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INTRACAVERNOUS ALPROSTADIL ALFADEX (EDEX/VIRIDAL) IS EFFECTIVE AND SAFE IN PATIENTS WITH ERECTILE DYSFUNCTION AFTER FAILING SILDENAFIL (VIAGRA)

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ABSTRACT

Objectives. Sildenafil (Viagra), an oral treatment for erectile dysfunction, has proved popular since its introduction in 1998. However, not all patients respond to this form of therapy. Consequently, this study investigated the efficacy of intracavernous alprostadil alfadex (EDEX/VIRIDAL) treatment in patients not responding to sildenafil.

Methods. In an open-label, multicenter study, patients with erectile dysfunction were treated with sildenafil for 4 weeks. The initial dose was 50 mg, which was increased to 100 mg if no response was achieved. Patients not responding to treatment, measured using the International Index of Erectile Function (IIEF) questionnaire, entered an alprostadil alfadex in-office titration phase, to determine the optimal dose, up to 40 μg. A 6-week alprostadil alfadex at-home treatment phase followed.

Results. In 67 patients who did not respond satisfactorily to sildenafil, the alprostadil alfadex at-home therapy resulted in improvements in questions 3 and 4 of the IIEF in 60 (89.6%) and 57 (85.1%) patients, respectively. The mean improvement in IIEF score for these patients was 2.75 and 2.63 for questions 3 and 4, respectively. The most common side effect was penile pain in 25 (29.4%) of 85 patients treated with alprostadil alfadex in-office and at home.

Conclusions. Alprostadil alfadex therapy can be used effectively and safely in men who fail initial therapy with sildenafil. UROLOGY **55:** 477–480, 2000. © 2000, Elsevier Science Inc.

Erectile dysfunction (ED), defined as the consistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity, affects millions of men.[1] With the launch of sildenafil (Viagra) for the treatment of ED, a new algorithm of a step care model has been established, with oral medication as the first line of therapy. Sildenafil is a phosphodiesterase type 5 (PDE5) inhibitor. Response rates of up to 85% have been reported compared with a rate of up to 50% in the placebo control.[2] A recent meta-analysis of 10 sildenafil trials reported response rates of approximately 70% for sildenafil and 40% for placebo.[3]

There is a lack of information on the response to alprostadil alfadex (EDEX/VIRIDAL) in patients who did not respond to previous treatment with sildenafil. Alprostadil alfadex is delivered directly by injection to the intracavernous tissue, which results in an erection within 5 to 20 minutes. Efficacy rates of up to 94% have been reported.[4–6]

The aim of the current study was to evaluate the efficacy of alprostadil alfadex in patients who failed treatment with sildenafil.

MATERIAL AND METHODS

PATIENTS

A total of 134 men, 18 to 80 years old, with ED, who had an International Index of Erectile Function (IIEF) score of 3 or less for question 3 or 4, or both (Table I), were enrolled in the study. Standard inclusion/exclusion criteria for this type of

This multicenter clinical trial was sponsored by a grant from Schwarz Pharma. R. Shabsigh and H. Padma-Nathan are paid consultants to the sponsor. J. G. McMurray holds stock in Pfizer, Inc.

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Submitted: October 14, 1999, accepted (with revisions): December 1, 1999

0090-4295/00/$20.00
PII S0090-4295(99)00612-3

TABLE I. *International Index of Erectile Function, Questions 3 and 4*

Question 3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
Question 4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
Response
0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

trial were used. Patients were enrolled in compliance with the prescribing information for both products. Institutional Review Board approval of the trial was obtained, as well as informed consent from all patients.

Study Design

The study was conducted at six centers in the United States. The study was divided into three phases.

Phase 1—Sildenafil Screening/Failure Confirmation. During the initial sildenafil screening/failure confirmation phase, patients were given nine tablets, each containing 50 mg. The drug was used according to the prescribing information. An initial dose of 50 mg on at least one occasion was advised, which, if unsuccessful, was increased to 100 mg (50 mg $\times$ 2). The patient then continued to use the 100-mg dose even if a rigid erection was not achieved. Patients were asked to use all of the medication during a maximum period of 4 weeks. In the case of over-response or side effects, the patient could return to the 50-mg dose. Patients were assessed using the IIEF questionnaire. Any patients achieving a score of 3 or less for question 3 or 4, or both, who also were not satisfied with sildenafil were classified as nonresponders and entered into the second phase of the study. Patients with a score of 4 or more for questions 3 and 4 and/or satisfied with sildenafil treatment no longer participated in the trial.

Phase 2—Alprostadil Alfadex In-office Titration. Patients were titrated to their individual optimal dose (1 to 40 μg) of alprostadil alfadex using a double-chamber cartridge. Erectile response was assessed by the physician using a four-grade scale: 0, no tumescence; 1, partial tumescence with inadequate rigidity for vaginal penetration; 2, full tumescence with moderate rigidity allowing for vaginal penetration (with some difficulty/bending); and 3, full rigidity (penetrates vagina easily without difficulty/bending). Patients achieving a grade 2 (full tumescence with moderate rigidity) or grade 3 (fully rigid) erection by the end of the titration phase were included in phase 3 of the study. Patients with an inadequate response (grade 0 or 1) to the maximum dose were withdrawn from the study. Similarly, those patients having an over-response (full rigidity for more than 60 minutes) at the lowest dose were withdrawn. In addition, patients assessed their sexual function using the IIEF.

Phase 3—Alprostadil Alfadex At-home Treatment. A minimum of 6 and a maximum of 18 administrations of alprostadil alfadex using the double-chamber cartridge system were recommended during the 6-week alprostadil alfadex at-home treatment phase. Patient assessment of treatment was based on questions 3 and 4 of the IIEF.

Statistical Analysis

Primary end points were improvement in obtaining an erection and maintenance of the erection after vaginal penetration (IIEF questions 3 and 4). Improvement was defined as an increase of 1 or more in the IIEF score for questions 3 or 4 at the end of phase 3 (alprostadil alfadex at-home phase) compared with the start of phase 2 (alprostail alfadex in-office titration phase) similar to previously published sildenafil studies serving for the approval by the Food and Drug Administration.[2] According to the open-label character of the multicenter trial, the evaluation of the end points was done within an exploratory data analysis. The improvement rates and the corresponding two-sided 95% confidence intervals were calculated.

RESULTS

The mean $\pm$ SD patient age was 58.6 $\pm$ 9.3 years and the mean $\pm$ SD duration of ED was 4.8 $\pm$ 2.9 years. The cause of the ED was determined by the medical and sexual history and by urologic examinations in the study populations (Table II). The mean baseline score for questions 3 and 4 at the beginning of the trial was 1.03 and 0.85, respectively.

The mean number of administrations of sildenafil for the patients entering phase 2 of the study was 4.9; the mean number of tablets taken per administration was 1.75. Ninety-nine percent of the patients who did not respond to sildenafil tried the 100-mg dose at least once. The mean change in the IIEF score from baseline to after sildenafil therapy for the 67 patients entering phase 3 of the study was 0.19 and 0.24 for questions 3 and 4, respectively. The mean change in questions 3 and 4 for the 134 patients taking sildenafil in phase 1 of the study was 0.94 and 0.87, respectively.

In phase 2 of the study, 85 patients had at least one administration of alprostadil alfadex in-office. The mean dose administered was 23.9 μg (range 2.5 to 40). The physician's assessment of the best response was as follows: grade 0, 1 patient (1.2%); grade 1, 4 patients (4.7%); grade 2, 19 patients (22.4%); and grade 3, 61 patients (71.8%). These results indicate that most patients (94.1%) were able to obtain an erection sufficient for sexual intercourse (grade 2 or 3) during the alprostadil alfadex titration phase after failing therapy with sildenafil.

Of the 80 men who had responded to the drug in office (grade 2 and 3 erections), 67 chose to participate in phase 3 of the study and had at least one administration of alprostadil alfadex at home. The mean dose was 28.3 μg. Overall, 561 administrations were recorded in 66 patients (mean 8.5 administrations) (1 patient lost his diary and could not be included; however, the IIEF questionnaire was filled in). Of these, 438 led to an erection adequate for sexual intercourse. Fifty-nine patients (88.1%) reported successful injections (ie, resulting in erection sufficient for sexual intercourse).

TABLE II. *Causes of erectile dysfunction as diagnosed by the urologist by routinely used methods in the different study populations (multiple answers possible)*

	Phase 1 (Sildenafil)	Phase 2 (Alprostadil Alfadex Titration)	Phase 3 (Alprostadil Alfadex At-Home)
Patients (n)	134 (100)	85 (100)	67 (100)
Category of ED (n)			
Psychogenic	30 (22.4)	15 (17.6)	10 (14.9)
Organic	124 (92.5)	83 (97.6)	66 (98.5)
Specific cause of ED (n)			
Arterial	85 (63.4)	51 (60)	38 (56.7)
Endocrine	17 (12.7)	14 (16.5)	11 (16.4)
Cavernous	17 (12.7)	9 (10.6)	7 (10.4)
Neurogenic	29 (21.6)	25 (29.4)	23 (34.3)
Prostatectomy	26 (19.4)	22 (25.9)	21 (31.3)

KEY: ED = erectile dysfunction.
Numbers in parentheses are percentages.

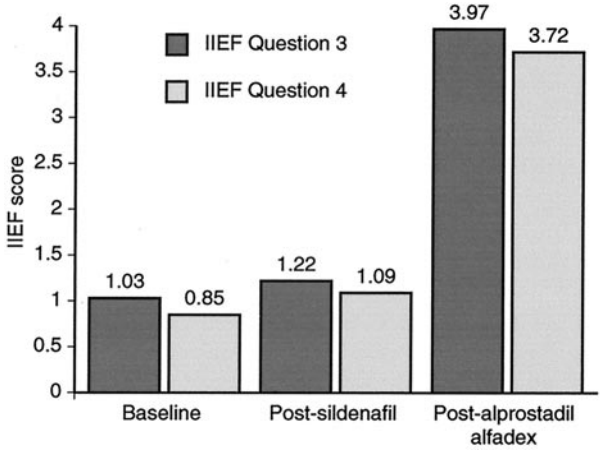

FIGURE 1. *Improvement in the IIEF score after treatment with sildenafil and alprostadil alfadex in 67 nonresponders to sildenafil.*

TABLE III. *Most frequently reported adverse events*

Adverse Event	No. of Patients
Sildenafil treatment (n = 134)	
Headache	27 (20.1)
Flushing	17 (12.7)
Rhinitis	13 (9.7)
Chromatopsia	8 (6.0)
Dyspepsia	6 (4.5)
Dizziness	6 (4.5)
Alprostadil treatment (n = 85)	
Pain	25 (29.4)
Paraesthesia	9 (10.6)
Influenza-like symptoms	4 (4.7)

Numbers in parentheses are percentages.

The number of patients not responding to sildenafil and reporting an improvement of 1 or more in response to questions 3 and 4 of the IIEF was 60 (89.6%) and 57 (85.1%), respectively. Overall, the mean improvement in response to questions 3 and 4 during treatment with alprostadil alfadex (phases 2 and 3) was 2.75 and 2.63, respectively (Fig. 1). The number of patients achieving a response of 4 or 5 to IIEF questions 3 and 4 was 47 (70.1%) and 43 (64.2%), respectively, with 42 patients (62.7%) achieving a score of 4 or 5 to both questions.

The most commonly reported adverse events with each drug are included in Table III.

COMMENT

Sildenafil has proved immensely popular as the first oral treatment for ED since its introduction in 1998. A total of 88.1% of patients in the current study reported a positive response to alprostadil alfadex at home after they had been identified as nonresponders to sidlenafil. Since the response rate of alprostadil alfadex in this trial is as high as in previously published trials, it can be concluded that the response rate of intracavernous self-injection therapy is not different in the general ED population compared with a population of severely affected sildenafil nonresponders with a score of about 1 for IIEF questions 3 and 4.

The incidence of adverse events, including serious ones, reported with either study medication were similar, although diverse in nature. Headache was most commonly reported with sildenafil use and penile pain with alprostadil alfadex.

This study confirms, in conjunction with results of an intraindividual crossover trial[7] between intracavernous and intraurethral alprostadil administrations, that intracavernous alprostadil alfadex injections are the best second-line drug therapy after oral therapy in the new algorithm of ED therapy. Moreover, the confirmed efficacy makes it first-line therapy for those patients in whom sildenafil is contraindicated.

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