A DOUBLE-BLIND, PLACEBO-CONTROLLED, EFFICACY AND SAFETY STUDY OF TOPICAL GEL FORMULATION OF 1% ALPROSTADIL (TOPIGLAN) FOR THE IN-OFFICE TREATMENT OF ERECTILE DYSFUNCTION

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ABSTRACT

Objectives. To assess the efficacy and safety of Topiglan (1% alprostadil in a formulation with 5% SEPA [soft enhancer of percutaneous absorption]) or placebo gel (0.25 mL) applied to the glans penis only in 60 patients with moderate to severe erectile dysfunction in a two-visit, in-office clinical trial.

Methods. During the first visit, open-label placebo gel was applied. At the second visit, blind, random allocation to Topiglan (n = 31) or placebo gel (n = 29) occurred. Thirty minutes after application, an erotic movie showing heterosexual sex began; at 45 minutes, a penile vibrator was used. Audiovisual and tactile stimulation were discontinued at 65 minutes, and the patient was observed until 90 minutes after application. At the scheduled time points, the erection response was assessed by both the investigator and the patient and signs and symptoms of tolerance were evaluated.

Results. Topiglan produced a greater angle of erection (P = 0.003) and maximum rigidity (P = 0.033) compared with the placebo gel. The responses to Topiglan were greater than to placebo gel at all time points after application, with the greatest differences observed at 45 and 60 minutes. Of the 31 patients treated with Topiglan, 12 (38.9%) achieved an erection judged sufficient for vaginal penetration (P = 0.005); 2 (6.9%) of the 29 patients who received placebo gel did so. Penile erythema was more common with Topiglan; symptoms of minor to mild warmth or burning and, less commonly, tingling and coolness were reported by most patients after both Topiglan and placebo gel application. No significant changes in vital signs were noted.

Conclusions. Topiglan applied to the glans penis increased penile rigidity and expectations regarding vaginal penetration in patients with erectile dysfunction.


Vasoactive pharmacologic agents have been shown to enhance penile erection by facilitating corporal smooth muscle relaxation in men with erectile dysfunction.1–3 Topical drug delivery is simple, reversible, noninvasive, spontaneous, and safe, consistent with first-line treatment for erectile dysfunction,4 but has previously been documented as only minimally effective in erectile dysfunction.5–13 This Phase II study examined the efficacy and safety of a novel, topical gel formulation of 1% prostaglandin E₁ and the penetration enhancer SEPA (soft enhancer of percutaneous absorption)14,15 applied exclusively to the glans penis in male patients with erectile dysfunction in an office-based setting.

MATERIAL AND METHODS

SUBJECTS

The study was approved by our Institutional Review Board. All subjects provided signed informed consent before study participation. Subject inclusion criteria included being a heterosexual male at least 21 years of age, with at least a 6-month history of erectile dysfunction. Additional entry criteria included a history during the past 6 months of a reduced, but not
absent, incidence of awakening with a full erection, difficulty obtaining an erection before intercourse, trouble maintaining an erection once intercourse began, and being neutral to extremely dissatisfied regarding one's sex life.

Patients were excluded from the study if they had been previously enrolled in studies of Topiglan or had untreated endocrine or Peyronie's disease, or had undergone radical prostatectomy. Patients with symptomatic coronary artery disease, hypertension at screening, or symptomatic postural hypotension within the prior 6 months were also excluded. Patients could not use pharmacologic therapy for erectile dysfunction within 7 days of study entry.

**STUDY DESIGN**

The study, consisting of two office visits, was a double-blind, placebo-controlled, single-institution, randomized, efficacy and safety evaluation of the effects of 1% prostaglandin E1 (PGE1) in a topical formulation. The study medication was a clear gel composed of 1% alprostadil, ethanol, hydroxypropyl cellulose, water, and the excipient SEPA (5%). The placebo vehicle was identical without alprostadil. The medication was supplied in coded 2-mL screw-cap vials stored at 2° to 8°C. Each vial was removed from refrigeration 15 to 30 minutes before use. A plastic syringe was filled with 0.25 mL of the study medication by the investigator.

The initial office visit involved the completion of the patient's medical history, physical examination, vital signs, and baseline sexual activity questionnaire. Each patient was exposed to audiovisual and tactile stimulation in conjunction with an open-label application of the placebo in the sexual response assessment laboratory. The patient applied 0.25 mL of placebo gel from a plastic, needleless syringe to his glans penis, spread it evenly over the glans with his finger, then washed his finger with soap and water. Subjects were instructed to remain seated in an upright position for the remainder of the test session. A symptom questionnaire, the patient's assessment of erectile response, and an objective measure of response by the physician were recorded at baseline, at 15-minute intervals during the first hour, and 90 minutes after dosing when the test session ended. During the first 30 minutes after dosing, the patient was offered nonerotic magazines to read and videos to view. Subsequently, the subject was shown four 3-minute videotape segments portraying heterosexual intercourse. The patient chose one videotape to finish viewing, approximately 20 minutes. At 45 minutes after dosing, a vibrator (FertiCare Personal, Multiclip ApS, Rungsted, Denmark) set to an approximate frequency of 70 Hz and amplitude of 1 mm was applied by the subject to the ventral surface of his penis. The tactile stimulation was used as long as desired during the remainder of the movie, until a full erection was reached. After completion of the sexual response assessment 90 minutes after application of the test dose, the patient washed off the placebo gel. If the patient demonstrated an erectile response of 70° or greater by physician's assessment or grade 3 by the patient's assessment, he was withdrawn from the study.

The second visit was completed within 2 weeks of visit 1. After the recording of vital signs, the patient underwent the same procedure as at visit 1, except that the test dose applied to the penis was either the study medication or placebo, distributed randomly in a double-blind fashion. The patient was discharged after 90 minutes of monitoring after dosing unless a complete erection was present, in which case he was detained until the erection showed signs of detumescence.

**EFFICACY OUTCOME MEASURES**

The two primary efficacy variables were the patient and physician assessments of erection. The physician assessment was performed at baseline, at 15-minute intervals during the first hour, and 90 minutes after dosing. Erections were measured by placing a protractor next to the penis with the patient standing. To the nearest 5°, the angle of the erection from the vertical axis was recorded and a Polaroid photograph taken. The penis was not touched by the investigator. The patient assessment was made at the same times by scoring the erection on a scale of 1 to 5, with 1 indicating no evidence of any tumescence or erection; 2, partial tumescence (not likely to be sufficient for penetration); 3, greater tumescence sufficient for vaginal penetration but not fully rigid; 4, full rigidity; and 5, excessive rigidity.

**SAFETY OUTCOME MEASURES**

At the same time points as above, local irritation and erythema were assessed and recorded on a scale of 0 to 5, where 0 was no evidence of any irritation or erythema and 5 was deep red erythema with or without vesiculation or weeping. The Patient Symptom Score was determined by following a three-question algorithm. The patient was asked how he felt at that moment and since the last evaluation, and the answer was recorded. If a symptom was reported, the patient was asked to describe it in one word and to score the severity from 0 to 4, where 0 was absent and 4 was severe.

**STATISTICAL ANALYSIS**

Two primary variables were analyzed for efficacy, the patient and physician assessments of erection. For continuous data, an analysis of variance model with an effect for treatment was used. For ordered categorical data, Wilcoxon’s rank sum test was used, and for dichotomous data, Fisher’s exact test was used. No adjustments for multiplicity were made in this study. Statistical significance was declared when alpha was found to be 0.05 or less. On the basis of previous experience, 30 patients per group were chosen, to provide an 80% power to detect a difference with an alpha of 0.05 between the placebo and the active drug, assuming a 20% and 60% response rate, respectively.

**RESULTS**

A total of 62 men (age range 24 to 78 years) participated in this study, forming the safety sample population. Thirty subjects were randomized to the placebo group and 32 to the active drug group. Differences in demographics were not statistically significant in terms of mean age, weight, height, and number circumcised. Of these subjects, 60 formed the intent-to-treat (ITT) sample, all receiving a dose of placebo at visit 1, 29 receiving placebo and 31 the active drug at visit 2. Of the 2 patients not included in the ITT population, one demonstrated a grade 3 erectile response at visit 1 and one did not return for visit 2.

Patients from the placebo and test groups had similar experiences as to the frequency of intercourse, number of morning erections and hard erections per 24 hours, and ability to achieve and maintain an erection sufficient for satisfactory sexual intercourse. Ninety-seven percent of the patients treated had a vascular etiology for their erectile dysfunction, established by diagnostic color duplex ultrasound, in-office intracavernosal injection testing, dynamic infusion cavernosometry and
cavernosography testing, and/or the presence of coexisting cardiovascular disease. Of the 58 patients with vascular etiology, 50 had undergone invasive intracavernosal testing. Most patients had previously been treated with oral, intracavernosal, or intrarectal therapies, with variable success. On the basis of an adequate erection for vaginal penetration, responses were positive for 13 of 23 patients treated with sildenafil, 0 of 8 treated with PGE1 (intrarectal), 2 of 3 treated with PGE1 (intracavernosal), 32 of 43 treated with combined PGE1, papaverine, and phentolamine (intracavernosal), and 1 of 1 treated with papaverine and phentolamine (intracavernosal).

**PHYSICIAN ASSESSMENT**

The mean physician-assessed erectile rigidity remained relatively consistent for all patients during the six time measurements at visit 1. At visit 2, before the initiation of the erotic videotape, the mean angle of the erection changed little compared with baseline, although the increase in the alprostadil group was significantly greater than that in the placebo group at 15 minutes. At 45 minutes, the increase became apparent, with the mean angle of erection for the active drug group at 42.9° and at 32.4° for the placebo group. At 60 minutes, the mean angle measurements were 39.2° and 31.2° for the active drug and placebo groups, respectively. At 90 minutes, after the erotic video and tactile stimulation were discontinued, the angles returned toward the baseline values.

Analysis using the highest rigidity assessment for each patient revealed a statistically significant difference between the group treated with the study drug (44.5° ± 3.8° [mean ± SE]) and those given placebo (33.5° ± 3.4°; \( P = 0.033 \)). The active drug group had a statistically significant higher mean change from baseline in angle of erection score than the placebo group, 24.2° versus 13.5°, respectively (\( P = 0.039 \)).

**PATIENT AND PHYSICIAN ASSESSMENTS**

The patient assessments of rigidity during the six time points at visit 1 were either no erection or only partial tumescence. At visit 2, no tumescence or rigidity was reported by patients in either group at baseline (Fig. 1). At all subsequent points, there were statistically significant increases in rigidity among subjects using the active drug rather than placebo.

Analysis of the primary efficacy variable, the physician’s assessment of erection, revealed at visit 2 a statistically significant improvement among patients using the test drug (\( P = 0.003 \)). Three patients (9.7%) in the active drug group reported no tumescence, and 8 (27.6%) in the placebo group did so. Twelve subjects (38.7%) in the study group (seven circumcised) and two (6.9%) in the placebo group reported an erection sufficient for vaginal penetration, a statistically significant difference (\( P = 0.005 \)).

**SAFETY RESULTS**

The physician’s evaluation of local irritation and erythema at visit 1 yielded no evidence of local erythema in any patient before application of the placebo gel. At various times after gel application, 87% to 97% of patients had no local erythema and the remaining patients had only minimal (faint or spotty) erythema.

At visit 2, again no local erythema was evident at baseline. At 15 minutes, significantly greater erythema was reported in the alprostadil group than in the placebo group (\( P < 0.001 \)). This significant difference remained throughout the 90-minute observation period but was maximal 45 minutes after application. The most severe erythema observed (in up to 3% of patients) involved a pink-red coloration over the entire application site. Most of the differences seen between the active drug and placebo-treated patients consisted of a greater frequency in the incidence of minimal erythema or a pink, uniform coloration on most of the application site in the alprostadil group. No evidence of petechiae or vesiculation was seen in any subject.

At visit 1, patients reported no symptoms at baseline. After application of placebo gel, minor (“I don’t notice it unless I think about it”) to mild (“I am constantly aware of it, but it doesn’t interfere...”
with what I am doing”) symptoms were reported by 34% and 50%, respectively, and 50% and 43%, respectively, of the alprostadil and placebo groups. Symptoms described as localized burning, warmth, stinging, coolness, heat, and tingling were reported thereafter. These symptoms were maximum at 15 minutes, reduced at 30 minutes, and largely absent 45 minutes after application of the placebo gel.

At visit 2, symptoms were reported by 30% of patients treated with placebo and 50% of those treated with the active drug (Fig. 2). The placebo symptoms reported during visit 2 were similar to those reported during visit 1. Most symptoms were attributed to the application site, minor or mild in intensity, and described as at visit 1. In addition, 2 patients in the active group reported conjunctivitis, and 1 patient had symptoms of hypotension. This latter event occurred in a 53-year-old man whose medical history was unremarkable. Ninety minutes after gel application, he was mildly diaphoretic and light-headed. His blood pressure fell from 126/78 mm Hg at baseline to 128/54 mm Hg. He recovered almost immediately after lying down with his legs raised.

**COMMENT**

Topical vasoactive agents for the treatment of erectile dysfunction must overcome “effective” barriers, the skin epidermis and the corpora cavernosa tunica albuginea, to pass into the corpora cavernosa erectile tissue. SEPA is an amphiphilic molecule with the property of reversibly altering the lipid structure of the stratum corneum, the major barrier to the penetration of external agents through the skin. SEPA disorders the stratum corneum lipids to increase fluidity, allowing drugs of lower molecular weight through; bacteria and viruses cannot pass through the skin. Once a drug enters the dermis, it can pass easily to the hypodermis. No connective tissue tunica albuginea layer is between the hypodermis of the glans and the corpus spongiosum erectile tissue, allowing drugs entering the glans hypodermis to pass easily into the erectile tissue of the corpus spongiosum. Thus, a drug with an appropriate concentration gradient, molecular weight, solubility, and chemical nature, in the presence of an enhancer applied topically to the glans penis, could pass to the corpora cavernosa erectile tissue and facilitate penile erection.

The efficacy of intraurethral alprostadil in treating erectile dysfunction indicates that vasoactive agents passing into the corpus spongiosum erectile tissue transfer into the corpus cavernosum erectile tissue, facilitating penile erection. The most likely drug transfer route from the corpus spongiosum to the corpus cavernosum is by retrograde passage through shared emissary veins and subcutaneous venules. During corpus spongiosography, contrast placed within the glans penis erectile tissue can be seen to pass retrogradely into the corpus cavernosum erectile tissue.

**FIGURE 2.** Effect of 1% alprostadil (Topiglan) and placebo on patient symptoms as a function of time after application to the glans penis during visit 2. No patients complained of severe or moderate symptoms at any time during this study. In both the placebo and active drug groups, the most common time for complaints of symptoms was at 15 minutes. After 15 minutes, symptoms decreased in both placebo and active drug groups.
(1% alprostadil in a formulation containing SEPA, a transdermal penetration enhancer) was effective in increasing penile tumescence and rigidity. Increased expectations about vaginal penetration in patients with erectile dysfunction were demonstrated. Additional research is required to establish this agent as a clinically safe and effective first-line therapy for erectile dysfunction.

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References
