Any drug that causes smooth muscle relaxation and arteriolar dilatation is capable of producing penile erection. This can be achieved by alpha-adrenergic blockade, calcium channel blockade, activation of the adenyl cyclase system, or direct smooth muscle action. The drugs mainly used in humans for this purpose are papaverine or a combination of papaverine and phentolamine. However, these two agents are known to induce severe side effects, including fibrosis and priapism. Patients with venogenic impotence may experience reactions such as hot flushes, dizziness or hypotension.

Experimental data about the drugs used for intracavernous injections are scarce. In monkeys that underwent up to 100 papaverine injections, Abozeid et al. [1] reported minimal to marked fibrosis at the injection site and hypertrophy of the smooth muscles in the non-injected area of the corpus. They also found increased sensitivity to papaverine injections. It is not known if these reactions are related to the drug itself or to the trauma from the injection or the needle.

One aim of this study was to find other drugs for intracavernous injection with fewer side effects or none. Phenoxybenzamine, an alpha adrenergic blocking agent, has been used in humans with varying degrees of success [3, 10]. If erection occurs, its duration is not predictable. Additionally, the manufacturer has not endorsed its use for this purpose, citing the lack of controlled studies, the low pH (2.7–2.8)

and the mutagenic nature of this substance [4]. The severe inflammation and local reactions found in our rabbit study underscore this cautionary restriction. Papaverine is a phospodiesterase inhibitor with an osmolarity of 101 to 143 and a pH of 3.2. It increases levels of cyclic adenosine monophosphate and thus produces smooth muscle relaxation in the penile arterioles and corporal sinusoids. It is the most commonly used drug in humans for intracavernous injection and is known to produce erections. However, its main disadvantages are fibrosis and priapism, which can occur in up to 8% of patients [12]. In our study, it produced erections in some rabbits, but also induced severe to moderate inflammatory reactions in some. Urapidil and labetalol are alpha-adrenergic receptor blockaders, and labetalol also has a combined beta blocking effect. These substances are not used in humans and could not produce full erection in the rabbit. In contrast, phentolamine, another alpha-adrenergic antagonist, produced the most constant erections in the rabbit. Sectioning of the adrenergic vasoconstrictor nerves to the penis results in penile protrusion, indicating that constant adrenergic tone maintains penile flaccidity [9]. This explains how alpha-blockade can affect the rabbit penis, but it does not explain why phentolamine produces erections and labetalol and urapidil do not. In humans, phentolamine alone cannot produce sufficient erection but increases the effect of papaverine [2]. Prostaglandin E1 relaxes the human corpus cavernosum muscle in vitro [7] and produces erections in men with nonvasculogenic impotence [11]. In rabbits, no erection was obtained with PGE1. Therefore, even though the structure of the human and rabbit penis is similar microscopically [5], their concentrations of the prostaglandin receptor must differ.

The inflammatory reactions were most severe in the phenoxybenzamine group and least in the control and prostaglandin groups. We do not think that this is due to a different osmolarity and pH because the osmolarity of the phenoxybenzamine solution was between 1727 and 1785, while prostaglandin ranged between 1074 and 1080, and the pH of the solutions ranged from 3.2 (papaverine) to 5.6 (urapidil). Osmolarity and pH bore no correlation to the development of inflammation. Therefore, we think that the tissue damage results from the drug itself, but further studies are necessary to corroborate these data.

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