Microvascular Complications in Diabetic Erectile Dysfunction

Do we need other alternatives?

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Advances in the management of erectile dysfunction (ED) and its adverse effects on the quality of life of men and their partners have encouraged researchers to look for new solutions for treating and curing ED. The introduction of phosphodiesterase type 5 inhibitors to treat ED in 1998 was revolutionary in that it heralded the onset of a new era of effective and safe treatment for restoring male sexual function.

Today, PDE5 inhibitors are used as first-line therapy for the management of ED irrespective of its etiology. Despite the fact that millions of men with ED worldwide have been treated successfully with these drugs, several questions regarding their efficacy and safety and the high dropout rate in men to whom these medications are prescribed remain unanswered. This is especially evident in diabetes because the frequency of ED in men with diabetes is higher than that of the general population. In fact, the frequency of ED in diabetic men has been reported to be as high as 75% in men with longstanding disease (1–3). In contrast to the high efficacy rate of PDE5 inhibitors in the general population (70–89%), just over 50% of diabetic men with ED respond favorably to these drugs (4). Impaired neural and penile vascular functions are believed to be the main reasons for the high incidence of ED in men with diabetes, and the underlying causes of this drug resistance are not fully understood.

Recent data indicate that PDE5 inhibitors have beneficial effects in other chronic diseases. Sildenafil has been approved recently for the treatment of idiopathic pulmonary hypertension (5). Lately, several reports have suggested that PDE5 inhibitors may improve arterial function (6–9). Moreover, improvement of lower urinary tract symptoms in patients with benign prostatic hyperplasia has also been reported (10). Finally, the results of research in the basic sciences and clinical studies have yielded promising therapeutic results regarding the continual use of PDE5 inhibitors to treat a variety of diseases including ED.

PDE5 INHIBITORS: LESSONS LEARNED FROM CLINICAL PRACTICE

Efficacy

All three PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) have undergone extensive evaluation in patients with ED secondary to either hypertension, peripheral vascular disease, nerve injury, diabetes, or postradical pelvic surgeries. The response rate of ED patients with these conditions is impressive and can be as high as 60–70%. Diabetic men have displayed impaired response rates in all therapeutic trials (11,12). The major predictors for treatment success have been identified as having few diabetic complications and good glycemic control (13). Patients with ED secondary to radical prostatectomy is another difficult-to-treat group of patients with ED and are of major interest for urologists.

Differences in pharmacokinetic profiles

Several recent publications have emphasized that the onset time of response after the oral administration of sildenafil, tadalafil, and vardenafil may be as short as 15 min (14–16). However, such data may lead to mistreatment because the onset of response in the majority of the patients occurs usually when the maximum plasma concentration is reached (~1 h for sildenafil and vardenafil and ~2 h for tadalafil). Furthermore, patients taking PDE5 inhibitors should be told to avoid fatty meals when taking these drugs orally, especially sildenafil and vardenafil, to get a satisfying erection.

The duration of action of the different PDE5 inhibitors has been well documented in all premarketing clinical trials. Initially, it was reported that sildenafil and vardenafil have a short duration of action (maximum 4 h). Clinical experience has now shown that their duration of action is longer and that it may be as long as 8–12 h (17). On the other hand, the duration of action of tadalafil was reported initially to be 24 h. Consecutive trials and clinical use have shown a consistent efficacy of tadalafil for up to 36 h (18).

It is quite common that physicians prescribe drugs to their patients without any explanation. When prescribing PDE5 inhibitors, the importance of taking medication on an empty stomach and timing between drug intake and intercourse, as well as the need for sexual stimulation to get an erectile response, are crucial issues that need to be explained to patients to ensure drug efficacy. The results of several studies have identified inappropriate instructions and lack of follow-up as the most common causes for the poor response to PDE5 inhibitors or poor drug compliance. It has been reported that 30–50% of the initial nonresponders to PDE5 inhibitors can be converted to responders when patients are given proper instructions on how to use the drug (19,20).

Safety

PDE5 inhibitors are safe drugs, and the main contraindications for their use is the concomitant use of nitrates and use in patients with retinitis pigmentosa. Although several cardiovascular safety issues have been raised since their clinical introduc-

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tion, the results of recent clinical trials and clinical pharmacologic surveillance data have demonstrated no increase in myocardial infarction rates in patients taking these agents compared with the expected rates in age-matched populations (21,22). Furthermore, the results of numerous studies have proven not only the cardiovascular safety of PDE5 inhibitors, but even possible cardiovascular benefits (7,8).

One important safety issue is the co-administration of PDE5 inhibitors with α-adrenoceptor blockers in patients with benign prostatic hyperplasia. All PDE5 inhibitors appear to have some interaction with α-adrenoceptor blockers with respect to lowering blood pressure, but co-administration rarely results in clinically significant orthostatic hypotension (23).

Recently, the U.S. Food and Drug Administration (FDA) alerted health providers about a possible association between the use of PDE5 inhibitors and nonarteritic anterior ischemic optic neuropathy (NAION) in response to a small number (>50 cases) of postmarketing reports of vision loss in men taking PDE5 inhibitors (24). Based on currently available data, it is recommended that patients with a history of mono-ocular NAION be cautioned that the administration of PDE5 inhibitors may increase the risk of NAION in the fellow eye. Patients who have risk factors for the development of NAION should be referred to an ophthalmologist before being prescribed PDE5 inhibitors. Furthermore, any man taking a PDE5 inhibitor who develops visual problems should stop taking the PDE5 inhibitor and be seen by an ophthalmologist.

NEW THERAPEUTIC STRATEGIES: CHRONIC ADMINISTRATION OF PDE5 INHIBITORS

— Since sildenafil was first introduced to treat ED, on-demand administration was the recommended mode of its administration and this became the standard. When newer PDE5 inhibitors entered the market, the same on-demand mode of administration was maintained. In an attempt to improve efficacy, particularly in patients with severe ED, results of several independent studies have shown that daily use of a PDE5 inhibitor may play a role not only in improving their efficacy, but also in curing ED (25) and that the long-term administration of PDE5 inhibitors is beneficial for the early rehabilitation of penile endothelial function after radical prostatectomy (26). Moreover, current data suggest that endothelial dysfunction is common to both ED and cardiovascular diseases (27). Endothelial dysfunction results in reduced ability of the endothelial cells to release vasorelaxants, such as nitric oxide (28,29). Consequently, the ability of the arteriolar smooth muscle cells to relax efficiently is impaired, and an inadequate increase in local blood flow ensues. The administration of PDE5 inhibitors has been reported to improve endothelium-dependent, flow-mediated vasodilation in smokers and in patients with diabetes or chronic heart failure (30,31). De Young et al. (32) have shown recently that daily administration of PDE5 inhibitors can lead to improvements in the functioning of the erectile tissue in a diabetic animal model. The results of other studies have established that physiological and cellular changes that occur in ED can be reversed with long-term administration of PDE5 inhibitors. In addition, Ayala et al. reported that chronic inhibition of PDE5 in high fat-fed conscious mice counters the effects of the high-fat diet–induced endothelial dysfunction and insulin resistance by improving energy balance and enhancing insulin action in vivo (33).

Emerging clinical evidence indicates that this beneficial chronic effect of PDE5 inhibitors on endothelial and erectile function may also occur in humans. Chronic therapy with tadalafil has been reported to improve endothelial function and erectile function in ED patients with cardiovascular risk factors (28,34). Initially, long-term use of PDE5 inhibitors was recommended in patients who did not respond when treated on-demand. In this setting, McMahon (35) reported that a significant proportion of patients who were previously considered as nonresponders to on-demand tadalafil and then prescribed 10 mg tadalafil every 3 days were able to achieve intercourse 58% of the time. In another study, Mirone et al. (36) compared the response of 4,262 men with ED and cardiovascular risk factors that were using either tadalafil on-demand or in a daily regimen and reported that those men with ED who used tadalafil on scheduled regimen had more attempted sexual encounters than the on-demand group. In addition, the authors of both studies reported an excellent safety profile of tadalafil in the chronically treated group.

Another advantage of daily administration of a PDE5 inhibitor, at least for some couples, is not only the efficacy profile, but the greater spontaneity that this regimen can give to their sex life. Chronic usage breaks the associative relationship between taking a medication and having sex 1 h later, which is one of the most frustrating disadvantages of the on-demand regimen.

Because of its pharmacokinetic profile, tadalafil is probably the more suitable medication for long-term use due to its pharmacokinetic properties. The plasma levels of tadalafil taken daily are higher than those obtained when taken on-demand (37).

Regardless of its enormous potential, the concept of daily oral treatment with PDE5 inhibitors has been received with some skepticism by several clinical investigators. Some key questions and concerns have to be answered—namely, tolerability, tachyphylaxis, and safety in those patients who suffer from multiple comorbidities—before this new treatment regimen will be widely accepted.

CONCLUSIONS

— The unique mechanism of action and high efficacy of PDE5 inhibitors has generated immense interest among researchers dealing with sexual dysfunction. From the launch of sildenafil, which occurred >10 years ago, a new focus for basic and clinical research had emerged regarding the safety profile and effect on other organs (vascular, pulmonary, and urinary system) of PDE5 inhibitors because of their potential to treat other chronic diseases. Moreover, use of PDE5 inhibitors, which have been established as an efficacious and safe class of drugs when prescribed to most men with ED, restored sexual function to normal. One of the major breakthroughs recently achieved is probably the accumulating evidence that chronically administered PDE5 inhibitors can improve endothelial and sexual function. Daily treatment with PDE5 inhibitors is now the preferred method of treatment in several groups of men with ED due to radical prostatectomy and with severe endothelial and vascular dysfunction such as diabetes. This treatment regimen has also been shown to benefit younger men, in whom this new treatment approach is able to restore their sexual habits to normal, thereby removing the stigma of having a disease. Nevertheless, lack of knowledge regarding detailed mechanisms, safety and tolerability concerns, and costs may prevent a broad application of this regimen.

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References

1. Benet AE, Melman A. The epidemiology of erectile dysfunction. Urol Clin N Am 1995;22:699–703
2. Maatman TJ, Montague DK, Martin LM. Erectile dysfunction in men with diabetes mellitus. Urology 1987;29:589–592
3. McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. Diabetologia 1980; 18:279–283
4. Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial: Sildenafil Diabetes Study Group. JAMA 1999;281:421–426
5. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353: 2148–2157
6. Halcox JP, Nour KR, Zalos G, Mincemoyer RA, Waclawiw M, Rivera CE, Willie G, Ellahham S, Quyyumi AA. The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. J Am Coll Cardiol 2002;40: 1232–1240
7. Gori T, Sicuro S, Dragoni S, Donati G, Forconi S, Parker JD. Sildenafil prevent endothelial dysfunction induced by ischemia and reperfusion via opening of adenosine triphosphate-sensitive potassium channels: a human in vivo study. Circulation 2005;111:742–746
8. Vlachopoulos C, Hirata K, O'Rourke MF. Effect of sildenafil on arterial stiffness and wave reflection. Vasc Med 2003;8:243–248
9. Kimura M, Higashi Y, Hara K, Noma K, Sasaki S, Nakagawa K, Goto C, Oshima T, Yoshizumi M, Chayama K. PDE5 inhibitor sildenafil citrate augments endothelium-dependent vasodilation in smokers. Hypertension 2003;41:1106–1110
10. Sairam K, Kulinskaya E, McNicholas TA, Boustead GB, Hanbury DC. Sildenafil influences lower urinary tract symptoms. BJU Int 2002;90:836–839
11. Perimenis P, Markou S, Gyftopoulos K, Athanasopoulos A, Giannitsas K, Barbalias G. Switching from long-term treatment with self-injections to oral sildenafil in diabetic patients with severe erectile dysfunction. Eur Urol 2002;41:387–391
12. Tsujimura A, Yamanaka M, Takahashi T, Miura H, Nishimura K, Koga M, Iwasa A, Takeyama M, Matsumiya K, Takahara S, Okuyama A. The clinical studies of sildenafil for the ageing male. Int J Androl 2002;25:28–33
13. Basu A, Ryder RE. New treatment options for erectile dysfunction in patients with diabetes mellitus. Drugs 2004;64:2667–2688
14. Padma-Nathan H, Stecher VJ, Sweeney M, Orazem J, Tseng LJ, Deriesthal H. Minimal time to successful intercourse after sildenafil citrate: results of a randomized, double-blind, placebo-controlled trial. Urology 2003;62:400–403
15. Rosen RC, Padma-Nathan H, Shabsigh R, Saikali K, Watkins V, Pullman W. Determining the earliest time within 30 minutes to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study. J Sex Med 2004;1:193–200
16. Montorsi F, Padma-Nathan H, Buvat J, Schwaibold H, Beneke M, Ulbrich E, Bandel TJ, Porst H. Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial. J Sex Med 2004;1: 168–178
17. Moncada I, Jara J, Subira D, Castano I, Hernandez C. Efficacy of sildenafil citrate at 12 hours after dosing: re-exploring the therapeutic window. Eur Urol 2004;46: 357–361
18. Porst H, Padma-Nathan H, Giuliano F, Anglin G, Varanese L, Rosen R. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. Urology 2003;62:121–125
19. Hatzimouratidis K, Moysidis K, Bekos A, Tsimtsiou Z, Ioannidis E, Hatzichristou D. Treatment strategy for "non-responders" to tadalafil and vardenafil: a real-life study. Eur Urol 2006;50:126–133
20. Gruenwald I, Shenfeld O, Chen J, Raviv G, Richter S, Cohen A, Vardi Y. Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. Eur Urol 2006;50:134–140
21. Hatzichristou D, Montorsi F, Buvat J, Laferriere N, Bandel TJ, Porst H. The efficacy and safety of flexible-dose vardenafil (Levitra®) in a broad population of European men. Eur Urol 2004;45:634–641
22. Jackson G, Kloner RA, Costigan TM, Warner MR, Emmick JT. Update on clinical trials of tadalafil demonstrates no increased risk of cardiovascular adverse events. J Sex Med 2004;1:161–167
23. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, Carson C 3rd, Cheitlin M, Debusk R, Fonseca V, Ganz P, Goldstein I, Guay A, Hatzichristou D, Hollander JE, Hutter A, Katz S, Kloner RA, Mittleman M, Montorsi F, Montorsi P, Nehra A, Sadovsky R, Shabsigh R. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol 2005;96:313–321
24. Hatzichristou D. Phosphodiesterase 5 inhibitors and nonarteritic anterior ischemic optic neuropathy (NAION): coincidence or causality? J Sex Med 2005;2: 751–758
25. Hellstrom WJ, Kendirci M. Type 5 phosphodiesterase inhibitors: curing erectile dysfunction. Eur Urol 2006;49:942–945
26. Montorsi F, McCullough A. Efficacy of sildenafil citrate in men with erectile dysfunction following radical prostatectomy: a systematic review of clinical data. J Sex Med 2005;2:658–667
27. Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. J Am Coll Cardiol 2004; 43:1405–1411
28. Meredith IT, Currie KE, Anderson TJ, Roddy MA, Ganz P, Creager MA. Postischemic vasodilation in human forearm is dependent on endothelium-derived nitric oxide. Am J Physiol 1996;270: H1435–H1440
29. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Luscher TF. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation 1995; 91:1314–1319
30. Kaya C, Uslu Z, Karaman I. Is endothelial function impaired in erectile dysfunction patients? Int J Impot Res 2006;18:55–60
31. Fonseca V, Jawa A: Endothelial and erectile dysfunction, diabetes mellitus, and the metabolic syndrome: common pathways and treatments? Am J Cardiol 2005; 96:13M–18M
32. De Young L, Yu D, Freeman D, Brock GB. Effect of PDE5 inhibition combined with free oxygen radical scavenger therapy on erectile function in a diabetic animal model. Int J Impot Res 2003;15:347–352
33. Ayala JE, Bracy DP, Julien BM, Rottman JN. Chronic treatment with sildenafil improves energy balance and insulin action in high fat-fed conscious mice. Diabetes 2007;56:1025–1033
34. Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart 2003;89:251–253
35. McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. J Sex Med 2004;1:292–300
36. Mirone V, Costa P, Damber JE, Holmes S, Moncada I, Van Ahlen H, Wespes E, Cordell WH, Chan M, Lembo D, Varanese L. An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. Eur Urol 2005;47:846–854
37. McMahon C. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. J Sex Med 2005;2:415–423