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EFFICACY AND SAFETY OF INTRACAVERNOSAL ALPROSTADIL IN MEN WITH ERECTILE DYSFUNCTION

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Abstract Background. Erectile dysfunction is a common medical problem affecting many men. Although several intracavernosal therapies are available, their efficacy and safety have not been studied systematically.

Methods. We investigated the efficacy and safety of alprostadil formulated for intracavernosal treatment in three separate multi-institutional, prospective studies in men with erectile dysfunction of vasculogenic, neurogenic, psychogenic, and mixed causes. Clinical and laboratory evaluations of erection and the feasibility and satisfactoriness of sexual activity as assessed both by the men and by their partners were the primary measures of efficacy.

Results. In a dose-response study of 296 men, all doses of alprostadil were superior to placebo and there was a significant dose-response relation ($P \leq 0.001$), resulting in higher response rates with increasing doses of alprostadil (from 2.5 to 20 μg). In a dose-finding study of

201 men, the minimal effective dose was $\leq 2 \mu\text{g}$ in 23, 20, 38, and 23 percent of men with erectile dysfunction of neurogenic, vasculogenic, psychogenic, or mixed causes, respectively. In a six-month self-injection study in 683 men, the participants reported being able to have sexual activity after 94 percent of the injections. The men and their partners rated the sexual activity as satisfactory after 87 and 86 percent of the injections, respectively. Penile pain, usually mild, occurred in 50 percent of the men at some time but after only 11 percent of the injections. Prolonged erections occurred in 5 percent of the men, priapism in 1 percent, penile fibrotic complications in 2 percent, and hematoma or ecchymosis in 8 percent.

Conclusions. In men with erectile dysfunction, intracavernosal injection of alprostadil is an effective therapy with tolerable side effects. (N Engl J Med 1996;334:873-7.)

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ERECTILE dysfunction, the consistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse, may affect 20 million to 30 million American men.^{1,2} It impairs men's mental well-being and interactions with their family and associates. Most men with erectile dysfunction are thought to have organic impairment,³ especially circulatory insufficiency, with psychological problems as important contributing factors. The available treatments include psychological and medical therapy, vacuum constriction devices, drug therapies involving intracavernosal self-injection, microvascular arterial or venous surgery, and penile-prosthesis implantation.³ With self-injection therapies, a man can treat himself after the desirable dose of the drug is selected by his physician and he has been instructed in the self-injection technique.⁴

Intracavernosal-injection therapy is an important therapeutic option for men with erectile dysfunction of various causes. It does not involve surgery or devices and

has reproducible erection responses and tolerable side effects. Physiologic mechanisms that relax penile smooth muscle and elicit erections are mimicked by vasoactive drugs administered intracavernosally that directly relax the smooth muscle.^{5,6} Published reports on the intracavernosal use of alprostadil since 1986^{7,8} consist primarily of data derived from uncontrolled, retrospective studies with different formulations. Although these data indicate the efficacy and safety of alprostadil for the treatment of erectile dysfunction,^{9,10} they have not usually been based on investigational designs that meet strict standards. Accordingly, we conducted three prospective studies, each in a separate group of impotent men, to address the issues of effective dosing, efficacy, responses of patients and their partners, and the safety of a new formulation of alprostadil sterile powder (Caverject) for intracavernosal injection.

METHODS

We conducted the three studies at 51 sites throughout the United States. The protocols were approved by the institutional review boards, and all participants gave written informed consent. Men with erectile dysfunction of vasculogenic, neurogenic, psychogenic, or mixed origin lasting at least four months who were seen in urology clinics at these sites were enrolled. Screening procedures consisted of medical histories and physical examinations, including testing for the bul-

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bocavernous reflex. The presence of this reflex suggests an intact sacral arc. Laboratory evaluation included a complete blood count, serum biochemical tests, and urinalysis. Men were excluded from the study if they had penile deformities (including fibrosis), a history of priapism, the sickle-cell trait, recent major illness, uncontrolled diabetes mellitus or hypertension, a major psychiatric disorder, infection with the human immunodeficiency virus, or other transmissible disease. Heavy smokers (>40 cigarettes per day) were also excluded. Serum testosterone (in the morning), prolactin, free thyroxine, and thyrotropin were measured to rule out endocrine causes of erectile dysfunction.

Alprostadil was supplied as a sterile, freeze-dried powder in a 5-ml vial. After it was reconstituted with 1 ml of bacteriostatic water, each vial contained 20 μg of alprostadil, 173 mg per milliliter of lactose, and 47 μg per milliliter of sodium citrate. The placebo contained lactose and sodium citrate and had the same appearance.

Only one person (either an investigator or a research nurse) gave the injections at each center. The penis was pulled away from the body until the skin was taut. A syringe with a 27- to 30-gauge $\frac{1}{2}$ -inch needle was held at a right angle to the penis, and the injection was given at the base of the penis on either side, avoiding visible veins. Pressure was applied to the injection site for five minutes or until bleeding stopped.

The same person who gave the injection palpated the penis and rated the rigidity as absent, partial, or full at specified times after the injection; full rigidity implied an erection sufficient for intercourse. In the first two studies, radial rigidity was measured by the RigiScan Ambulatory Rigidity and Tumescence System³ (Dacomed, Minneapolis) before injection and for two hours afterward. The RigiScan was attached to a personal computer during monitoring and used special software developed for this project. A response was defined as ≥ 70 percent rigidity at the tip or the base of the penis lasting 10 consecutive minutes or longer. The duration of erection was also measured. Prolonged erection was defined clinically as an erection lasting from four to six hours, and priapism as an erection lasting more than six hours. Statistical evaluations were based on an intention-to-treat analysis including all the men who entered the study and received at least one dose of drug or placebo.

Dose-Response Study

In this parallel-design, double-blind study, fixed doses of alprostadil or placebo were administered. A total of 296 men, 21 to 74 years old (mean, 54), were enrolled at 14 sites, with 9 to 40 men enrolled per site. The cause of erectile dysfunction in these men was determined on the basis of the medical history, physical examination, and laboratory evaluation. The men were randomly assigned to one of five groups and received a single 1.0-ml injection of either placebo (59 men) or alprostadil in doses of 2.5 μg (57 men), 5 μg (60 men), 10 μg (62 men), or 20 μg (58 men). Both the person who gave the injection and the patient were unaware of what was given.

Dose-Finding Study

This single-blind dose-escalation study was conducted at 15 sites with a total of 201 men (including 12 who had participated in the dose-response study) who were 20 to 72 years of age (mean, 54); 5 to 30 men were enrolled per site. In these men, the diagnosis of erectile dysfunction was made on the basis of medical history, physical examination, laboratory evaluation, duplex or color Doppler sonography, penile-brachial index (penile systolic pressure divided by brachial systolic pressure), and penile biothesiometry.^{3,4} The diagnosis of psychogenic erectile dysfunction was based on the history and the exclusion of other causes. The initial dose of alprostadil was 0.5 μg , followed by 1, 2, 3, 4, 5, 7.5, 10, 15, 20, 25, and 30 μg at intervals of 2 to 14 days, until a minimal effective dose (resulting in ≥ 70 percent rigidity for ≥ 10 minutes by RigiScan testing) was established or the maximal dose of 30 μg was reached.

Study of Efficacy and Safety

This open-label, flexible-dose study in 683 men (including 40 who had participated in the dose-response study) 20 to 79 years of age (mean, 58) with stable sexual relationships was undertaken at 33 sites

to investigate the safety and efficacy of alprostadil and the feasibility of self-injection at home. Three to 61 men were enrolled per site. The cause of erectile dysfunction in these men was assessed by history taking, physical examination, and laboratory evaluation. Penile ultrasonography was performed to rule out preexisting fibrosis of the corpora cavernosa. The optimal dose of alprostadil, defined as the dose inducing an erection sufficient for vaginal penetration and lasting ≤ 60 minutes, was established for each man by titration. The men were trained to inject themselves before beginning the six-month trial, during which they recorded in diaries the frequency of drug use as well as evaluations of the erection (none, partial, full) and of intercourse after each injection. The sexual activity after each injection was rated by the men and their partners as satisfactory or unsatisfactory. The partners also had the option of not rating satisfaction. During monthly clinic visits, the data from the diaries were transferred to the case-report form, and open-ended questions were asked to elicit information about adverse medical reactions. If necessary, the dose of alprostadil was adjusted by the investigator during the study. Physical examination and laboratory evaluation were repeated at the end of the study.

Statistical Analysis

For the categorical variables in the dose-response study (erection response to injection, based on clinical and RigiScan evaluations), the extended Mantel-Haenszel test¹¹ was used to assess the overall dose effect. Pairwise comparisons of alprostadil doses with placebo were performed with the use of the Mantel-Haenszel test. The overall dose-response relation among alprostadil doses was determined with logistic-regression analysis. The duration of erection was analyzed by analysis of variance, with pairwise comparisons performed within the analysis-of-variance model. Adjustment was made for multiple testing by the requirement that the overall test results be significant before pairwise comparisons were considered.

When the minimal effective dose or optimal dose was calculated (in the dose-finding and the efficacy and safety studies), the data on men who did not respond were included in the calculations and treated as censored observations.

RESULTS

Dose-Response Study

Of the 296 men, 130 (44 percent) were judged to have a vasculogenic cause of erectile dysfunction, 41 (14 percent) to have a psychogenic cause, 39 (13 percent) to have a neurogenic cause, and 86 (29 percent) to have mixed causes. Only seven men (2 percent) had received previous intracavernosal treatment. All the men completed the study. Figure 1 shows the percentage of men who responded to each dose of alprostadil. No man responded to placebo. The differences in the response rates in both the clinical and the RigiScan evaluations between each of the doses of alprostadil and placebo were statistically significant ($P \leq 0.01$ or $P \leq 0.001$). There was also a statistically significant dose-response relation, with higher clinical response rates ($P \leq 0.001$) and higher RigiScan response rates ($P = 0.005$, except with the 10- μg dose) with increasing doses of alprostadil.

The mean duration of erection after alprostadil injection ranged from 12 minutes after the 2.5- μg dose to 44 minutes after the 20- μg dose (Fig. 2), and the relation was linear ($P = 0.025$). Penile pain was reported by 54 of the 237 men (23 percent) who received alprostadil, but the pain was not related to the dose. Priapism developed in one man after he received 5 μg ; it was treated with blood aspiration and irrigation with ephedrine.

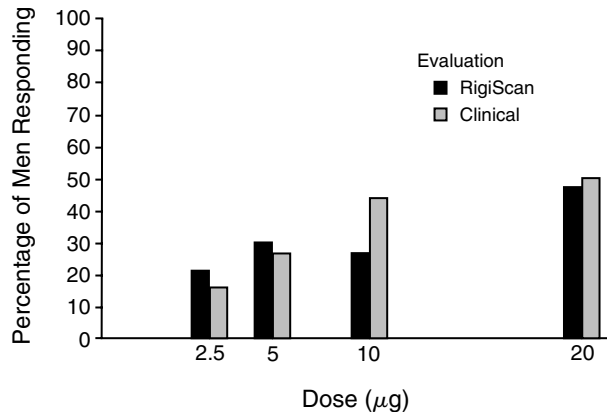


Figure 1. Percentages of 296 Men with Erectile Responses to Single Injections of Placebo or Alprostadil as Evaluated Clinically ("Full Rigidity") and by RigiScan (≥ 70 Percent Rigidity for ≥ 10 Minutes).

None of the 59 men who received placebo had a response. There were 57 men in the 2.5- μg group, 60 in the 5- μg group, 62 in the 10- μg group, and 58 in the 20- μg group.

Five men reported prolonged erections, but only in two of them did the erection last four hours or more. One man had received 5 μg of alprostadil, two 10 μg , and two 20 μg .

Dose-Finding Study

Of the 201 men in this study, 73 (36 percent) had a vasculogenic cause of erectile dysfunction, 48 (24 percent) had a neurogenic cause, 33 (16 percent) had a psychogenic cause, and 47 (23 percent) had mixed causes. None had been treated before with intracavernosal therapy. A total of 135 men completed the study. The reasons for discontinuation were protocol violation (3 men), nonserious medical events (4), loss to follow-up (14), misinterpretation of RigiScan data (32), and premature termination of study (13). Among the men who completed the study, the minimal effective dose (resulting in ≥ 70 percent rigidity for ≥ 10 minutes) was ≤ 2 μg in 9 of 24 (38 percent), 7 of 31 (23 percent), 10 of 50 (20 percent), and 7 of 30 (23 percent) men with erectile dysfunction of psychogenic, neurogenic, vasculogenic, and mixed causes, respectively. Eleven men responded to the lowest alprostadil dose tested (0.5 μg). The median effective dose was 3.0, 4.0, and 5.0 μg in the psychogenic, neurogenic, and vasculogenic groups, respectively, and 4.5 μg in the mixed group. The duration of the erection was 11 to 100 minutes (mean, 37). Penile pain occurred in 69 of the 201 men (34 percent), 2 of whom refused further treatment. However, only 148 of all 1382 injections (11 percent) caused pain. No man had prolonged erection or priapism.

Study of Efficacy and Safety

Of the 683 men in this study, 389 (57 percent), 92 (13 percent), 67 (10 percent), and 135 (20 percent) were judged to have vasculogenic, neurogenic, psychogenic, and mixed causes of erectile dysfunction, respectively.

Thirty-nine percent of these men had received intracavernosal treatment previously. Adequate doses of alprostadil (between 0.2 and 80 μg) were determined in the clinic for 606 (89 percent) of the 683 men. These doses were between 7.5 and 20 μg for 364 (60 percent) and ≤ 20 μg for 475 (78 percent). Of the 606 men, 577 began treatment with the drug at home by self-injection (29 chose not to begin home treatment). Four hundred seventy-one (69 percent) completed the six-month study. The reasons for discontinuation were nonserious adverse reactions, most often penile pain (in 64 men), lack of efficacy (56), loss to follow-up (27), dislike of self-injection (19), violation of the protocol (14), difficulty in scheduling visits (10), problems with partners (8), no need for the drug (5), difficulty with injection technique (4), intercurrent illness (3), lack of sex drive (1), and death (1, unrelated to the study drug).

The initial adequate dose was continued by 247 (43 percent) of the 577 men who began self-treatment at home; the dose was increased for 231 (40 percent) and reduced for 99 (17 percent) during the six months of therapy. The mean dose was 20.7 μg at the end of the study, as compared with 17.7 μg at the start. The distribution of initial and final doses is shown in Figure 3.

Of the 13,762 alprostadil injections after which sexual activity was recorded, 11,924 (87 percent) resulted in satisfactory sexual activity. According to the partners, satisfactory intercourse resulted from 8496 of 9892 injections (86 percent) (Table 1).

Penile pain was reported by 343 of the 683 men (50 percent) (Table 2), but pain occurred after only 1873 of all 16,575 injections (11 percent), indicating that many men had pain after only some injections. In most instances, the pain was mild, but 43 men (6 percent) withdrew from the study because of pain. Prolonged erection was reported by 35 men (5 percent), of whom

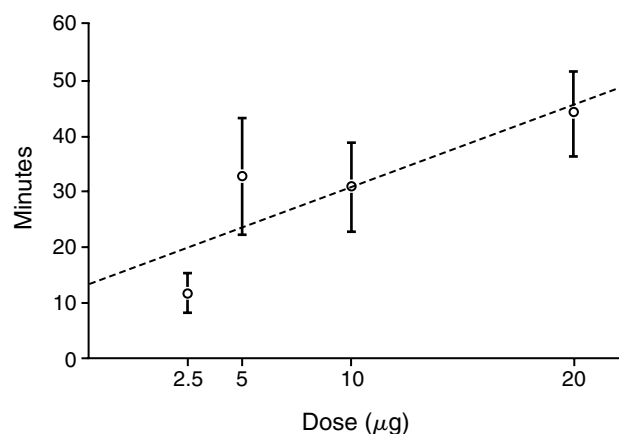


Figure 2. Relation between Alprostadil Doses and the Mean (\pm SE) Duration of Erection as Measured by RigiScan (≥ 70 Percent Rigidity for ≥ 10 Minutes) in 296 Men with Erectile Dysfunction.

None of the 59 men who received placebo had a response. There were 57 men in the 2.5- μg group, 60 in the 5- μg group, 62 in the 10- μg group, and 58 in the 20- μg group.

3 discontinued treatment. Priapism occurred in five men (1 percent) after doses of 5 to 12 μg ; only one man required drug therapy, and none discontinued treatment. Penile fibrosis (including Peyronie's disease, deviation or curvature, and nodules) was detected in 15 men (2 percent) during the study.

Systemic medical events possibly related to alprostadil occurred in 39 men (6 percent). Most of these events affected the urogenital system (e.g., testicular pain and swelling; scrotal pain and edema; decreased or increased urinary frequency; hematuria; and pelvic pain). None were considered serious. One man died of cardiac arrest judged to be unrelated to alprostadil. Only nine men (1 percent) reported side effects potentially related to hypotension, such as irregular pulse, lightheadedness, dizziness, diaphoresis, vasodilation, and vasovagal reaction. Results of laboratory tests revealed no evidence of alprostadil-induced abnormalities.

DISCUSSION

The in-office erection response in the first two studies was assessed by objective, computerized RigiScan technology for measuring penile rigidity. The selected RigiScan response was based on a nocturnal penile-tumescence study, in which a rigidity of ≥ 70 percent was considered sufficient for intercourse and a rigidity of 40 to 70 percent was considered only partially sufficient.¹² Our criteria for response were more conservative than those used in another recent study of intracavernosal therapy.¹³

In the dose-response study, placebo failed to induce a clinical or RigiScan response. This confirms the re-

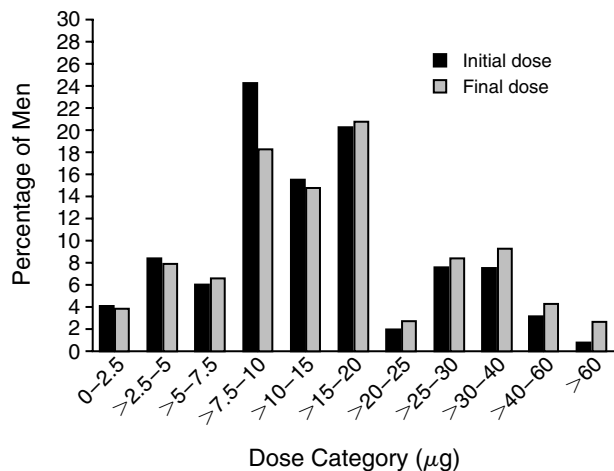


Figure 3. Distribution of Initial and Final Doses of Alprostadil in 577 Men with Erectile Dysfunction in the Study of Efficacy and Safety, According to Dose Category.

Table 1. Assessment by the Men and Their Partners of Sexual Activity after Self-Injection with Alprostadil at Home in the Study of Efficacy and Safety.

RESPONDENT	NO. OF INJECTIONS	NO. (%) OF INJECTIONS FOLLOWED BY SATISFACTORY ACTIVITY		
		INTERCOURSE	MASTURBATION	TOTAL
Men (n = 577)*	13,762†	11,223 (82)	701 (5)	11,924 (87)
Partners (n = 552)	9,892‡	8,496 (86)	NA§	8,496 (86)

*Five hundred fifty-one men reported information about sexual activity; 507 of these (92 percent) reported satisfactory sexual activity at least once during the study.

†There was a total of 14,586 injections; the men did not record sexual activity for 824 of the injections.

‡The partners did not agree to rate the satisfactoriness of sexual activity after 2954 of the total of 14,856 injections and provided no information after 1740 injections.

§NA denotes not applicable.

sults of a crossover study of alprostadil in men with psychogenic impotence.¹⁴ Alprostadil was increasingly effective as doses increased from 2.5 to 20 μg . A dose-response relation was also found in another trial of alprostadil by von Heyden et al.¹⁵ The lower response rates in our trial, as compared with earlier studies of alprostadil,^{16,17} may have resulted from our use of a random, single injection of alprostadil at fixed doses, not arrived at by titration; our liberal entry criteria; and the administration of injections in the doctor's office.

Although men with neurogenic erectile dysfunction were reported to respond to alprostadil with increased sensitivity,¹⁸ men with vasculogenic dysfunction responded less well.¹⁹ In the dose-finding study, a similar percentage of men in each of these two groups responded to a dose of 2 μg of alprostadil or less, although the median effective dose was higher in the vasculogenic group. It is possible that men with milder vasculogenic dysfunction responded to the dose of 2 μg or less.

The results of all three studies indicate the need for the individualization of optimal doses of alprostadil, which should be established by dose titration in the physician's office, starting with a low dose. We recommend an initial dose of 2 to 3 μg , followed by small increments. Doses self-injected during home therapy should be adjusted as needed.

The results of the study of efficacy and safety reflected the expected use of alprostadil in real-life situations. The rate of dropout for therapy-related reasons was lower than that reported elsewhere,¹⁸ possibly because of the close monitoring and because of the free drug supply. With respect to the most important clinical end point — satisfaction with sexual activity — a high percentage of both the men and their partners were satisfied with alprostadil treatment. The side effects were similar to those reported in studies using different formulations of alprostadil.^{16,17} Penile pain was the principal side effect; its frequency was highest in the study of efficacy and safety. Though it was rated mostly as mild, it was a limiting factor for some men. Pain is probably induced by alprostadil itself, since prostaglandins of the E group have a pain-sensitizing action.²⁰ Comparison of the frequency of prolonged erection or priapism after the administration of alprostadil with the frequency in studies of other

Table 2. Frequency of Local Medical Events among 683 Men Treated with Alprostadil in the Study of Efficacy and Safety.

LOCAL MEDICAL EVENT	No. OF MEN (%)
Penile pain	343 (50)
Hematoma or ecchymosis	57 (8)
Prolonged erection (4 to 6 hr)	35 (5)
Priapism (>6 hr)	5 (1)
Other penile disorders*	29 (4)
Penile edema	17 (2)
Penile fibrotic complications	15 (2)
Peyronie's disease	9 (1)
Curvature or deviation	4 (1)
Fibrotic nodules	2 (0.3)

*Other penile disorders include side effects such as penile numbness, irritation, sensitivity, erythema, pruritus, and yeast infection.

vasoactive drugs is difficult because of different definitions of these events and different doses. Nevertheless, in a review of eight large studies,²¹ 11 percent of men treated with papaverine had prolonged erections (lasting three to six hours). Clinicians who prescribe self-injection therapy with vasoactive drugs must inform men of the potential seriousness of priapism and the need to seek prompt treatment if it occurs.

Penile fibrosis was observed in the study of alprostadil's efficacy and safety. However, it also occurs without intracavernosal therapy,²² appears to be more common in men with erectile failure,²³ and has also been reported after injections of other vasoactive drugs.^{21,24,25} Repeated needle injury²⁶ and chronic microtrauma induced by sexual activity, especially with a partially erect penis, may be other contributing factors. Proper training of men in the injection technique may minimize the risk of this complication. Men who are treated with alprostadil should be instructed to report any new side effects related to the penis and should be supervised periodically during self-injection. If penile fibrosis is detected, the treatment should be discontinued.

In conclusion, intracavernosal alprostadil is an effective and safe therapy for men with erectile dysfunction, provided the individual dose is established by titration and the men are trained in the injection technique and are supervised periodically during self-injection.

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APPENDIX

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