A DOUBLE-BLIND, PLACEBO-CONTROLLED EVALUATION OF THE ERECTILE RESPONSE TO TRANSURETHRAL ALPROSTADIL*

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ABSTRACT

Objectives. Previous studies have indicated that the urethra may provide an effective route for administering vasoactive medication for the treatment of erectile dysfunction. We evaluated the safety and efficacy of alprostadil administered intraurethrally at home for the treatment of this disorder.

Methods. This prospective, multicenter, double-blind, placebo-controlled study evaluated the erectile response to randomly assigned doses of transurethral alprostadil at home in 68 men with long-standing (mean 41 months) erectile dysfunction of primarily organic etiology. Patients completing the study each administered a random sequence of four different doses (125, 250, 500, and 1000 µg) and placebo over a 2 to 4-week period. Assessments included the couples' ability to have intercourse, patient ratings of erectile response by both categorical and visual analogue scales, penile volume measurements, and overall assessments of comfort and ease of administration.

Results. Overall, 75.4% (49 of 65) of study patients achieved full enlargement of the penis and 49.2% (32 of 65) achieved an erection judged by the patient to be sufficient for intercourse. In addition, 63.6% (42 of 66) of patients reported intercourse. Efficacy was similar across etiologies. The most common side effect was penile pain, which occurred in association with 9.1% to 18.3% of alprostadil administrations, depending on dose. Mean comfort ratings ranged from 79 to 87, depending on dose, where 0 = severe discomfort and 100 = comfortable; ease of administration scores were above 90 for each dose, where 0 = difficult and 100 = easy. There were no episodes of priapism in this study.

Conclusions. Short-term treatment with transurethral alprostadil produced erections resulting in sexual intercourse in most patients with chronic erectile dysfunction. This therapy may be a useful treatment option for patients with erectile dysfunction.

THE USE OF INTRACORPORAL PHARMACOTHERAPY HAS BECOME AN INCREASINGLY WIDESPREAD METHOD FOR THE TREATMENT OF ERECTILE DYSFUNCTION (IMPOTENCE), A CONDITION AFFECTING AN ESTIMATED 10 TO 20 MILLION MEN IN THE UNITED STATES.1,2 UNTIL RECENTLY, HOWEVER, THE ONLY PRACTICAL METHOD OF DELIVERING PHARMACOLOGIC AGENTS LOCALLY TO THE CORPORA CAVERNOSA WAS BY DIRECT INJECTION. ALTHOUGH INTRACORPORAL INJECTIONS ARE EFFICACIOUS3-6 AND MAY HAVE A FAVORABLE RISK-BENEFIT PROFILE COMPARED WITH SURGICAL AND OTHER NON-SURGICAL TREATMENT OPTIONS,1,2,7-13 LONG-TERM COMPLIANCE IS LOW,4,6,14-16 AND AVERSION TO PENILE SELF-INJECTION MAY PREVENT MANY PATIENTS FROM INITIATING INJECTION THERAPY.14 SIDE EFFECTS INCLUDE PAIN, HEMATOMA, PRIAPISM, AND FIBROTIC COMPLICATIONS, INCLUDING PENILE NODULES, CURVATURE, AND FIBROTIC PLAQUES.3-6,16-19 THE AVAILABILITY OF A SAFE, EFFECTIVE, AND LESS-INVASIVE METHOD FOR DELIVERING PHARMACOLOGIC AGENTS TO THE ERECTAL BODY PROVIDES A POTENTIAL ALTERNATIVE TO INTRACORPORAL INJECTIONS.
tile bodies may provide a new treatment option to many patients with erectile dysfunction.

Vasoactive agents can be administered topically to the urethral mucosa for absorption into the corpus spongiosum and transfer to the corpora cavernosa. Significant hemodynamic effects of transurethral administration of alprostadil were observed by color duplex ultrasonography of the penis in 10 patients. In a study of 247 patients in the clinic, transurethral administration of alprostadil and alprostadil/prazosin combinations was demonstrated to produce erections in a majority of patients with chronic, organic erectile dysfunction. The present study evaluates the response at home to randomly assigned doses of transurethral alprostadil in a subset of these patients.

MATERIAL AND METHODS

A proprietary drug-delivery system (MUSE, VIVUS, Inc., Menlo Park, Calif) was used to administer alprostadil topically to the urethral mucosa. This system consisted of a polypropylene applicator with a hollow stem measuring 3.2 cm in length and 3.5 mm in diameter, the tip of which contained a semisolid pellet of medication (Fig. 1). Each single-use system was prefilled with the desired dose of medication and supplied in a sterile package. To administer the medication, the stem of the applicator was inserted into the urethra, a button on the end of the applicator was depressed to deposit the pellet against the urethral mucosa, and the applicator was removed. Urinating immediately prior to application of the system permitted the residual urine in the urethra to act both as a urethral lubricant and as a solvent for drug dispersion.

Upon study entry, each patient received a medication kit containing randomly ordered doses of medication, including placebo, to be used at home. This report presents results from 68 patients, each of whom self-administered one dose of placebo and four doses of transurethral alprostadil (125, 250, 500, and 1000 µg).

STUDY SUBJECTS

This study evaluated 68 men between 26.8 and 76.4 years of age who had previously completed an in-clinic evaluation of transurethral alprostadil, prazosin, and alprostadil/prazosin combinations. All patients had chronic (mean 41 months) erectile dysfunction that was primarily of organic etiology, as confirmed by medical history, physical examination, laboratory evaluation, and other diagnostic tests as needed: etiologies included vascular disease, surgery or trauma, and other organic causes such as diabetes mellitus, age, tobacco or alcohol abuse, and side effects from prescription drug use. Patients had been unable to achieve a spontaneous erection sufficient for intercourse on any occasion within the previous 3 months without the aid of therapy. To be eligible, patients were required to be in a stable, monogamous marital relationship. Other pertinent patient demographics are summarized in Table 1.

The principal exclusion criteria were history of urethral stricture; anuria, indwelling urethral catheter, or prior penile surgery; sickle cell disease; unstable angina or a recent myocardial infarction; poorly controlled diabetes mellitus or congestive heart failure; or recent use of another investigational treatment. Written informed consent was obtained from each study patient and his spouse prior to treatment. Spouses were required to accompany study patients to clinic visits. The experimental protocol and informed consent documents were approved by the Institutional Review Board at each of the participating study sites.

STUDY END POINTS

With the use of each system, couples recorded pertinent safety and efficacy information in a study diary. The principal efficacy assessments were based on each study couple's ability to have sexual intercourse with each dose. In addition, erectile response was scored on a 1 to 5 Erection Assessment Scale (EAS) adapted from Waldhauser and Schramek and Ishii et al., where 1 = no response, 2 = some enlargement, 3 = full enlargement, 4 = erection sufficient for intercourse, and 5 = rigid erection. Couples measured penile length and circumference (for penile volume calculations) and assessed penile response on a 0 to 100 visual analogue scale (VAS), where 0 corresponded to “no effect” and 100 corresponded to a “rigid” erection. Each of the end points listed above was assessed immediately prior to and then again at 7, 15, 20, 40, and 60 minutes after drug administration. Couples also noted the times to “onset of effect,” “peak effect,” and “return to nonerect state,” and provided 0 to 100 VAS assessments of “ease of administration” (0 = difficult; 100 = easy) and “overall comfort” (0 = severe discomfort; 100 = comfortable).

STATISTICAL METHODS

The randomized dosing sequences used in this study were designed to allow for paired (within-patient) comparisons between each alprostadil dose and placebo. Differences between the frequencies of intercourse associated with the various doses of medication were analyzed by applying the sign test to the discordant pairs among the groups being evaluated (McNemar test). For most other assessments, group differences were evaluated using paired t tests. All reported P values
TABLE I. Patient demographics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean (± SD)</th>
<th>Range</th>
<th>Primary etiology</th>
<th>Onset of erectile dysfunction</th>
<th>Duration of complaint (months)</th>
<th>Previous therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58.6 ± 10.7</td>
<td>26.8–76.4</td>
<td>Vascular disease</td>
<td>Acute</td>
<td>Overall (mean ± SD)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>32 (47.1%)</td>
<td></td>
<td>Surgery/trauma</td>
<td>Gradual</td>
<td>Acute onset (mean ± SD)</td>
<td>Counseling</td>
</tr>
<tr>
<td></td>
<td>18 (26.5%)</td>
<td></td>
<td>Diabetes</td>
<td>Gradual</td>
<td>Gradual onset (mean ± SD)</td>
<td>Hormones</td>
</tr>
<tr>
<td></td>
<td>10 (14.7%)</td>
<td></td>
<td>Other</td>
<td></td>
<td></td>
<td>Cavernosal injections</td>
</tr>
<tr>
<td></td>
<td>8 (11.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Band therapy</td>
</tr>
</tbody>
</table>

Key: SD = standard deviation.
*Some patients had previously attempted more than one other therapy for erectile dysfunction; thus the percentages do not add up to 100.

RESULTS

ERECTILE RESPONSE AT HOME

Intraurethral administration of alprostadil at home resulted in 75.4% (49 of 65) of patients achieving an EAS response of 3, 4, or 5 (full enlargement or an erection sufficient for intercourse) on at least one dose. A penile response of 3, 4, or 5 was reported in 45.5% of patients at the 125-µg dose, 51.5% at 250 µg, 53.3% at 500 µg, and 55.0% at 1000 µg. An EAS response of 4 or 5 (erection sufficient for intercourse) was reported by 49.2% (32 of 65) of patients on at least one dose. The percentage of patients achieving a penile response of 4 or 5 was 19.7% at the 125-µg dose, 30.3% at 250 µg, 26.7% at 500 µg, and 31.7% at 1000 µg. As judged by the EAS, each alprostadil dose was significantly better than placebo (P <0.001, paired t test); placebo administration resulted in scores of 3 or better in 12.7% of patients and of 4 or better in 4.8% of patients.

Overall, 63.6% (42 of 66) of patients reported sexual intercourse on at least one dose. The percentage of patients who had intercourse for each individual alprostadil dose (Fig. 2) was 39.4% at 125 µg, 33.3% at 250 µg, 40.0% at 500 µg, and 50.0% at 1000 µg, compared with 12.5% of patients on placebo (P ≤0.01 for each active dose compared with placebo, McNemar's test). As shown in Figure 2, the percentage of doses resulting in sexual intercourse in the study population was greater than would be predicted by the percentage of patients achieving an EAS response of 4 (erection sufficient for intercourse) or better. The response rate was similar across etiologies (Fig. 3).

Significant differences between each alprostadil dose tested and placebo (P <0.001) were also ob-
TABLE II. Secondary efficacy results

<table>
<thead>
<tr>
<th>Alprostadil Dose (µg)</th>
<th>VAS (0–100) Comfort Mean</th>
<th>VAS (0–100) Ease of Administration Mean</th>
<th>Change in Volume* (log2) Mean</th>
<th>Duration of Response (min) Mean</th>
<th>VAS (0–100) Penile Response Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>93.1</td>
<td>92.8</td>
<td>0.5</td>
<td>7.0</td>
<td>18.4</td>
</tr>
<tr>
<td>125</td>
<td>86.7</td>
<td>92.8</td>
<td>0.9</td>
<td>31.7</td>
<td>41.8</td>
</tr>
<tr>
<td>250</td>
<td>83.4</td>
<td>91.1</td>
<td>1.0</td>
<td>38.5</td>
<td>44.2</td>
</tr>
<tr>
<td>500</td>
<td>82.7</td>
<td>90.3</td>
<td>1.0</td>
<td>50.7</td>
<td>47.8</td>
</tr>
<tr>
<td>1000</td>
<td>78.9</td>
<td>91.5</td>
<td>1.0</td>
<td>57.0</td>
<td>54.3</td>
</tr>
</tbody>
</table>

Key: VAS = visual analogue scale.
* The volume was calculated by assuming a cylindrical volume (πr²h). The ratio of peak to pretreatment volumes was transformed log₂ to normalize the distribution of values for this ratio.

erved for measurements of penile volume change, penile response by the 0 to 100 VAS, and duration of response (Table II). Conversely, each alprostadil dose was significantly less comfortable than placebo as rated by the 0 to 100 VAS (P < 0.05). Overall comfort ratings for the various alprostadil doses ranged from 78.9 (1000 µg) to 86.7 (125 µg), where a VAS score of 0 corresponded to "severe discomfort" and a score of 100 corresponded to "comfortable." By comparison, the mean comfort score for placebo was 93.1. Ease of administration ratings (VAS) were generally high for all alprostadil doses tested (90 or greater, where 0 corresponded to "difficult" and 100 corresponded to "easy").

A significant within-patient dose response across the four alprostadil doses was observed for efficacy measurements, including penile response by the 0 to 100 VAS (P < 0.001), penile volume changes (P = 0.05), and duration of response (P < 0.001), indicating that the erectile response to alprostadil is clearly a dose-dependent one (Table II). The significant inverse relationship between overall comfort ratings and alprostadil dose (P < 0.001) shows that penile pain is also a dose-dependent effect of intraurethral alprostadil administration.

ADVERSE EFFECTS

Penile pain or discomfort, the most commonly observed adverse effect in this study, was reported at frequencies ranging from 9.1% (125 µg) to 18.3% (1000 µg) of doses. By contrast, penile pain was not reported in association with placebo administration. Although pain was commonly reported, patient ratings of overall comfort associated with alprostadil use were relatively high (Table II).

In previous experience with transurethral alprostadil therapy in clinic, hypotension and related symptoms of dizziness and syncope were observed.21 At home, where vital signs are not routinely monitored, reports of hypotension would not be expected unless a patient experienced symptoms that clearly indicated a hypotensive response. Accordingly, "hypotension" was not reported during this home study. Syncope was reported by 1 patient; however, this event was associated with an ongoing illness and did not appear to be a hypotensive response to study medication. Dizziness (reported by 1 patient) and sweating (reported by 1 patient) were the only reported events that were potentially related to hypotension.

There were no episodes of priapism (defined as a continuous, rigid erection lasting 6 or more hours), fibrotic complications, or urinary tract infections during the study. One episode of "prolonged erection," defined as a painful or unwanted erection lasting between 4 and 6 hours, and two episodes of "sustained engorgement," defined as a prolonged erection of up to 4 hours' duration, were reported. All of these occurrences, however, were reported by the same patient, and none required treatment other than oral pseudoephedrine to bring about resolution. Minor urethral trauma occurred in 1 patient and did not affect the patient's continued study participation.

COMMENT

The rationale for using corporal pharmacotherapy to treat erectile dysfunction is that locally administered vasodilators can initiate the physiologic hemodynamic events that lead to penile erection. Although medications have typically been administered by direct intracorporal injection,3-6,16-19,22 previous studies have indicated that the transurethral delivery route may be a viable option for local administration of pharmacologic agents to the corpora cavernosa.20,21,23 In a double-blind, placebo-controlled evaluation of over 200 patients with a 3-month history of complete, organic erectile dysfunction, randomly assigned doses of transurethral alprostadil and alprostadil/prazosin combinations administered in the clinic resulted in full penile enlargement or an "erection
sufficient for intercourse" in a majority of patients. The patient group included in the present study consisted of the first 68 patients who completed the above in-clinic evaluation of transurethral therapy: the group was not selected based on a favorable response in the previous study. In the current study, each patient received a total of five doses (four active and one placebo) at home over a 2 to 4-week period. EAS scores measured at home in the present study were consistent overall with those previously observed in the clinic. The most notable differences between clinic and home dosing were a slightly higher placebo rate and a greater percentage of patients reporting an EAS score of 3 or greater at each dose level at home. In the home setting, transurethral alprostadil administration resulted in EAS scores of 3 (full penile enlargement) or greater on 45.5% of administrations at the 125-µg dose level, on 51.5% of administrations at the 250-µg dose level, on >55.3% of administrations at the 500-µg dose level, and on 55.0% of administrations at the 1000-µg dose level. These observations may be a result of sexual stimulation, a factor that was present in the home setting and not in the clinic.

The EAS defines a score of "4" as being an "erection sufficient for intercourse"; therefore, the percentage of systems resulting in scores of 4 or greater for any given dose was expected to be a good predictor for the percentage that actually resulted in intercourse. In the present study, however, the percentage of systems that resulted in successful intercourse was higher than would be predicted from the EAS scores. Whereas EAS scores of 4 or greater were reported by 49.2% of patients, intercourse was reported by 63.6% of patients. As shown in Figure 2, the percentage of patients reporting intercourse for each alprostadil dose was generally between the percentage reporting FAS scores of 4 or greater and the percentage reporting EAS scores of 3 or greater.

The erectile response, as measured by penile response by the 0 to 100 VAS, penile volume changes, and duration of response, was consistent with the intercourse and EAS results, and each of these end points confirmed the efficacy of transurethral alprostadil in the home setting. Because these surrogate end points assessed erectile response on a more continuous scale (as opposed to the dichotomous nature of the intercourse variable), they provided a particularly powerful assessment of the dose-response relationship to transurethral alprostadil. This relationship was highly significant (P < 0.001) for penile response and duration of response, indicating that the erectile response to alprostadil is indeed a dose-dependent one. Nonetheless, data for intercourse and EAS response (Fig. 2) indicate that the observed dose response is relatively shallow in the population as a whole. This may be due, in part, to the within-patient variability in responsiveness to alprostadil. Whereas some patients were successful at the 125-µg level, some required much higher doses, and others were not responsive even at doses of 1000 µg. These data would indicate that the doses for patients initiating transurethral alprostadil therapy should be individually titrated to an appropriate level.

The dose of transurethral alprostadil required for a suitable effect (125 to 1000 µg) appears to be higher than that required by direct injection therapy (0.2 to 80 µg). To gain patient acceptance, therefore, the pricing of this new treatment will likely need to be cost-competitive with currently approved drug treatments.

As previously observed in clinics, local urogenital pain was the most commonly reported adverse event associated with transurethral therapy. As observed in this study, however, urogenital pain was generally rated as being "mild" to "moderate" in severity, was transient, and did not pose significant medical consequences. Hypotension, an event that had been observed in the clinic setting, was not observed in the present study, and only 2 patients reported symptoms associated with a lowering of blood pressure. Priapism, urinary tract infections, or penile fibrotic complications were not observed; however, this study was of relatively limited duration, and longer term evaluations in larger patient populations would be more appropriate for assessing the comprehensive safety profile.

In summary, this study provides short-term data in 68 patients supporting that transurethral alprostadil can be well tolerated and restore erections and sexual intercourse in many men with complete, organic erectile dysfunction. More extensive trials, however, will be required for better assessment of the long-term efficacy, safety, and patient acceptance of this novel therapy.

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