Journal of Ancient Diseases & Preventive Remedies

Cohen, J Anc Dis Prev Rem 2014, 2:2
http://dx.doi.org/10.4172/2329-8731.1000116

Review Article Open Access

Update on Short-Acting vs. Long-Acting PDE5i + Life-Style Changes vs. PDE5i

Seth D. Cohen*

Department of Sexual Medicine, University of Alvarado Hospital, USA

***Corresponding author:** Seth D. Cohen, Department of Sexual Medicine, University of Alvarado Hospital, San Diego CA, 92120, USA, Tel: 619-265-8865; Fax: 619-265-7696; E-mail: cohensethmd@gmail.com

Rec date: Jul 10, 2014, **Acc date:** Sep 22, 2014, **Pub date:** Sep 24, 2014

Abstract

The medical management of erectile dysfunction(ED) has evolved greatly over the past 20 years. Prior to the early 80's we were able to offer patients one of two definitive surgical therapies for the management of their erectile dysfunction: implantation of penile prosthesis and penile revascularization. The first approved phosphodiesterase inhibitors (PDE5i) for the treatment of ED was sildenafil citrate (1998). Currently, there are four FDA approved oral medications indicated for the treatment of ED (sildenafil, vardenafil, tadalafil and avanafil), all of which predominantly inhibit PDE5.

Despite their similar modes of action, PDE5i differ in their biochemical properties, pharmacokinetic profiles, and clinical performance. Most distinctive is their half-life, with sildenafil, vardenafil and avanafil having half-lives of approximately 4-5 hours, compared with tadalafil, with a half-life of 17.5 hours. The median time to maximum concentration (t max) is 30 minutes for avanafil, 1 hour for sildenafil and vardenafil, and 2 hours for tadalafil.

The abundance of choices poses the question, "which PDE-5 inhibitor?" relevant for clinicians, patients and their partners. A significant percentage of men initiating treatment will ultimately switch between inhibitors or discontinue therapy (poor compliance). Properly counseling patients and their partners as to the appropriate treatment choice is paramount to optimizing compliance. It is widely accepted that there are no significant differences in the safety and efficacy of the 4 PDE5i, although avanafil has shown great promise in reducing the typical side effects.

Lifestyle modifications should be certainly considered an integral part of the treatment regimen for ED, both independently and in conjunction with other management options. The risk of developing ED is closely associated with the presence of co-morbidities such as diabetes, cardiovascular disease, and metabolic syndrome. Prevention or appropriate treatment of these disease states, can positively impact sexual health.

Keywords: Erectile dysfunction; Impotence; Phosphodiesterase 5 inhibitor; Sildenafil; Vardenafil; Tadalafil; Avanafil

Overview of ED and Medications

The medical management of erectile dysfunction(ED) has evolved greatly over the past 20 years. Prior to the early 80's we were able to offer patients one of two definitive surgical therapies for the management of their erectile dysfunction: implantation of penile prosthesis and penile revascularization. Aside from these options, outpatient management was relegated to sex therapy, psychoanalysis and an endocrine workup for presumed hypogonadism [1]. In 1984 Brindley published his series describing pharmacologic penile injection therapy [2]. Although effective, this treatment has a low long term compliance rate. With the advent of oral phosphodiesterase inhibitors (PDE5i), medical providers have been able to offer a safe, effective and easy to administer oral medication to correct ED.

Although PDE5i were approved in 1998 by the FDA, the basic science for this class of medications dates back to 1958. Sutherland and Rall (1958) were the first to discover the enzyme phosphodiesterase whose mechanism of action is the conversion of the intracellular second messenger molecule cyclic guanosine monophosphate (cGMP) to its inactive form. By blocking this conversion, the active form of cGMP catalyzes a biochemical cascade resulting in corporal smooth muscle relaxation and, hence, penile erection [3,4].

The first approved PDE5i for the treatment of ED was sildenafil citrate. This was initially investigated as a treatment for angina pectoris but was found to have several side effects, one of which was improved erectile function. Currently, there are four FDA approved oral medications indicated for the treatment of ED (sildenafil, vardenafil, tadalafil and avanafil), all of which predominantly inhibit PDE5 [5]. The introduction of these three drugs has resulted in an increase in marketing to the general public by direct consumer advertising. This awareness has fueled the surge in their demand. The availability of the four distinct agents raises the question of which PDE5i is best suited for the individual needs of the patient? The approach taken by several physicians is to prescribe each of these agents to a particular patient with ED, and to let him decide which medication is best suited for his lifestyle [6].

Short Acting vs. Long Acting PDE5i

Despite their similar modes of action, PDE5i differ in their biochemical properties, pharmacokinetic profiles, and clinical performance. Most distinctive is their half-life, with sildenafil,vardenafil and avanafil having half-lives of approximately 4-5 hours, compared with tadalafil, with a half-life of 17.5 hours. All

three medications have been shown to be rapidly absorbed after oral administration. The median time to maximum concentration (t max) is 30 minutes for avanafil, 1 hour for sildenafil and vardenafil, and 2 hours for tadalafil. Median (t max) values as low as 30 minutes have been reported with avanafil at the 50, 100 and 200 mg dose [7,8]. High-fat meal intake influences the absorption profiles of both sildenafil and vardenafil but not tadalafil or avanafil [4,7,8]. The differences in their pharmacokinetic properties offer a basis for clinical selections of PDE5 inhibitors, based on patient needs and preferences.

The side effect profile of these three drugs is important to recognize and may affect patient safety and compliance. Since PDE5i have an additive effects on the nitric oxide (NO) pathway, their use is contraindicated in patients taking any form of nitrates as they may produce life threatening hypotension. The American Heart Association/American College of Cardiology consensus panel recommended that nitrates not be administered within 24 h after sildenafil dosing [9]. Similar to other PDE5 inhibitors, tadalafil should not be administered in combination with organic nitrates. In the event that nitrates are given, especially within this critical time interval, it is essential to have the capability to support the patient with fluid resuscitation and alpha-adrenergic agonists if needed. In patients with recurring angina after sildenafil use, other non-nitrate antianginal agents, such as b-blockers, should be available [9]. In addition, PDE5i can cross react with multiple different PDE receptors causing variable effects on olfaction (PDE1), insulin action (PDE3), and platelet aggregation and vascular tone (PDE3, PDE5) [5]. Because of the cross-reactivity of sildenafil and vardenfil with PDE6 receptors, patients should be counseled about color changes in vision (chromatopsia) and more infrequently, increased sensitivity to light and blurred vision. These visual affects are not seen with tadalafil and avanfil.

According to standard dosing recommendations for sildenafil and vardenfil, patients are instructed to take the medications on demand approximately one hour before intended sexual activity. Tadalafil 20 mg can have effects lasting up to 36 hours. However, a daily dosing regimen has been approved for tadalafil based on its extended half-life, to provide patients with the ability to have sexual intercourse on demand with greater spontaneity [10,11]. In a randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction successful intercourse by subjects was seen within 15 minutes of dosing at all three doses [7].

The abundance of choices makes the question "which PDE-5 inhibitor?" relevant for clinicians, patients and their partners. A significant percentage of men initiating treatment will ultimately switch between inhibitors or discontinue therapy (poor compliance). Properly counseling patients and their partners as to the appropriate treatment choice is paramount to optimizing compliance. It is widely accepted that there are no significant differences in the safety and efficacy of the 4 PDEi, although avanafil has shown great promise in reducing the typical side effects from PDE5i [7]. This has led to the initiation of studies aimed at evaluating patient preferences. Strodeburg et al. (2006) showed high success rates when giving the patients the freedom to try all available PDE5i [6]. Similarly, Lunjunggren et al. (2007) evaluated 127 men at a mean age 60 years (range: 36–79 years), who were given the option of taking any of three PDE5i [12]. Seventy-five percent of the men used only one drug; the others alternated between a short and long-acting drug, depending on their situation and preference. Of the 127 men, 109 (86%) were still using PDE5 inhibitors at the end of the 2 year period. The most common reason for discontinuation of therapy was a return of satisfactory spontaneous erections. The authors concluded that allowing patients to choose any of the three medications resulted in a high compliance rate over an extended period of time [12]. In another study evaluating compliance rates, 1,900 men with ED taking tadalafil were enrolled in a 1-year trial. Available data from 1,567 men at 12-months indicated that 1,319 (85.9%) were still taking tadalafil. The most important factor in predicting long-term compliance was patient satisfaction at 1 month [13].

In the Endotrial (2009), the authors evaluated the efficacy of sildenafil, tadalafil, and vardenafil in a randomly assigned 8-week fixed regimen study [14]. The primary outcome was the post-treatment erectile function scores from the abridged International Index of Erectile Function (IIEF5+1). Subjects were sub-divided into four treatment groups: sildenafil 50 mg, sildenafil 100 mg, tadalafil 20 mg, and vardenafil 20 mg. All groups demonstrated a statistically significant baseline-to-end point improvement in subjective perception of erectile function measured by IIEF5+1. Overall equivalence was demonstrated in the subjective perception of treatment benefits for all the PDE5i tested. However, only sildenafil, in a dose-dependent manner resulted in improvement in penile flow parameters within the 8-week treatment period [14].

PDE5i + Lifestyle Changes

Lifestyle modifications should be certainly considered an integral part of the treatment regimen for ED, both independently and in conjunction with other management options. While seemingly easy to recommend, in practice can be quite difficult to implement. The risk of developing ED is closely associated with the presence of co-morbidities such as diabetes, cardiovascular disease, and metabolic syndrome. Prevention or appropriate treatment of these disease states, can positively impact sexual health [15]. For example, several reports have suggested that discontinuation of cigarette smoking results in a recovery of functional erection status [16-18]. In addition, exercise and weight control have been shown to improve ED status. Miroglu et al. evaluated the effects of lifestyle changes ED. Their data suggest a link between the occurrence of ED and a number of lifestyle factors, including smoking, obesity, alcohol consumption, and lack of physical activity. They concluded that appropriate modification in these lifestyle factors could help improve ED, as well as reduce the risks of developing cardiovascular disease [19].

Gupta et al. (2011) performed a multi-center study investigating the effect of lifestyle modification on cardiovascular risk factor reduction and ED [20]. In this multi-center trial, a total of 740 participants from 4 countries were evaluated. The effective change in ED was measured using the IIEF-5 questionnaire. Lifestyle modifications and pharmacotherapy for cardiovascular risk factors were associated with a statistically significant improvement in sexual function. Specifically, the mean change in IIEF-5 score was 2.7 points for the entire cohort. Patients with mild ED demonstrated a more significant improvement than those with more severe ED [20]. Other investigators have demonstrated the specific dietary changes and their effects on ED. Esposito et al (2006), analyzed patients with ED who were on a Mediterranean diet. This diet rich in whole grain, fruits, vegetables, legumes, walnuts, and olive oil was associated with improvement in both ED and metabolic syndrome [21].

Conclusion

This review is an in-depth look at PDE5i medications with particular emphasis on the pharmacodynamics of PDE5i as well as improvement in ED symptoms with lifestyle changes. The data confirms that no one PDE5i has any specific advantage over the other. Rather, all four drugs should be used interchangeably, with the patient and his partner(s) making the ultimate decision as to which is preferable. Finally, there is ample data confirming that the appropriate lifestyle changes can have a beneficial effect on ED, either independently or in conjunction with medical treatment.

References

1. Burnett AL (2012) Evaluation and Management of Erectile Dysfunction, in Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA: Campbells Urology, Philadelphia, Saunders Elsevier 1: 24.
2. Brindley GS (1983) Cavernosal alpha-blockade: a new technique for investigating and treating erectile impotence. Br J Psychiatry 143: 332-337.
3. Sutherland EW, Rall TW (1958) Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles. J Biol Chem 232: 1077-1091.
4. Burnett AL (2005) Phosphodiesterase 5 mechanisms and therapeutic applications. Am J Cardiol 96: 29M-31M.
5. Carson CC, Lue TF (2005) Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int 96: 257-280.
6. Ströberg P, Hedelin H, Ljunggren C (2006) Treatment of erectile dysfunction with PDE-5 inhibitors. Difficult for the physician to choose between the preparations--the patient should be given the opportunity to try out all three. Lakartidningen 103: 1107-11108, 1110-1111.
7. Goldstein I, McCullough AR, Jones LA, Hellstrom WJ, Bowden CH, et al. (2012) A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. J Sex Med 9: 1122-1133.
8. Limin M, Johnsen N, Hellstrom WJ (2010) Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. Expert Opin Investig Drugs 19: 1427-1437.
9. Cheitlin MD, Hutter AM Jr, Brindis RG, Ganz P, Kaul S, et al. (1999) ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American College of Cardiology/ American Heart Association. J Am Coll Cardiol 33: 273-282.
10. Porst H, Giuliano F, Glina S, Ralph D, Casabé AR, et al. (2006) Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 50: 351-359.
11. Shabsigh R, Donatucci C, Costabile R, Perelman MA, Burns P, et al. (2010) Reliability of efficacy in men with erectile dysfunction treated with tadalafil once daily after initial success. Int J Impot Res 22: 1-8.
12. Ljunggren C, Hedelin H, Salomonsson K, Ströberg P (2008) Giving patients with erectile dysfunction the opportunity to try all three available phosphodiesterase type 5 inhibitors contributes to better long-term treatment compliance. J Sex Med 5: 469-475.
13. Perimenis P, Roumeguere T, Heidler H, Roos E, Belger M, et al. (2009) Evaluation of patient expectations and treatment satisfaction after 1-year tadalafil therapy for erectile dysfunction: the DETECT study. J Sex Med 6: 257-267.
14. Jannini EA, Isidori AM, Gravina GL, Aversa A, Balercia G, et al. (2009) The ENDOTRIAL study: a spontaneous, open-label, randomized, multicenter, crossover study on the efficacy of sildenafil, tadalafil, and vardenafil in the treatment of erectile dysfunction. J Sex Med 6: 2547-2560.
15. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, et al. (2005) Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol 96: 85M-93M.
16. Mannino DM, Klevens RM, Flanders WD (1994) Cigarette smoking: an independent risk factor for impotence? Am J Epidemiol 140: 1003-1008.
17. Feldman HA, Johannes CB, Derby CA, Kleinman KP, Mohr BA, et al. (2000) Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med 30: 328-338.
18. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, et al. (2006) A prospective study of risk factors for erectile dysfunction. J Urol 176: 217-221.
19. Horasanli K, Boylu U, Kendirci M, Miroglu C (2008) Do lifestyle changes work for improving erectile dysfunction? Asian J Androl 10: 28-35.
20. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, et al. (2011) The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med 171: 1797-1803.
21. Esposito K, Ciotola M, Giugliano F, De Sio M, Giugliano G, et al. (2006) Mediterranean diet improves erectile function in subjects with the metabolic syndrome. Int J Impot Res 18: 405-410.