Sildenafil or Vardenafil Nonresponders' Erectile Response to Tadalafil

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Introduction: Erectile dysfunction has usually been treated by a phosphodiesterase 5 inhibitor in men, especially in the past decade. Although sildenafil and vardenafil are widely used, there is a high percentage of people who do not respond to these drugs. This study was performed in order to evaluate the efficacy of the lastly presented phosphodiesterase 5 inhibitor, tadalafil, in nonresponder group of patients to sildenafil and vardenafil.

Materials and Methods: Forty married men with erectile dysfunction who had taken sildenafil or vardenafil at the maximum recommended doses and had not responded to the treatment were included. They were treated with tadalafil, 20 mg, at least 4 doses on different days. The effectiveness of the treatment was reviewed by different questionnaires, including the International Index of Erectile Function-5 (IIEF-5), Sexual Encounter Profile (SEP) questions 2 and 3, and the Global Assessment Question (GAQ), at the end of the 12th week.

Results: The IIEF-5 scores were 11.90 ± 4.78 and 12.67±6.70, before and after at least 4 doses of tadalafil, respectively (P = .30). The rate of positive responses to SEP2, SEP3, and GAQ questions were also insignificantly different after the treatment. During this period, flushing was seen in 10 and headache was seen in 5 patients.

Conclusion: The recommended maximum dose for tadalafil insignificantly improved the IIEF5, SEP2, SEP3, and GAQ scores in patients with erectile dysfunction who had not responded to sildenafil and vardenafil. The other treatment alternatives should be in mind after getting no response to the optimum doses and enough trials of sildenafil or vardenafil before trying a tadalafil regimen.

Keywords: tadalafil, erectile dysfunction, sildenafil, vardenafil, treatment failure

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INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or maintain a satisfactory erection for sexual activity.[1] For an erection, relaxation of the corpora cavernosa of the penis through noncholinergic nonadrenergic receptors is mediated by nitric oxide and cyclic guanosine monophosphate. Inhibition of phosphodiesterase type 5 (PDE5) isoenzyme results in increased corporal levels of cyclic guanosine monophosphate and an augmented penile erection.[2] The development of the PDE5 inhibitors, sildenafil, vardenafil, and lastly tadalafil, potentiated nitrergic cavernosal relaxation, and they are all effective in the treatment of male ED. The introduction of these compounds, as orally active drugs for the treatment of ED, have demonstrated improvement in

erectile function and shown to be well tolerated in many populations all over the world.[3]

Compared with sildenafil and vardenafil, the last agent, tadalafil, is characterized by a practical dosing, good efficacy, long elimination half life, that allows for more flexibility of timing for patients. The duration of action of tadalafil is much longer than that of sildenafil or vardenafil (nearly 36 hours), and because of such reasons, it has quickly become one of the favorite choices of patients with ED and their partners.[4]

Although for patients who are proven nonresponders to PDE5 inhibitors, some alternatives exist; such as vacuum constriction devices, intracavernosal injections of vasoactive agents (such as prostaglandin E_1), transurethral delivery of alprostadil, implantation of penile prostheses, and venous or arterial surgery; failure to achieve successful intercourse after the use of maximum recommended dose of sildenafil or vardenafil is always a problem if the patient is not desirous to such treatments.

The aim of this study was to evaluate the efficacy of high-dose lastly presented PDE5 inhibitor, tadalafil, as an alternative therapy for patients refractory to the maximum recommended dose of sildenafil or vardenafil in order to maintain an alternative before suggesting more invasive therapies.

MATERIALS AND METHODS

This study was carried out in 2 different centers in Ankara during the period from June 2005 to January 2008. Patients with ED who had not responded to sildenafil or vardenafil were approached to participate in the study. All other options such as intracavernosal injection, vacuum constriction device, or penile prostheses were introduced to the patients before starting tadalafil. Men who preferred more invasive therapies or who did not consent to participate in the study were also excluded. We included only men who were married with an available partner. Patients were excluded if they had a history of radical prostatectomy, penile anatomical defects, a primary diagnosis of premature ejaculation, spinal cord injury, uncontrolled diabetes mellitus, low testosterone levels, major hematologic, renal or hepatic abnormalities, or a recent myocardial infarction and also if they were receiving nitrates, anti-androgens, and α-blockers.

Forty consecutively selected patients with ED who had taken sildenafil or vardenafil properly, at least 4 maximum recommended dose of 100 mg/d for sildenafil and 20 mg/d for vardenafil and maximum 1 dose per day before sexual activity, and did not respond to the treatment during an average period of 4 months were included. The diagnosis of ED and response to either of the PDE5 inhibitors was evaluated by the International Index of Erectile Function-5 (IIEF-5) questionnaire. Scores of 20 or lower indicates an abnormal degree of erectile functioning.

All patients received 12 weeks of treatment with tadalafil, 20 mg, for at least 4 and a maximum of 10 doses on different days that they intended sexual attempts. The 20 mg tadalafil (Cialis, Eli Lilly, Indianapolis, IN, USA) dose was selected according to the recommended maximum dose for the majority of patients.[5] The patients were advised to dispense 1 tablet per instance of intended sexual intercourse, at least 30 minutes before sexual intercourse, with a maximum of 1 dose daily. All of the patients were asked to supply the drugs on their own as the manufacturer of tadalafil had no relation with this study.

During the treatment phase all patients were seen in the clinic at the end of 1st, 2nd, and 3rd months of treatment. At the interviews, a self-administered questionnaire form that consisted questions about drug taking time, number of drugs taken, days a sexual attempt was tried, any adverse effects were given to patients. Control of the complete administration of the drugs by the patients was established by these visits. Response to the treatment was interrogated by the IIEF-5, the percentage of positive responses to Sexual Encounter Profile (SEP) questions 2 and 3 (SEP2 and SEP3), and the Global Assessment Question (GAQ) at the end of the 12th week. The International Index of Erectile Function-5 questionnaire is one of the most frequently used forms for the patients applying with sexual dysfunction that consist of 5 selected easy

questions about sexual activity. Patients choose the appropriate column for each question about their sexual abilities over the past 4 weeks.[6] The SEP2 ("Were you able to insert your penis into your partner's vagina?") and SEP3 ("Did your erection last long enough for you to have sexual intercourse?") were two different forms which were also asked from our patients. The baseline and endpoint score for each SEP question was the patient's mean percentage of "yes" responses to that question before the treatment period and the posttreatment period.[7]

We analyzed IIEF erectile function domain scores using a last-observation carried forward convention. Statistical analysis of the GAQ was performed with logistic regression analysis. For each SEP question, pretreatment and posttreatment scores were considered the percentage of "yes" responses relative to the number of sexual encounters during the run-in period and the treatment period, respectively. Posttreatment SEP questions included percentage of positive responses relative to the number of sexual attempts in the treatment period. For diary questions, mean success rates over the baseline and treatment periods were averaged for all patients, and were reported as the overall mean. A *P* value less than .05 was considered significant.

RESULTS

The mean age of the 40 enrolled patients was 60 ± 8.2 years (range, 50 to 74 years). Thirty-two patients (80.0%) had a history of ED of 1 year or longer. In the remaining 8 patients, ED history was at least 6 months. Many of the participants had concomitant diseases as hypertension (30.0%), controlled diabetes mellitus (25.0%), or hyperlipidemia (22.5%).

The number of sexual attempts by the couple was only 1, at least 30 minutes after taking recommended dose of tadalafil. Overall, the mean IIEF-5 scores before and after the treatment were 11.90 ± 4.78 and 12.67 ± 6.70, respectively. Tadalafil did not improve the mean IIEF-5 intercourse satisfaction ($P = .30$). The percentage of positive answers to the SEP-2 and SEP-3 questions were both 10.0% before the treatment and 12.5% after the treatment, and only 1 patient mentioned positive response to the maximum dose of tadalafil on the questionnaire forms. The GAQ used to assess the overall effect of the treatment indicated that tadalafil was not superior to prior therapies ($P = .47$) in improving erections (tadalafil, 22.5%; prior therapies, 20.0%).

The most common treatment adverse events seen frequently (≥ 5%) with tadalafil were headache (12.5%), dyspepsia (10.0%), flushing (25.0%), back pain (5.0%), and myalgia (5.0%). These adverse events were mostly mild to moderate that did not affect the patient's daily life, lead to take any drugs, or require hospitalization.

DISCUSSION

The Food and Drug Administration has approved the three drugs of the PDE5 inhibitors for clinical use in the treatment of ED. Sildenafil was the first drug in this class, followed by vardenafiland tadalafil. These drugs are potent and selective inhibitors of PDE5, acting by potentiating the action of intracavernosal nitric oxide, thereby leading to a more sustained erection.[8] Sildenafil was the first PDE5 inhibitor to undergo evaluation and has been studied extensively in many trials.[9-12] More recently, other agents, vardenafil and lastly tadalafil, have been introduced. All the drugs have been shown to be effective across a wide range of etiologies of ED. The drugs have been shown to improve erectile function domain scores and penetration and maintenance of erection, resulting in more successful intercourse. Their effects are greater at higher doses. Sildenafil and vardenafil are shorter-acting agents, while tadalafil has a longer half-life allowing the user more flexibility in sexual activity. The drugs are generally well tolerated and withdrawals from the clinical studies as a result of drug-related adverse effects were rare. Common adverse effects include headache, nasal congestion, flushing, myalgia, and dyspepsia, all actions related to inhibition of PDE5.[13]

All the three PDE5 drugs have similar efficacy and toxicity profiles. Sildenafil and vardenafil have similar molecular structures, but tadalafil is different in structure, which is reflected in its pharmacokinetic profile. With regard to the onset of action, achievement of an erection that leads

to successful intercourse, sildenafil and vardenafil both have half lives of approximately 4 hours, but the half life of tadalafil is approximately 18 hours. Another difference between the PDE5 inhibitors is that fatty food especially affects the pharmacokinetic profiles of sildenafil and vardenafil, but not that of tadalafil, giving comfort about the meals to the patients.[14]

In our cohort, the improvement in the erectile function domain score on the IIEF-5 and the percentage of sexual intercourse attempts marked by successful vaginal penetration and completion was insignificantly greater with tadalafil, 20 mg, than prior therapies in trials of 12 weeks duration. Improvement in scores on other domains of the IIEF and the percentage of positive responses to a GAQ measuring erection improvement were also insignificantly greater with on demand tadalafil than other PDE5 inhibitors. The adverse events associated with tadalafil were generally mild to moderate and decreased in frequency with continued administration. The most commonly reported adverse events were flushing and headache. The incidence of cardiovascular adverse events was not significantly different in tadalafil.[15] It seems that if the patient has not responded to sildenafil or vardenafil, the maximum recommended dose of tadalafil also seems ineffective.

Satisfaction with the sexual experience is considered important when evaluating the impact of treatments for ED, yet enhanced satisfaction has been infrequently assessed in the sexual trials. We evaluated the efficacy of sildenafil and vardenafil versus tadalafil in Turkish men with ED and determined the self-based rating of medicinal preference. Sildenafil and vardenafil are the potent inhibitors of the PDE5, in the corpus cavernosa, and therefore, they increase the penile response to sexual stimulation. Tadalafil is also a PDE5 inhibitor that increases the level of cyclic guanosine monophosphate in cavernous smooth muscle cells, which is a second messenger for the vasodilator effects of nitric oxide causing smooth muscle relaxation. In this study, sildenafil and vardenafil nonresponders treated with 20 mg of tadalafil were found to be associated with insignificant higher mean scores for the questions of the IIEF-5. Also frequency of penetration and maintenance of erection after sexual penetration were not found to be enhanced significantly with tadalafil in nonresponder patients to sildenafil and vardenafil. Similarly, overall erectile satisfaction also did not show a significantly positive improvement in the treated group, as shown by the GAQ scores. This study further concludes that there is not a major point of difference between the short-acting agents sildenafil and vardenafil and the longer-acting tadalafil.[16]

Several factors can contribute to the failure of ED treatments using PDE-5 inhibitors. The reasons for acute or delayed failure include severe ED at presentation, worsening of endothelial dysfunction, and progression of penile atherosclerosis because of some factors such as diabetes mellitus, anxiety of performance, erectile dysfunction after radical surgeries, unidentified hypogonadism, inadequate patient education, incorrect usage of the prescribed drugs, development of tachyphylaxis, and some psychosocial factors.[17]

CONCLUSION

In practice, PDE5 inhibitors are often used once or twice a week, so a patient would have to spend at least 3 months trying the various compounds and dosages to achieve adequate exposure to all the three PDE5 inhibitors; this would seem an unrealistic strategy in current clinical practice. Compared with the other two PDE5 inhibitors, sildenafil and vardenafil, tadalafil is characterized by rapid onset, independence of meals before taking the drug, convenient dosing (especially the 36-hour duration of effectiveness deriving from long elimination half-life), and allowing for more flexibility to scheduled medication. Higher satisfaction of patients and their partners with tadalafil is mainly due to such psychosocial benefits as decreased time concerns. The duration of action of tadalafil is longer than that of sildenafil or vardenafil. Tadalafil is well-tolerated, consistent with the principle of safely, effectiveness, and convenient dosing and is becoming the favorite choice of patients with ED and their partners. However, in our study, although it was not a placebo-controlled

randomized trial, it was demonstrated that tadalafil is not an effective agent for sildenafil and tadalafil nonresponders' group. It might be an option that the urologist should talk about the other treatment alternatives such as intracavernosal injection, vacuum constriction device, or penile prostheses with the patient after getting no response to the maximal recommended doses and enough trials of sildenafil or vardenafil without trying a new tadalafil regimen protocol or try it at first if the patient wishes a more flexible and meal-independent drug with a longer period for taking the drug before sexual activity.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Lue TF. Erectile dysfunction. N Engl J Med. 2000;342:1802-13.
2. McMahon CG. High dose sildenafil citrate as a salvage therapy for severe erectile dysfunction. Int J Impot Res. 2002;14:533-8.
3. Becker AJ, Uckert S, Stief CG. The basics of phosphodiesterase type 5 (PDE5) inhibition in urology. Urologe A. 2008;47:1582-7
4. Deng SM. Tadalafil for erectile dysfunction: outstanding efficacy for 36 hours. Zhonghua Nan Ke Xue.2008;14:857-60.
5. Kuan J, Brock G. Selective phosphodiesterase type 5 inhibition using tadalafil for the treatment of erectile dysfunction. Expert Opin Investig Drugs. 2002;11:1605-13.
6. Rosen R, Riley A, Wagner G, et al. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49:822-30.
7. Curran M, Keating G. Tadalafil. Drugs. 2003;63:2203-12.
8. Savas M, Yeni E, Ciftci H, Topal U, Utangac M, Verit A. Is Penile Length a Factor in Treatment of Erectile Dysfunction with PDE-5 Inhibitor? J Androl. 2009;30:515-9
9. Rendell MS, Raifer J, Wicker PA, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: A randomized controlled trial. Sildenafil Diabetes Study Group. JAMA. 1999;3;281:421-6.
10. Aubin S, Heiman JR, Berger RE, Murallo AV, Yung-Wen L. Comparing Sildenafil alone vs. Sildenafil plus brief couple sex therapy on erectile dysfunction and couples' sexual and marital quality of life: a pilot study. J Sex Marital Ther. 2009;35:122-43.
11. Montorsi F, Padma Nathan H, Glina S. Erectile function and assessments of erection hardness correlate positively with measures of emotional well-being, sexual satisfaction, and treatment satisfaction in men with erectile dysfunction treated with sildenafil citrate. Urology. 2006;68:26-37.
12. Hellstrom WJG, Elhilali M, Homering M, et al. Vardenafil in patients with erectile dysfunction: Achieving treatment optimization. J Androl. 2005;26:604-9.
13. Basu A, Ryder RE. New treatment options for erectile dysfunction in patients with diabetes mellitus. Drugs. 2004;64:2667-88.
14. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. Int J Clin Pract. 2006;60:967-75.
15. Yip WC, Chiang HS, Mendoza JB, Tan HM, Li MK, Wang WC, Kopernicky V. Efficacy and safety of on demand tadalafil in the treatment of East and Southeast Asian men with erectile dysfunction: a randomized double-blind, parallel, placebo-controlled clinical study. Asian J Androl. 2006;8:685-92.
16. Syed T. Effectiveness of sildenafil citrate and tadalafil on sexual responses in Saudi men with erectile dysfunction in routine clinical practice. Pak J Pharm Sci. 2008;21:275-81.
17. Chelsea N, McMahon, Christopher J Smith, Ridwan Shabsigh. Treating erectile dysfunction when PDE-5 inhibitors fail. BMJ. 2006;332:589-92.