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Cover illustration. Representation of St. Cosmas and St. Damian in a drug formulary by Ortloff von Bayrlandt (Augsburg 1477).

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## Intracavernous Drug Delivery System: An Alternative to Intracavernous Injection in the Treatment of Impotence?

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**Key Words.** Erection · Intracavernous injection · Drug delivery system · Cavernous fibrosis

**Abstract.** In 6 monkeys, the feasibility of chronic intracavernous drug application via a permanent intracavernous catheter was examined. In 4 monkeys, a combination of papaverine (15 mg/ml) and phentolamine (0.5 mg/ml) was injected via the drug delivery system; in 2 monkeys each, 30 or 100 injections were done. As a control, saline was injected in 2 monkeys. The dose of the papaverine-phentolamine mixture to induce full erection had to be increased by a mean of 240%, comparing the 1st to the 30th injection. The dose then remained stable. After 100 injections, penile histology showed a thin fibrotic layer around the implantation site of the catheter. Beside slight smooth muscle hypertrophy in the papaverine-phentolamine group, there were no abnormal findings in the proximal and medial part of the cavernous bodies. The distal part of the cavernous bodies showed extensive fibrosis due to mechanical irritation by the tip of the intracavernous catheter. Given appropriate selection and indication, implantation of an intracavernous drug delivery system may be an alternative to chronic intracavernous injection in the treatment of impotence.

### Introduction

Within a few years after its first description [1, 2], intracavernous injection of vasoactive drugs became a standard therapy in the treatment of erectile dysfunction. Under the condition of careful patient selection and close follow-up [3-9] many studies showed this therapeutic option to be efficient and relatively safe. With an increasing number of both treated patients and applied injections per patient, cavernous fibrosis due to intracavernous (auto)injections were increasingly reported [10-14].

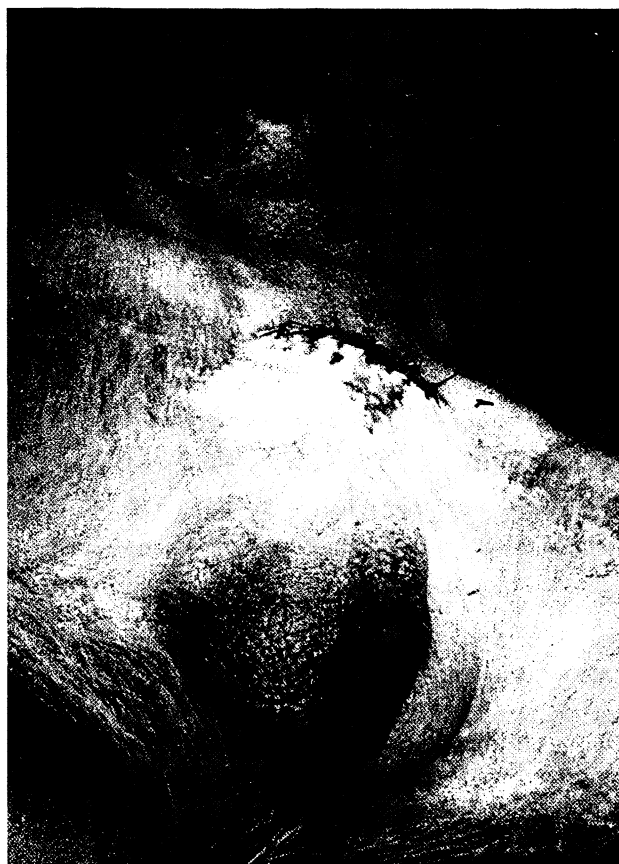
Recent studies in monkeys [15, 16] showed that the cavernous fibrosis is not only caused by the injected drug(s) itself, but also by the repeated trauma of the cavernous tissue by the puncture. An implantable drug delivery system into the cavernous bodies could be an alternative method of intracavernous drug administra-

tion without the need for repeated intracavernous injections.

The aim of our study was to evaluate the feasibility of intracavernous drug administration via an implantable drug delivery system in the treatment of erectile dysfunction.

### Material and Methods

Seven *Sinomolgus* monkeys weighing 5.2-8.7 kg were used for the study. After adequate anesthesia with ketamine (6 mg/kg body weight i.m.), the monkeys were placed in supine position. From an infrapubic incision, the drug port (Implantofix A, Braun Melsungen, Melsungen, FRG) was placed subcutaneously in the lower right abdominal quadrant (fig. 1). For intracavernous delivery, an intra-arterial catheter with a valved tip (No. 443953/1, Braun Melsungen) was chosen. After careful dissection, the right cavernous body was opened proximally between the dorsal vein and the right dorsal artery. To prevent slipping out of the cavernous body, the



**Fig. 1.** From an infrapubic approach, the drug port was placed in the lower right abdominal quadrant.

length of the intracavernous catheter was 3–4 cm. The tunica albuginea was closed using a watertight technique. The catheter length was then adjusted and the catheter connected to the drug port. The dead space of the complete system was less than 0.25 cm<sup>3</sup>. For injection into the port, 22-gauge Huber needles (that do not destroy the membrane of the port by the puncture; Braun Melsungen) were used.

Two monkeys presented postoperative wound infection. After removal of the drug delivery system and adequate conservative therapy, another drug delivery system could be implanted. One of these 2 monkeys was finally excluded from the study after scratching out the second drug delivery system. Before the implantation, drug port and catheter were filled with heparinized saline. Two weeks postoperatively, a standardized solution of papaverine (15 mg/ml) and phentolamine (0.5 mg/ml) was injected transcutaneously into the drug port 3 times a week in 4 monkeys, followed each time by a flush of 0.5 cm<sup>3</sup> heparinized saline. The injected dose was chosen dependent on the previous erectile response; a full erection of at least 30 min was projected. The initial dose was 0.4 ml, the mean dose after 30 injections was 1.02 ml. To minimize possible systemic side effects, the maximal dose was set to be 1.6 ml. Two monkeys were sacrificed after 30 and 2 after 100 injections. All injections were

done under ketamine anesthesia. The erectile response was monitored by a urologist by inspection and palpation.

Two monkeys served as controls. They were injected heparinized saline alone, following the above-mentioned injection protocol. They were sacrificed after 100 injections.

## Results

Beside the above-mentioned wound infections in 2/7 monkeys, no major surgical complications were observed. In 1 monkey, 2 episodes of tachycardia occurred after injection of 2 ml of the papaverine-phentolamine mixture. One monkey died of laryngospasm shortly after intramuscular ketamine injection (88 injections of papaverine-phentolamine).

Comparing the 1st to the 30st injection, the amount of the papaverine-phentolamine mixture increased from a mean of 0.3 to 1.02 ml (240%). The dose to induce full erection then remained relatively constant during the study (fig. 2). No monkey developed priapism, the maximal duration of full erection was 80 min.

After 30 injections of the vasoactive drug mixture, 2 monkeys were sacrificed. With the exception of the tip of the penis, the cavernous bodies did not reveal significant signs of localized or generalized fibrosis on palpation. Histology showed a thin fibrotic layer around the implantation site of the catheter. In the proximal and medial part of the cavernous bodies, the cavernous tissue surrounding the implantation site showed only scattered, nonsignificant increase in collagen (fibrous tissue; fig. 3a, b). In the distal part of the cavernous body, where the valved tip of the catheter filled almost the complete cavernous body, histology showed extensive replacement of cavernous smooth muscles by fibrous tissue. Here, multiple areas with hemosiderosis were found (fig. 4).

After 100 and 88 injections, respectively, the monkeys of the papaverine and phentolamine group were sacrificed. In addition, after 100 injections, the 2 monkeys in the saline control group were sacrificed. In both groups, palpation of the cavernous bodies suggested fibrosis of the distal part. Histologic examination showed similar findings in the saline and the papaverine-phentolamine groups. The implantation site of the catheter was surrounded by a thin fibrous sheath. This fibrous sheath showed no intraluminal protrusions in any sections. In the proximal and medial part of the penis, cavernous tissue showed no significant increase in collagen, whereas cavernous smooth muscles of the distal part were widely replaced by fibrous tissue. Caver-

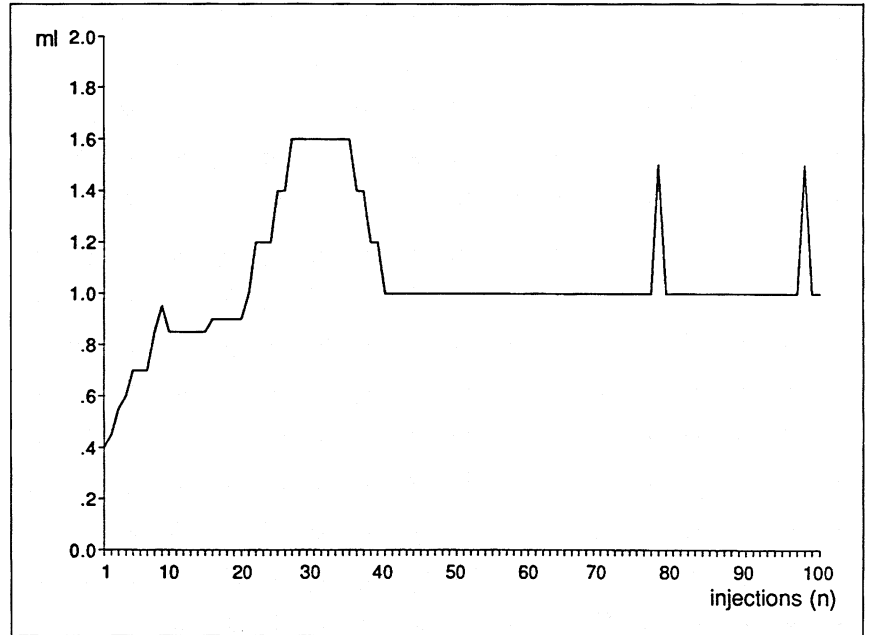


Fig. 2. Injection protocol of monkey No. 3, receiving 100 injections of the papaverine (15 mg/ml)-phenolamine (0.5 mg/ml) mixture.

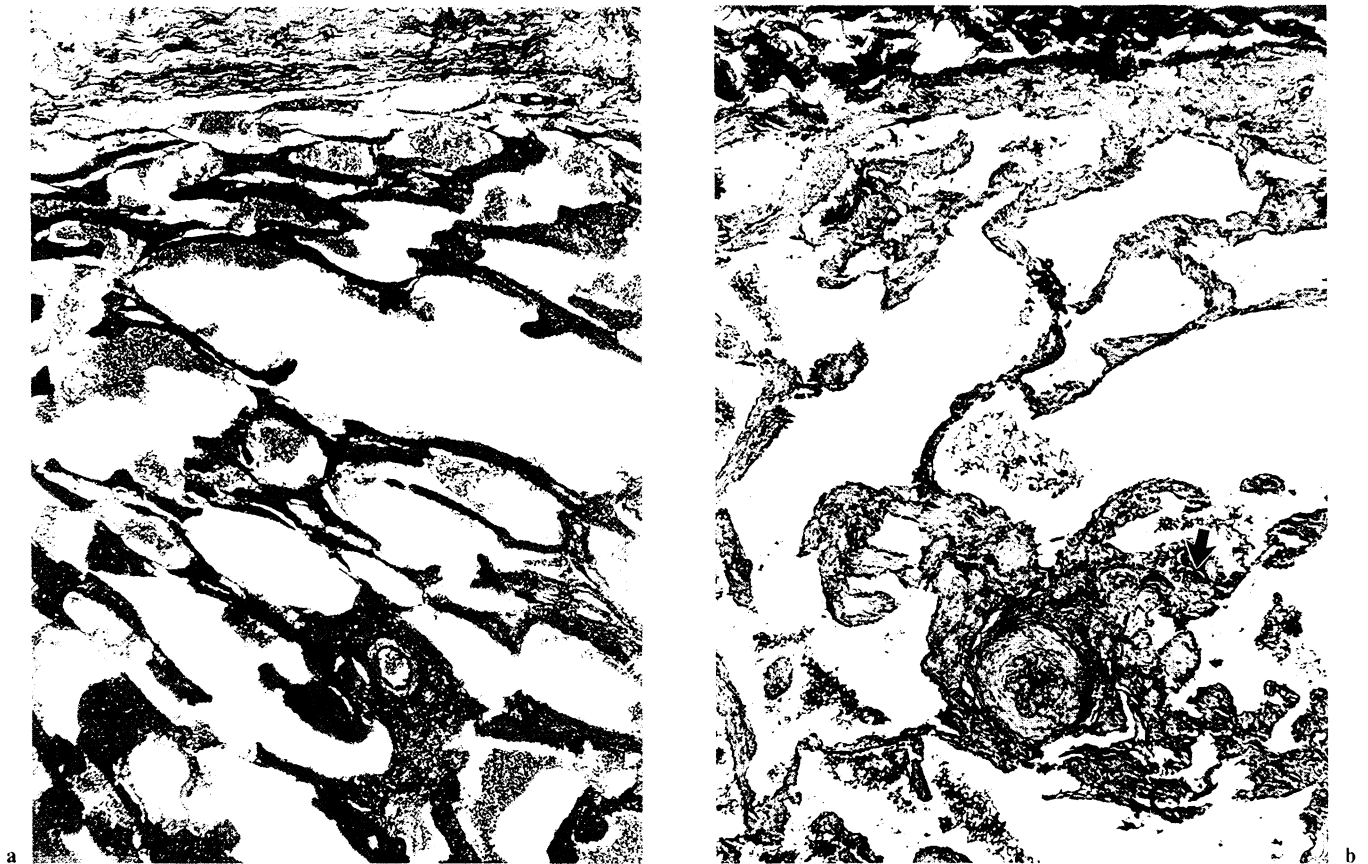


Fig. 3. **a** In the proximal and medial part of the cavernous bodies, the cavernous tissue of the saline group showed no abnormal findings. The cavernous sinusoids were partially filled with erythrocytes.  $\times 75$ . **b** In the proximal and medial part of the cavernous bodies, the cavernous tissue showed no fibrotic changes. The cavernous smooth muscles showed slight smooth muscle hypertrophy if compared to figure 3a. Note the arteriovenous anastomosis (arrow).  $\times 75$ .





**Fig. 4.** The fibrous sheath around the implantation site of the catheter is seen at the bottom, the tunica albuginea at the top of the figure. In all monkeys, the distal part of the cavernous bodies showed extensive fibrosis with few cavernous sinusoids left. The fibrous tissue showed hemosiderosis (dark dots) as a sign of chronic microtrauma with consecutive hemorrhage.  $\times 150$ .

nous smooth muscles in the papaverine-phenolamine group showed a slight but evident hypertrophy compared to the saline group (compare fig. 3a and 3b).

## Discussion

Our results show that at the implantation site of an intracavernous drug delivery system a thin fibrotic layer is formed by the cavernous tissue. It can be assumed that this fibrotic sheath was responsible for the need for augmentation of the dose of the papaverine-phenolamine mixture to constantly induce full erection. This phase of continuous augmentation lasted until about the 30th injection (about 3 months). The dose to induce full erection then remained rather constant (fig. 2). This stable erectile response is probably due to an unchanged diffu-

sion pattern for the vasoactive mixture of the fibrous sheath between the 30th and the 100th injection, i.e. the 3rd and the 9th month. The question if the permeability of the fibrous sheath will remain stable or further decline over a longer period of time cannot be answered by our study.

The assumption of a comparable fibrotic sheath around the catheter after 30 compared to 100 injections was supported by our histological findings. There was equal thickness of the fibrous sheets after 30 and 100 injections. Beside the fibrous sheath around the implantation site, no significant changes of the cavernous tissue were found in the proximal and medial part of the penis.

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Comparing the papaverine-phenolamine group to the saline group, we found discrete smooth muscle hypertrophy in the first. There is a dramatic difference comparing the slight cavernous smooth muscle hypertrophy to papaverine-phenolamine in our study and the extensive smooth muscle hypertrophy to papaverine alone [15, 16]. Although the monkey species used in the studies are different, the results are likely to be comparable because of a similar penile size and an identical injection protocol. The reason for the evident histologic difference between the study of Abozeid et al. [15] and Aboseif et al. [16] and ours is speculative, since there are still extensive gaps in our understanding of basic smooth muscle physiology. It seems that there is a significant difference in cavernous smooth muscle relaxation by papaverine (direct smooth muscle relaxant) and phenolamine (alpha receptor blocker and therefore acting by reduction of the sympathetic tone) on the cellular and/or subcellular level, thus inducing extensive smooth muscle hypertrophy in one and not in the other case.

Histology of the distal part of the cavernous body showed extensive fibrosis. This replacement of smooth muscles by fibrous tissue is probably due to the mechanical irritation by the valved catheter tip. At variance with the dog and similar to the human, erection of the monkey consists of tumescence and rigidity. During tumescence and detumescence, the valved tip slips within the cavernous body thus causing fibrous changes. This as-

sumption is supported by the extensive hemosiderosis in the fibrotic cavernous tip as a sign of frequent trauma with consecutive microhemorrhage. A further cause of the extensive distal fibrosis is the size of the valved catheter tip, that, although relatively small, filled almost the whole lumen of the distal cavernous body, therefore causing a localized continuous compression of the cavernous tissue.

Desai et al. [17] were the first to describe intracavernous implantation of a drug delivery system. It was applied in 3 patients with difficulties regarding direct intracavernous injections for the treatment of impotence. For intracavernous drug delivery, they used a catheter for intravenous implantation (without valved tip) with several holes at the end of the catheter. After explantation of the catheter in 1 patient, histologic examination revealed fibrous tissue protruding into the holes at the end of the catheter, which caused inacceptably high injection pressures [Desai, K.M.: personal commun.]. In our experimental study, we therefore chose a catheter with valved tip (instead of holes). Usually used for intra-arterial implantation, it can withstand the high intracavernous pressures during erection without the risk of retrograde blood flow into the catheter.

Beside the fibrous sheath around the implantation site of the catheter, we did not find a significant increase in fibrous tissue within the cavernous tissue. Although direct comparison with the chronic intracavernous injection studies [15, 16] is difficult due to different subspecies and different drug application, it seems that the addition of phentolamine to papaverine significantly reduced cavernous fibrosis compared to the intracavernous injection of papaverine alone [15, 16].

Our results show that an intracavernous drug delivery system can be used to apply drugs intracavernously over a certain period of time. Further long-term studies are needed before its application in carefully selected patients may be considered. In this case, combination with a miniature pump with reservoir would be advantageous.

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