Combination of Vacuum Erection Device and PDE5 Inhibitors as Salvage Therapy in PDE5 Inhibitor Nonresponders with Erectile Dysfunction

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ABSTRACT

Introduction. Oral phosphodiesterase type 5 inhibitors (PDE5i) have improved treatment options for erectile dysfunction (ED). In case of unresponsiveness to PDE5i, alternative therapies are considered.

Aim. To evaluate whether combination of vacuum erection device (VED) and PDE5i is effective as salvage therapy in subjects with ED in whom PDE5i alone failed.

Methods. From September 2007 to May 2008, we evaluated 69 men (aged 36–82 years) in whom PDE5i treatment at the highest recommended dose, with at least 4–6 attempts at intercourse during a 3 months period, had failed. The clinical efficacy of combination therapy was evaluated using the International Index of Erectile Function-5 (IIEF-5) questionnaire, Sexual Encounter Profile (SEP)-2, SEP-3, and Global Patient Assessment Scale (GPAS).

Main Outcome Measures. Scores on IIEF-5, SEP-2, SEP-3, and GPAS before and after combination therapy were measured.

Results. After 4 weeks of combination therapy, the mean IIEF-5 score increased significantly over baseline from 9.0 to 17.6 (P < 0.001). Of the 34 subjects with a SEP-2 response of “no” at baseline, 27 (79%) responded “yes” after combination therapy (P < 0.001). Of the 50 subjects with a SEP-3 response of “no” at baseline, 35 (70%) responded “yes” after combination therapy (P < 0.001). Furthermore, of the 42 subjects with a GPAS response of “not at all” or “slightly” improved at baseline, 31 (74%) responded “moderately” or “greatly” improved after combination therapy (P < 0.001). One subject (1.5%) experienced device-related intermittent penile pain, which resolved after 4 days without any action.

Conclusions. Statistically significant improvements over baseline were seen in IIEF-5, SEP-2, SEP-3, and GPAS measures following 4 weeks of combination therapy of PDE5i and VED. This study supports the use of PDE5i with VED in men in whom PDE5i alone failed. This combination therapy may be offered to patients not satisfied with PDE5i alone before being switched to more invasive alternatives. Canguven O, Bailen J, Fredriksson W, Bock D, and Burnett AL. Combination of vacuum erection device and PDE5 inhibitors as salvage therapy in PDE5 inhibitor nonresponders with erectile dysfunction. J Sex Med 2009;6:2561–2567.

Key Words. Combination Therapy; Patient Satisfaction; Penile Erection; Phosphodiesterase; VED

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [1]. The introduction of oral phosphodiesterase type 5 inhibitors (PDE5i) (i.e., sildenafil citrate, tadalafil, and vardenafil hydrochloride) has greatly enhanced ED treatment, and studies have demonstrated high tolerability and success rates for improved erectile function (EF).

To date, PDE5i are the first treatment choice for ED among physicians [1,2]. The efficacy of PDE5i demonstrates the importance of the nitric
oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway in EF because these agents counteract the degradation of NO-generated cGMP. If used properly, PDE5i have a rapid onset of action to facilitate EF. In most published clinical trials, the efficacy of PDE5i as judged by successful sexual intercourse ranges from 52% to 94% [3–5]. Because not all patients respond to PDE5i, additional therapies are being investigated, such as soluble guanylyl cyclase activators and NO donors, which act on NO-independent and NO-dependent pathways, respectively [6].

Alternative treatment choices for ED include vacuum erection devices (VEDs), intracavernosal injectable agents, and intracavernosal vascular agents [2]. Surgical treatments are still reserved for men who cannot use or fail to respond to these treatments. Patients who are not completely pleased with EF following the use of PDE5i and who are not interested in invasive therapy are offered the option of a VED before pursuing invasive alternatives. The VED mechanism depends on its ability to boost arterial inflow by a vacuum effect while decreasing venous outflow from the penis by applying a rubber constriction band after penile blood engorgement [7].

In this prospective open-label study, we tested the efficacy of combining VED and PDE5i for ED after failure to achieve an adequate erection using PDE5i alone.

Methods

Study Protocol

Patients who had been prescribed a maximum dose of at least one PDE5i (20 mg for tadalafil or vardenafil hydrochloride, 100 mg for sildenafil citrate) for ED were surveyed by mail or phone to determine their satisfaction with this therapy. Patients were defined as nonresponders by self-report after four to six unsuccessful attempts using the maximum drug dose over at least a 3 months period. Patients have received and were required to follow instructions for the proper use of PDE5i, including the need for sexual stimulation and the avoidance of alcohol as well as fatty food intake. Only those who declared that dissatisfaction was primarily because of inadequate efficacy, and not related to unwanted side effects, were considered eligible for this study.

Participants were also required to demonstrate competency with the use of VED and have a body mass index of less than 35.0 kg/m² at the time of enrollment. The latter was required because very overweight men have difficulty seeing their penis while using the VED and, thus, require more time to learn the correct process than this rather short study allows.

Patients were not screened with Sexual Encounter Profile Questions 2 or 3 (SEP-2 or SEP-3) prior to inclusion in the trial, and, as such, some subjects responded positively at baseline to one or both SEP questions despite declaring dissatisfaction with oral medications upon enrollment. It was suspected that some subjects reporting dissatisfaction with PDE5i were in fact able to have successful intercourse and still not be completely satisfied with their sexual experience. The study was designed to include these patients, despite the fact that they may have experienced partial or even functional responses to PDE5i.

Exclusion criteria were a history of any definitive treatment for prostate cancer (e.g., radical prostatectomy, radiation therapy, androgen deprivation) or unstable cardiovascular disease (e.g., unstable angina, recent myocardial infarction, cardiac failure, or life-threatening arrhythmia) within the past 6 months. Men with an anatomical deformity of the penis such as severe penile fibrosis or curvature, Peyronie’s disease, or history of penile surgery (except for circumcision) were excluded from study. Men with a history of sickle cell disease, multiple myeloma, leukemia, or any other hematologic disorders, men using medications that may cause priapism, and ED caused by low serum testosterone levels (<300 ng/dL) were also excluded.

All patients had to anticipate having the same female sexual partner (vaginal intercourse was a required study activity) throughout the study for consistency in recording responses to efficacy questionnaires. At the time of enrollment, the patient was required not to have participated in a clinical drug study within the last 30 days prior to entering this study. Prior to the administration of study questionnaires, the investigator obtained informed consent for participation.

Data were collected at visit 1 (baseline; study entry) and visit 2 (4 weeks after baseline; study end). During visit 1, a medical history was taken and baseline safety assessments were made, including a physical examination. Patients were instructed to continue taking the same PDE5i as they were taking prior to enrollment throughout the study so as not to introduce an additional variable to the trial. All questionnaires (the International Index of Erectile Function-5 [IIEF-5], SEP-2 and SEP-3, and the Global Patient Assess-
ment Scale (GPAS)) were administered at both visits. Patients were required to have completed a minimum of four attempts at sexual intercourse in order for results to be considered valid for the 4-week period. Patients self-reported whether they completed the required attempts, and the number of PDE5i doses used per subject were not accounted for in the trial. The study was approved by respective Institutional Review Boards of the participating medical centers.

**Treatments**

Men were instructed to take one tablet of PDE5i at a maximum dosage at least 1 hour before sexual activity and 2–3 hours after a meal. Instruction in the use of a VED included personal tutoring as well as watching an instructional video (Osbon Erectaid ESTEEM, Timm Medical Technologies, Eden Prairie, MN, USA).

**Treatment Evaluations**

The clinical efficacy of combining PDE5i and VED was evaluated using the IIEF-5 questionnaire, which is an abbreviated version of the IIEF [8]. In addition to completing the IIEF-5 questionnaire, men were assessed using SEP-2, SEP-3, and GPAS questionnaires [9], which rated performances and satisfaction with current ED treatment regardless of the IIEF-5 score. IIEF-5 and SEP questions were chosen in order to keep study questionnaires simple and brief while still using validated instruments. Questions asked were, for SEP-2, “Were you able to insert your penis into your partner’s vagina?” and for SEP-3, “Did your erection last long enough to successfully complete intercourse?” The GPAS is based on a 4-point Likert scale and is not a validated assessment tool. However, it was chosen for its simplicity as well as for the ability of patients to use a more continuous scale to monitor their progress. Its role in this trial was particularly useful to collect subjective patient responses relative to the use of tension rings during the study. The GPAS asked, “Has the treatment you have taken over the past four weeks improved your erections?” with response choices of “not applicable, not at all, slightly, moderately, and greatly.” At visit 2, patients were asked to respond to GPAS both with and without the use of tension rings.

**Statistics**

All efficacy analyses were performed on an intent-to-treat basis. Responses to the IIEF-5 were treated as continuous variables and are presented as means. Variables such as SEP-2, SEP-3, and GPAS are presented as counts and percentages. McNemar’s and paired t-tests were used and a probability of 5% or less was considered significant.

**Results**

**Patient Population**

In total, 69 subjects from four sites participated in this study. Men aged ≥18 years who had a minimum of 3 months history of mild, moderate, or severe ED of organic, psychogenic, or mixed causes (as determined by the investigator) were eligible to participate in the study. The diagnosis of ED was established according to the National Institutes of Health statement on ED [10]. Subjects were mostly white (87%) with an average age of 64 years. Thirty subjects (87%) had ED for at least 1 year, with 25 (36%) of those having ED for more than 5 years. Fifty-eight subjects (84%) had gradual onset ED, unassociated with any specific event. All subjects had previously received at least one oral PDE5i, with 91% receiving sildenafil citrate, 64% receiving vardenafil hydrochloride, and 67% receiving tadalafil. Additionally, 14 subjects (20%) had previously used intracavernosal injection (ICI) therapy. In all subjects, the main disease associations were hypertension and hyperlipidemia, and, to a lesser extent, diabetes mellitus (Table 1). Fifty-seven subjects (83%) were married, and 53 subjects (77%) had been with their current partner for more than 5 years (Table 2).

**IIEF-5**

The mean IIEF-5 score at visit 1 was 9.0 ± 5.74. After use of combination therapy (PDE5i + VED) for 4 weeks, the mean IIEF-5 score increased to 17.6 ± 7.18. The change in IIEF-5 after visit 2 was similar in all subgroups, including patients with hypertension and diabetes mellitus. This increase is statistically significant compared with visit 1 (P < 0.001). The mean change from visit 1 in the IIEF-5 score was 8.6, with a 95% confidence interval of 6.8–10.4.

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