EFFICACY AND SAFETY OF TADALAFIL FOR THE TREATMENT OF ERECTILE DYSFUNCTION IN DIABETIC PATIENTS

Dr. Hazim R. Akal FICMS (uoro)*, Dr. Ali N. Assi (CABS)*,
Dr. Akeel K. Alyacopy (MRCP(UK))**

ABSTRACT

Objective:

We evaluated the efficacy and safety of tadalafil, a potent, selective phosphodiesterase 5 inhibitor, for the treatment of erectile dysfunction in diabetic patients.

Patients And Methods:

Between September 2008 to July 2010, 124 men their mean age was 49.8 years with a clinical diagnosis of type 1 or type 2 diabetes (mean duration 11.7 years), a minimum 3-month history of mild-to-severe ED, (60.5%) of them had moderate ED of ≥1 year's duration were randomly allocated to one of two groups: the first group receive placebo (n = 61), the second group receive tadalafil 20 mg as needed (n = 63) for 12 weeks the dose taken as needed without food restrictions. Changes from baseline of erectile dysfunction to the ability to complete successful sexual intercourse and the side effect of the drug was noticed and fallowed.

Results:

A total of 109 (88%) of 124 patients completed the study. Patients receiving 20 mg tadalafil experienced a significant mean improvement, 75% of them were successfully completed intercourse attempts compared with 28% in the control group ($p < 0.001$). Compared with placebo, tadalafil significantly improve the outcomes. Tadalafil was consistently efficacious across disease severities and etiologies, as well as in patients of all ages. Tadalafil was well tolerated, and the most common adverse events were headache (11.2%), dyspepsia (6.0%), nasopharyngitis (4.7%), and flushing (2.8%) .

Conclusions:

Tadalafil therapy significantly enhanced erectile function and was well tolerated by men with diabetes and ED

INTRODUCTION

Impotence or "erectile dysfunction" is the inability to attain or sustain an erection for long enough for sexual activity. About 70% of cases of impotence are actually caused by an underlying disease, such as diabetes or kidney disease, rather than a mental or physical problem. Secondary impotence from various drugs and medications is common. Physical damage from injury or surgery is another common cause of impotence. Psychological causes of impotence are estimated to be only 10-20% of cases. Although psychological aspects such as anxiety and fear of sexual failure are commonly associated with impotence, they are not usually the real case, but are a reaction to having impotence.(1)

It is been estimated that about 35-75% of men with diabetes will experience at least some degree of erectile dysfunction during

* Assistant professors, Dept. of surgery, Medical college, Thi-Qar university
** Lecturer Dept. of medicine, Thi-Qar university

their lifetime.(2)Men with diabetes tend to develop erectile dysfunction 10 to 15 years earlier than men without diabetes. As men with diabetes age, erectile dysfunction becomes even more common. Above the age of 50, the likelihood of having difficulties with an erection occurs in approximately 50-60% of men with diabetes. Above age 70, there is about a 95% likelihood of having some difficulty with erectile function.(3)

Why Do Men With Diabetes Have Erectile Dysfunction?

The causes of erectile dysfunction in men with diabetes are complex and involve impairments in nerve, blood vessel and muscle function.

To get an erection, men need healthy blood vessels, nerves, male hormones, and a desire to be sexually stimulated. Diabetes can damage the blood vessels and nerves that control erection. Therefore, even if you have normal amounts of male hormones and you have the desire to have sex, you still may not be able to achieve a firm erection.(4)

In one study, ED affected 47% of men with type 1 diabetes aged 43 years, compared with 1.1% of those aged 21–30 years (P 0.0001).(5) According to one estimate (6), 50% of men will develop ED within 10 years of diabetes onset. Not only does diabetes increase the risk of ED nearly twofold, but ED may also be the first symptom of diabetes and was significantly predictive of neuropathic symptoms and poor glycemic control in a 5-year prospective study (7).

ED and diabetes each affect 150 million people worldwide, and this value is projected to double by the year 2025 (8-9). Recent trials demonstrated that the oral phosphodiesterase type 5 (PDE5) inhibitor tadalafil was effective and well tolerated in men with concomitant ED and diabetes (10,11).

The mechanism of action for PDE5 inhibitors is well established. In response to sexual stimulation in potent men, nitric oxide (NO) is released by nonadrenergic noncholinergic nerve terminals (12). NO induces relaxation of smooth muscle within the arterioles perfusing the lacunar tissues, sinusoidal endothelium, and trabecular erectile tissues of the corpus cavernosum (13,14). Lacunar expansion against the tunica albuginea surrounding the corpora compresses subtunical venules, resulting in venous congestion, engorgement of the corporal bodies, and thus physiological erection. The smooth muscle–relaxing properties of NO are mediated by cyclic 3,5 guanosine monophosphate (cGMP), a second messenger that is synthesized by guanylyl cyclase under the influence of NO. Blockade of PDE5, which hydrolyzes cGMP, thus potentiates the physiological NO-mediated erectile response. Tadalafil is a potent, reversible, and selective inhibitor of PDE5 in development as an oral therapy for mild-to-severe ED of psychogenic, organic, or mixed etiology. (15)

Pathophysiology of ED in diabetes

ED is the result of both structural and molecular abnormalities. Atrophy or apoptosis, of smooth muscle, and increased connective tissue synthesis, result in decreased compliance of cavernosal tissue(16).

Both these changes reduce or interfere with the gap junctions and K channels in cavernosal smooth muscle that are necessary for coordinated relaxation of cavernosal tissue(17). The chemical changes involve a shift in the balance between molecules that induce cavernosal smooth muscle contraction and those that induce smooth muscle relaxation.(18) The concentration of constrictors, including endothelin, prostanoids, and possibly angiotensin, increases with aging as the production of the relaxants, including nitric oxide (NO), vasointestinal peptide and prostacyclin, decreases.

Additionally, the endothelial cells that line the cavernosal arteries and sinusoids have a decreased response to nitric oxide due to increased production of advanced glycation end-products and changes associated with insulin resistance (19,20). The diabetic also experiences a decreased level of glutathione, a reducing agent that

protects against oxidative stress (21). This results in the premature death of the non-adenergic, non-cholinergic nerve endings in the penis, thus lowering levels of second messenger nitric oxide (22).

The end result of decreased production or decreased response to nitric oxide is a decrease in the stimulation of guanylate cyclase. This enzyme cleaves GTP with resultant production of cyclic guanosine monophosphate (cGMP), the power source for the relaxation of cavernosal smooth muscle. In situations in which sexual stimulation does not induce critical amounts of cGMP, calcium remains in its intracellular location, cavernosal muscle remains contracted and cavernosal blood vessels do not dilate. Blood flow into the penis is inadequate to engorge the sinusoids and compress the venules. Functional penile rigidity is not achieved (23,24).

The oral treatment of ED in the diabetic is based on amplification of the response to NO stimulation. Sub-erectile levels of cGMP are increased to critical

erectile levels by delaying the degradation of this molecule. This is achieved through the inhibition of the enzyme phosphodiesterase 5 (25).

PDE5 inhibitors in ED

The discovery of an oral drug that would dependably increase cGMP to levels that could promote cavernosal smooth muscle relaxation began in the vascular laboratory. Phosphodiesterase type 5 (PDE5) had been identified as the enzyme that degraded cGMP. It resides in vascular smooth muscle cells and platelets. Researchers theorized that inhibition of this enzyme offered potential benefits for patients with hypertension or angina (26).

In 1989, sildenafil was synthesized, a chemical that selectively targeted and powerfully inhibited PDE5. Clinical studies on sildenafil as a drug for angina began in 1991. The initial study, designed to assess the drug's safety, revealed no unusual findings. In 1992, a multiple-dose phase 1 trial was initiated. A few of the study patients reported an 'adverse event'—an increased tendency to get erections. Later that year the drug was tested in men with angina. The hemodynamic effects were 'fairly mild'(27,28).

In 1992, Rajfer and Ignarro published their work showing that nitric oxide (NO) caused smooth muscle relaxation in human cavernosal tissue. The basic mechanism involved sexual stimulation that triggered the release of NO from nerve endings in the penis. This NO in turn stimulated the production of

cGMP, which dilated penile blood vessels and relaxed the smooth muscle in the walls of the cavernosal sinusoids. These two effects promote engorgement of the penis and penile rigidity (29).

Even before scientists isolated PDE5 from human corpus cavernosal tissue (1994), the first study (1993) of sildenafil for treating ED was undertaken. Sixteen men with ED received sildenafil on a 25 mg, three times daily, outpatient basis. The study patients kept diaries in which they recorded when they had erections, whether the erections resulted from sexual stimulation, and how firm the erections were. The patients were also studied with the Rigiscan. The results were encouraging and showed a clear difference between the treatment and placebo (30).

Subsequent studies confirmed the efficacy and safety of PDE5 in the treatment of ED with a variety of etiologies, including vascular, psychogenic, and neurological. In 1998, the US FDA approved seldinafil for the treatment of ED. It soon became the first-line therapy. Soon, a search for novel, superior PDE5 inhibitors was initiated. Vardenafil (Bayer) and tadalafil (Lilly ICOS) are the products of these efforts and are presently candidates for US FDA approval. All three PDE5 inhibitors are similar in structure to cyclic guanosine monophosphate (31)

The criteria for the classification of ED, the percentage of patients with

psychogenic ED, the dosing methodology (fixed vs dose escalation), and the duration of the studies also vary. These differences likely impacted treatment outcomes. No

head-to-head comparative trials with the PDE5 inhibitors have been published (31).

AIM OF THE STUDY

We evaluated the efficacy and safety of tadalafil, a potent, selective phosphodiesterase 5 inhibitor, for the treatment of erectile dysfunction in diabetic patients.

PATIENTS & METHODS

Between September 2008 to July 2010, 124 men their mean age was 49.8 years with a clinical diagnosis of type 1 or type 2 diabetes (mean duration 11.7 years), a minimum 3-month history of mild-to-severe ED, (60.5%) of them had moderate ED of ≥1 year's duration were randomly allocated to one of two groups: the first group receive placebo (n = 61), the second group receive tadalafil 20 mg as needed (n = 63) for 12 weeks the dose taken as needed without food restrictions. Changes from baseline of erectile dysfunction to the ability to complete successful sexual intercourse and the side effect of the drug was noticed and fallowed.

RESULTS:

A total of 109 (88%) of 124 patients completed the study.

Patients receiving 20 mg tadalafil experienced a significant mean improvement, 75% of them were successfully completed intercourse attempts compared with 28% in the control group ($p < 0.001$). Compared with placebo, tadalafil significantly improve the outcomes. Tadalafil was consistently efficacious across disease severities and etiologies, as well as in patients of all ages. Tadalafil was well tolerated, and the most common adverse events were headache (11.2%), dyspepsia (6.0%), nasopharyngitis (4.7%), and flushing (2.8%) .

CONCLUSIONS:

Tadalafil therapy significantly enhanced erectile function and was well tolerated by men with diabetes and ED

DISCUSSION

Therapy with tadalafil consistently enhanced erectile function, significantly improving patients'ability to achieve and maintain erections. After 12 weeks of treatment taken whenever patients anticipated sexual activity, without restrictions on food or alcohol intake, nearly (75%) of patients in the tadalafil 20-mg group reported improved erections. questions concerning patients' ability to penetrate their partner and maintain erection to successful completion of intercourse in the present trial were significantly higher in patients taking tadalafil 20 than in the placebo arm. Treatment with tadalafil 20 mg improved these outcomes regardless of baseline level. The pathophysiology of diabetic ED has yet to be completely elucidated, but in vitro work demonstrated that corporal smooth muscle from men with diabetes exhibited diminished autonomically mediated or endothelium dependent relaxation compared with tissues from nondiabetic counterparts(32). A more recent immunohistochemical study suggested that advanced glycation end products (e.g., pentosidine and pyrraline) in diabetic men, when deposited within the penile tunica and corporal collagen, might result in downregulation of NO synthesis through modulation of endothelial and/or inducible NO synthase enzymatic activity. Therefore, treatment with a PDE5 inhibitor, which potentiates the effects of NO, is a rational therapeutic alternative in a setting of potentially attenuated NO output. However, improvements in erectile function were not as pronounced in this population as in ED patients without diabetes in other studies. (33)

Tadalafil was well tolerated in this study. The chief adverse events were headache and mild-to-moderate dyspepsia, and the incidences of these events were consistent with data from a other studies in a general population.

When taken as needed with no restrictions on either food or alcohol intake or the timing of dose administration relative to the onset of sexual intercourse,
tadalafil significantly enhanced erectile function and was well tolerated in men with diabetes and ED.

SUMMARY

Erectile dysfunction pharmacotherapy has undergone dramatic advances over the past decade, since the introduction of phosphodiesterase type 5 inhibitors (PDE5). The availability of an oral agent, tadalafil, able to restore erectile function in the majority of men with an organic basis to their dysfunction.
Tadalafil appears to play an important role in the management of ED across a broad spectrum of aetiologies, and have an enhanced period of responsiveness extending out to 36 hours in 60% of men using the 20 mg dose.
The numbers of men seeking medical attention for ED, along with the increased comfort of physicians treating it, has resulted in enhanced management of this condition. In spite of these advances, there exist a significant number of men who remain unsuccessfully treated with tadalafil.
However, because people with diabetes also tend to have problems with their heart, these medications may not be appropriate and cause dangerous interactions with your heart medicine. Every case should be managed accordingly to determine what treatment is best.(34)
Additional treatments men with diabetes might want to consider include intracavernous injection therapy, vacuum constriction devices, intraurethral therapy, and prostheses.(35)
So what treatment is best? It depends on many factors including a man's health and their ability to tolerate the treatment. The urologist has to work with the patient and his couple (family counseling) to determine the best individual treatment for every case peculiarly.(36)

REFERENCES

1. L.R. Derogatis and A.L. Burnett, The epidemiology of sexual dysfunctions, J Sex Med 5 (2008), p. 389.
2. J.B. Kostis, G. Jackson, R. Rosen, E. Barrett-Conner, K. Billups and A.L. Burnett et al., Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference), Am J Cardiol 96 (2005), p. 313.
3. A. Aversa, R. Bruzziches, M. Pili and G. Spera, Phosphodiesterase 5 inhibitors in the treatment of erectile dysfunction, Curr Pharm Des 12 (2006), p. 3467.
4. G.F. Watts, K.K. Chew and B.G. Stuckey, The erectile-endothelial dysfunction nexus: new opportunities for cardiovascular risk prevention, Nat Clin Pract Cardiovasc Med 4 (2007), p. 263.
5. Pfizer Inc. Protocol No. A1481146: A multicenter, double-blind study to evaluate the effect of pre-treatment with a daily dose of Viagra (sildenafil citrate) on the PRN efficacy of Viagra in men with erectile dysfunction and Type 2 diabetes. Available at www.ClinicalStudyResults.org. Accessed February 4, 2008.
6. R.C. Rosen, J.C. Cappelleri, M.D. Smith, J. Lopsky and B.M. Peña, Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction, Int J Impot Res 11 (1999), p. 319.
7. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Diabetes Care 26 (2003), p. S5.
8. J. Lincoln, C.H.V. Hoyle and G. Burnstock, Pharmacology, Nitric Oxide in Health and Disease, Cambridge University Press, Cambridge (1997), pp. 159–173 chapt 11.

9. C. Patrono and G.A. FitzGerald, Isoprostanes: potential markers of oxidant stress in atherothrombotic disease, Arterioscler Thromb Vasc Biol 17 (1997), p. 2309.
10. G.J. Blake and P.M. Ridker, Novel clinical markers of vascular wall inflammation, Circ Res 89 (2001), p. 763.
11. R.C. Rosen, Sexual function assessment in the male: physiological and self-report measures, Int J Impot Res 10 (1998), p. S59.
12. J.P. Mulhall, I. Goldstein, A.G. Bushmakin, J.C. Cappelleri and K. Hvidsten, Validation of the erection hardness score, J Sex Med 4 (2007), p. 1626.
13. D. Hatzichristou, M. Gambla, E. Rubio-Aurioles, J. Buvat, G.B. Brock and G. Spera et al., Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction, Diabet Med 25 (2008), p. 138
14. A. Aversa, R. Bruzziches, C. Vitale, G. Marazzi, D. Francomano and G. Barbaro et al., Chronic sildenafil in men with diabetes and erectile dysfunction, Expert Opin Drug Metab Toxicol 3 (2007), p. 451.
15. A. Aversa, C. Vitale, M. Volterrani, A. Fabbri, G. Spera and M. Fini et al., Chronic administration of sildenafil improves markers of endothelial function in men with Type 2 diabetes, Diabet Med 25 (2008), p. 37.
16. C. Desouza, A. Parulkar, D. Lumpkin, D. Akers and V.A. Fonseca, Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilation in type 2 diabetes, Diabetes Care 25 (2002), p. 1336.
17. G.M. Rosano, A. Aversa, C. Vitale, A. Fabbri, M. Fini and G. Spera, Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk, Eur Urol 47 (2005), p. 214.
18. N. Caretta, P. Palego, A. Ferlin, A. Garolla, A. Bettella and R. Selice et al., Resumption of spontaneous erections in selected patients affected by erectile dysfunction and various degrees of carotid wall alteration: role of tadalafil, Eur Urol 48 (2005), p. 326.
19. C. Foresta, N. Caretta, A. Lana, L. De Toni, A. Biagioli and C. Vinanzi et al., Relationship between vascular damage degrees and endothelial progenitor cells in patients with erectile dysfunction: effect of vardenafil administration and PDE5 expression in the bone marrow, Eur Urol 51 (2007), p. 1411.
20. H. Porst, F. Giuliano, S. Glina, D. Ralph, A.R. Casabé and A. Elion-Mboussa et al., Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial, Eur Urol 50 (2006), p. 351
21. B. Musicki, H.C. Champion, R.E. Becker, T. Liu, M.F. Kramer and A.L. Burnett, Erection capability is potentiated by long-term sildenafil treatment: role of blood flow-induced endothelial nitric oxide synthase phosphorylation, Mol Pharmacol 68 (2005), p. 226.
22. D. Behr-Roussel, D. Gorny, K. Mevel, S. Caisey, J. Bernabé and G. Burgess et al., Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: lack of tachyphylaxis, Eur Urol 47 (2005), p. 87.
23. N.E. Nielsen, J. Ahlner, J. Malmstedt, K.P. Ohman and E. Swahn, Plasma levels of cyclic GMP and endothelin in postmenopausal women with unstable coronary artery disease, Scand J Clin Lab Invest 59 (1999), p. 325.
24. J.E. Deanfield, J.P. Halcox and T.J. Rabelink, Endothelial function and dysfunction, Circulation 115 (2007), p. 1285
25. McKinlay JB: The worldwide prevalence and epidemiology of erectile dysfunction. Int J Impot Res 12(suppl 4): S6–S11, 2000.
26. Chun J, and Carson CC: Physician-patient dialogue and clinical evaluation of erectile dysfunction. Urol Clin NorthAm 28: 249–258, 2001.
27. McMahon CG, Samali R, and Johnson H: Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. J Urol 164: 1192–1196, 2000.

28. Guay AT, Perez JB, Jacobson J, et al: Efficacy and safety of sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. J Androl 22: 793–797, 2001.
29. Hultling C, Giuliano F, Quirk F, et al: Quality of life in patients with spinal cord injury receiving Viagra (sildenafil citrate) for the treatment of erectile dysfunction. Spinal Cord 38: 363–370, 2000.
30. Lewis R, Bennett CJ, Borkon WD, et al: Patient and partner satisfaction with Viagra (sildenafil citrate) treatment as determined by the Erectile Dysfunction Inventory of Treatment Satisfaction Questionnaire. Urology 57: 960–965, 2001.
31. Madduri SD: After two years, did Viagra live up to its expectations? Missouri Med 98: 243–245, 2001.
32. El-Galley R, Rutland H, Talic R, et al: Long-term efficacy of sildenafil and tachyphylaxis effect. J Urol 166: 927– 931, 2001.
33. Brock G, McMahon CG, Chen KK, et al: Efficacy and safety of tadalafil in the treatment of erectile dysfunction: results of integrated analyses. J Urol 168: 1332–1336, 2002.
34. Rosen RC, Padma-Nathan H, Shabsigh R: Cialis (IC351) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction (ED). Program and abstracts of the 96th Annual Meeting of the American Urological Association, June 2–7, 2001, Anaheim, California.
35. Viagra_ (sildenafil citrate) prescribing information. New York, New York, Pfizer, 2000.
36. Ixense_ (apomorphine hydrochloride) prescribing information. London, United Kingdom, Takeda Europe Research & Development Centre, 2001

استعمال عقار التدالافيل لمعالجة حالات العنه في مرضى داء السكر

الدكتور حازم ريسان الخفاجي*، الدكتور علي نايف عاصي* ،عقيل كريم اليعقوبي**

الخلاصة

أنجزت هذه الدراسة في الفترة الواقعة بين أيلول ٢٠٠٨ وتموز ٢٠١٠ لتقييم مدى فعالية عقار التدالافيل لعلاج حالات العنه التي يعاني منها المرضى المصابين بداء السكر.
وهي دراسة قسم فيها المرضى الذين يعانون من داء السكر ولديهم عنه لفترة لاتقل عن ثلاثة أشهر إلى مجموعتين الأولى وعددهم ٦٣ مريض تناولوا العلاج الفعال ٢٠ ملغم من التدالافيل في حين تناول الآخرون وعددهم ٦١ مريض علاج لايحتوي على مادة التدالافيل وقد تمت متابعة النتائج بعد فترة ثلاثة أشهر من العلاج الذي يتم تناوله عند الحاجة (قبل الاتصال الجنسي).
تبين من الدراسة إن ٧٥% من المرضى الذين يتناولون التدالافيل تحسنت حالتهم واستطاعوا ممارسة الجنس بصورة جيده، في حين ٢٨ % فقط من المرضى الذين تناولوا الأقراص غير ألفعاله تحسنت حالتهم.
هذا يدل على إن العقار فعال لمعالجة هذه الحالات علما إن التأثيرات الجانبية تعتبر قليلة الحدوث وهي كالتالي ١١,٢%يعانون من صداع، ٦% لديهم حرقه في المعدة، ٧,٤% احتقان الأنف والبلعوم، ٢,٨ % لديهم احمرار الوجه.
من كل هذا نستدل على إن عقار التدالافيل هو علاج فعال وقليل التأثيرات الجانبية لمعالجة حالات العنه التي هي مرض شائع عند المرضى المصابين بداء السكر.

* أستاذ مساعد \قسم الجراحة \ كلية الطب\جامعة ذي قار
** مدرس \قسم الباطنية \ كلية الطب\جامعة ذي قار