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

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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 followed.

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
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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 (PDE5) (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 sildenafil 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
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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:
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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**

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استعمال عقار التدالافيل لمعالجة حالات العنبة

في مرضى داء السكر

الخلاصة

أنجزت هذه الدراسة في الفترة الواقعة بين أيلول 2008 وتموز 2010 لتقديم مدى فعالية عقار التدالافيل لعلاج حالات العنبة التي يعاني منها المرضى المصابين بداء السكر. وهي دراسة قسم فيما المرضا الذين يعانون من داء السكر لديهم للمصابين بداء السكر عناية تلقى علاج التدالافيل عن ثلاثة أشهر إلى مجموعتين الأولى وعدد 33 مريض تناولوا العلاج الفعال 20 ملغ من التدالافيل في حين تناول الآخرون وعددهم 11 مريض علاج لايحتوي على مادة التدالافيل وقد تم تتزامن النتائج بعد فترة ثلاثة أشهر من العلاج الذي يتم تناوله عند الحاجة (قبل الاتصال الجنسي).

بين من الدراسة إن 75% من المرضى الذين تناولوا التدالافيل تحسن حالاتهم واستطاعوا ممارسة الجنس بصورة جيدة، في حين 25% فقط من المرضى الذين تناولوا الأقراص غير الفعاله تحسن حالاتهم.

هذا يدل على أن العقار فعال لمعالجة هذه الحالات وله تأثيرات جانبية تعتبر قليلة الحدوث وهي كالتالي 11.2% يعانون من صداع، 6% لديهم حرقة في المعدة، 7% احتقان الأنف والبلعوم، 2% لديهم ألم في الرئة.

من كل هذا نستخلص أن عقار التدالافيل هو علاج فعال وقليل التأثيرات الجانبية لمعالجة حالات العنبة التي هي مرض شائع عند المرضى المصابين بداء السكر.

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