

Evaluation of testosterone and prolactin hormones levels in erectile dysfunction patients after single oral dose of Tadalafil

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الخلاصة

يعرف العجز الجنسي بعدم القدرة على حصول الانتصاب اللازم للعملية الجنسية بصورة كافية لإتمام الاتصال الجنسي بشكل ناجح. استخدمت عدة علاجات لمعالجة هذه المشكلة ويعد التadalafil واحد من هذه العلاجات، حيث أنه يعد من المثبطات لإنزيم الفوسفودايستيراز-5 الذي يحطم الالغوانسين الحلقي اللازم لحصول عملية الانتصاب في النسيج التناسلي. رغم ذلك لا يمكن حدوث الانتصاب بدون التأثير العصبي. يعد الاختلال في الهرمون اللبني والذكري الأساس في حدوث العجز الجنسي. تم في هذا البحث شمول 20 مريضاً عراقياً بمستويات مختلفة من العجز الجنسي في هذه الدراسة وتمت معالجتهم فمويًا بـ 20 ملغ من التadalafil. جميع المرضى المشمولين في هذه الدراسة لوحظ حصول الانتصاب بعد المعالجة وتم استثناء غير المستجيبين للعلاج. تم تقدير مستوى الهرمون اللبني والذكري من خلال تقنية الإشعاع المناعي (RIA) وقد لوحظ انخفاض مميز في مستوى الهرمون اللبني ($p < 0.01$) وزيادة مميزة في الهرمون الذكري ($p < 0.00001$) مع ملاحظة زيادة نسبة مستوى الهرمون الذكري إلى اللبني. يمكن من خلال هذا البحث الاستنتاج أنه يجب أخذ مستوى الهرمون اللبني والذكري في الاعتبار عند استخدام هذا الدواء ولا يوصف للأشخاص الذين لديهم مستويات غير طبيعية من الهرمونيين المذكورين مع أخذ التوجيهات من طبيب مختص بالهورمونات قبل البدء باستخدام التadalafil.

Abstract

Erectile dysfunction (ED) is defined as a consistent inability to sustain an erection sufficient for sexual intercourse. Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation. Erection dysfunction could attribute abnormal levels of testosterone and prolactin levels.

Twenty Iraqi patients with different levels of ED were considered in this study treated with 20 mg. of tadalafil coated tablets. All patients considered in this study have been get erection after treatments with tadalafil. Prolactin and testosterone has been determined by radioimmunoassay (RIA). The evaluated results indicated significant decrease for prolactin ($p < 0.01$) and significant elevation for the testosterone ($p < 0.0001$). The ratio of prolactin/ testosterone was increased after treatments.

In conclusion: prolactin and testosterone hormonal levels must be considered with tadalafil treatments. Tadalafil must be not described to patients with abnormal levels of these hormones. Patients with testosterone and prolactin abnormalities need to take advice from the endocrinologist before use tadalafil with monitoring of prolactin and testosterone levels.

Keyword: Erectile dysfunction-prolactin-testosterone-radioimmuno assay.

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance ^[1].

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum ^[2]. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation ^[3].

Testosterone deficiency is potentially reversible and is a result of primary testicular failure or secondary to pituitary/hypothalamic causes ^[4]. Men with primary or secondary Hypogonadism will have low serum testosterone level and signs and symptoms of decreased libido ^[5]. This may result in ED secondarily to diminished libido ^[6]. Restoration of normal testosterone levels has been associated with return to normal sexual drive, but not necessarily normal erectile function ^[7].

The physiology of the erectile response is mostly understood, although gaps in our knowledge remain ^[8]. It has been demonstrated that penile erections are mediated by nitric oxide (NO) and are androgen-dependent. Direct or indirect stimuli can trigger an erectile response that starts with the release of relaxing substances, primarily the neurotransmitter NO, from the nerve endings in the corpora cavernosa ^[9, 10].

The aim of this research: The extensive uses of tadalafil and its close structure and effects to cAMP encourage us to monitoring the prolactin and testosterone levels after tadalafil treatment, especially these hormones could affected by the changes in cAMP concentration changes and no similar study concern with such changes. Both prolactin and testosterone hormones

considered the most interested when treatments started with tadalafil especially both have a wide range of clinical disorders associated with ED patients.

Material and Methods

Principle of the prolactin evaluation method:

RIA prolactin permits the in vitro determination of human prolactin in serum using two stage sandwich assays. A complex of antiprolactin antibodies (monoclonal mouse) which are bounded to tube wall, sample prolactin and I⁻¹²⁵ label antiprolactin antibodies formed during the process. The amount of samples tracer specifically bounded to the coated test tube is measured with gamma scintillation counter. Evaluation of the test is carried out using standard curve constructed under identical conditions. Monoclonal antibodies used in the RIA – kit are very specific for prolactin. There is virtually no risk of cross-reactivity with structurally similar hormones occurring at physiological relevant concentration range^[11].

Preparation of reagent:

The standard and the control are dissolved in 300 µL twice distilled water. The washing buffer is prepared by dissolving five buffer tablets in 500 ml twice distilled water according to the instructor supplied manual^[11].

Principle of the Testosterone evaluation method:

The principle of the assay is based on the completion between labeled testosterone and the testosterone in the sample against limited number of antibodies site bounded to the solid phase (coated tube), after incubation, the unbounded tracer is easily removed by washing step^[12].

Preparation of reagent:

Reconstitution the standard with 0.5 ml distilled water mix gently by inversion to ensure complete dissolution of frozen dried material. The standard should be stand at 30 minutes after reconstitution and before proceeding. Evaluation of testosterone results is described as in prolactin evaluation^[12].

Subjects collection:

Twenty Iraqi male patients with different levels of erectile dysfunction collected from Ibn Al-Nafees teaching hospital. These patients with age range from 50-55 years were collected in a period of two months under medical supervision. All collected patient were free from any other pathogenic condition. The administration of drugs was carried out without fat diet to increase the absorption of the drug. Serum sample were collected by venous puncture and allowed to clot at room temperature for 30 minutes than centrifuged at 3000rpm for 20 minutes. Serum was removed with micro pipette and stored at -20°C. Samples collection has been achieved before and after treatment in about 4.5-5.0 hours of tadalafil administration^[13].

Drugs:

The drug used in this study was given orally as film coated tablets containing 20 mg. tadalafil manufacturing from Lilly/ICOS, USA.

Result

The evaluations of prolactin before and after treatment with 20 mg. of tadalafil are represented in table (1) Prolactin mean level were significantly decreased ($p < 0.001$). The testosterone hormone was significantly elevated after tadalafil treatments as represents in table (2). The standard curve of testosterone for radioimmunoassay is plotted in figure (1). The testosterone /prolactin ratio before after treatments were plotted figure (2), the figures predicted elevation of these hormones after treatment Concentration changes of each patient for the prolactin and testosterone hormones are plotted in figure (3 and 4) respectively.

Groups	(Before-after) treatments
N	20
Mean	55.764
SD	23.566
correlation	0.743
p-values	0.01

Table 1: Prolactin evaluation before and after treatments

Groups	(Before-after) treatments
N	20
Mean	-0.184
SD	0.022
correlation	0.080
p-values	0.0001

Table 2: Testosterone evaluation before and after treatments

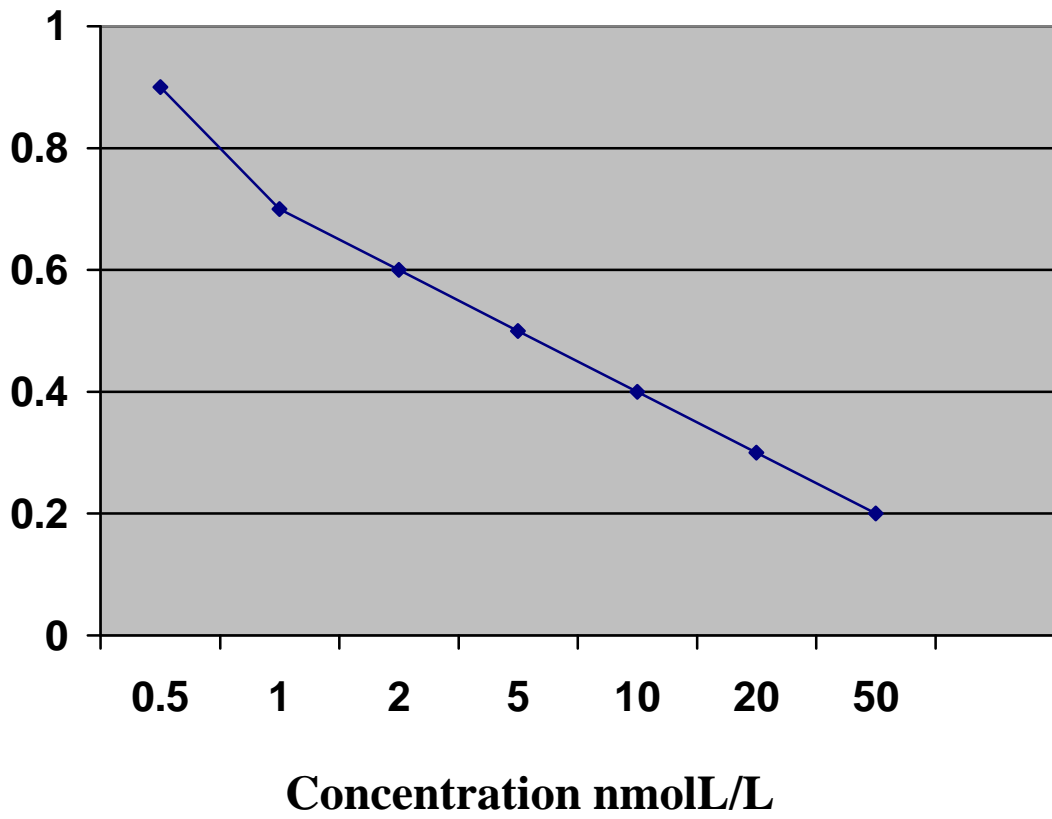


Figure 1: The calibration curve for testosterone

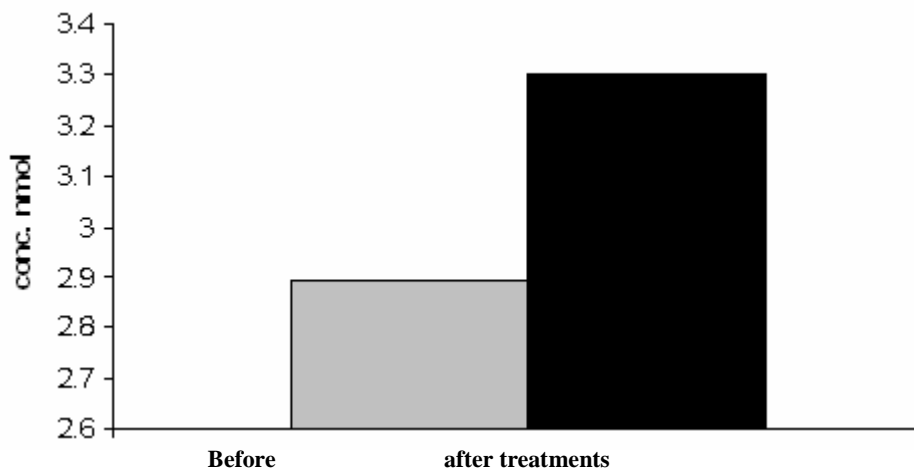


Figure 2: The ratio of testosterone to prolactin before and after treatments

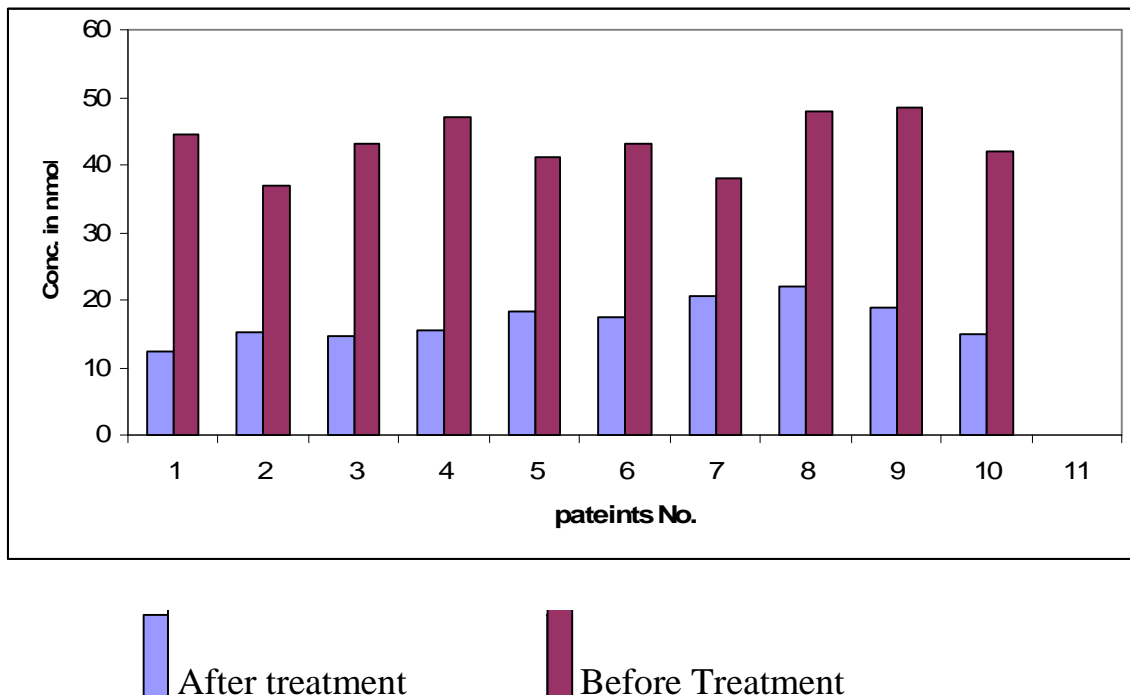


Figure 3: Plots represent the distribution of prolactin concentration to the patients after and before treatments.

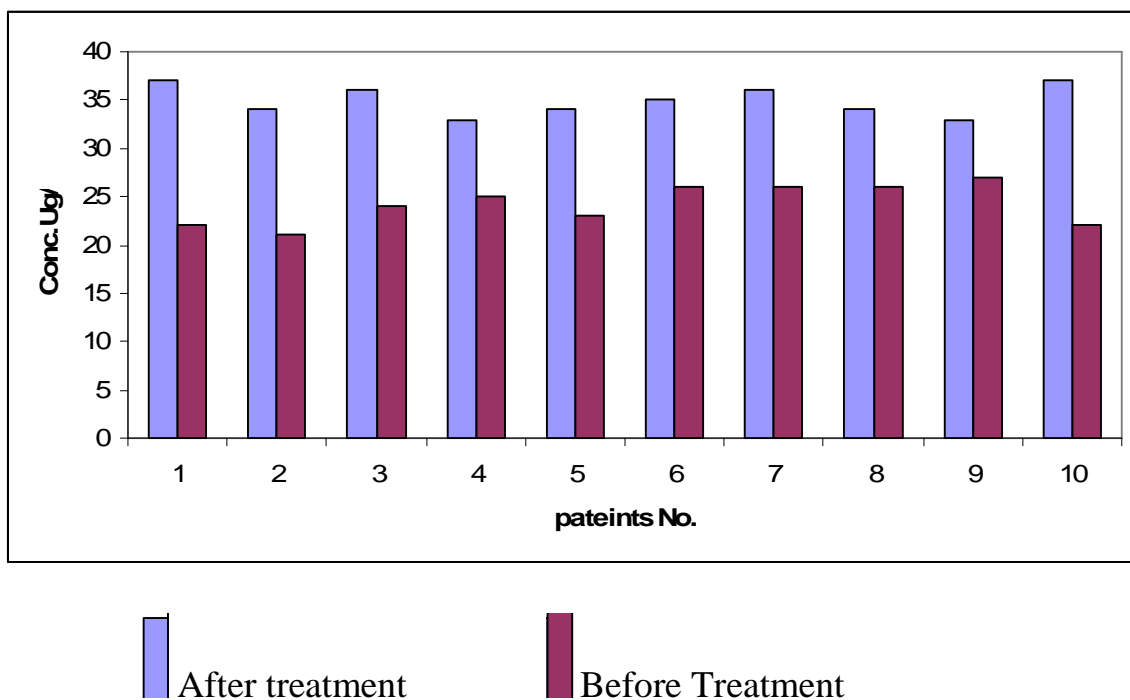


Figure 4: Plots represent the distribution of testosterone concentration to the patients after and before treatments with tadafail.

Discussion

Erection is a neurovascular phenomenon under hormonal control. It includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism^[8]. Several risk factors have been identified based on our knowledge of the physiology of erection^[14, 15]. Prolactin is regulated tonic inhibition. A significant decreased in level after treatments was observed, it could attributed to the inhibitory effects of tadalafil^[16]. The close structure of cAMP to tadalafil which considered as inhibitor factors of prolactin^[17]. The prolactin usually increased after sexual intercourse the reverse pattern was observed tadalafil treatment; however it decreased after tadalafil treatments. The patients with alcohols or smokers were not considered in this study. The main cause of rejection could attribute that cigarette smoking and alcohol could effects on prolactin levels, since nicotine and alcohol elevated the cAMP levels^[18, 19].

Total testosterone has been determined by immunoassay. The evaluated testosterone in this study was increased scientifically after treatments with single dose of tadalafil. However many studies predicted elevation of testosterone and other androgens with cAMP^[20]. The alcoholic patients were rejected in testosterone estimation this could be associated of the effects of alcoholic on decrease libido and direct effects on testosterone^[21, 22]. Smokers' rejection in this study could be attributed to the effects on nicotine on decrease the activity of Leydig cells and decrease the testosterone hormone level^[23, 24].

In conclusion: hormonal levels must be considered with tadalafil treatments. Testosterone increased significantly after tadalafil treatments while prolactin decreased significantly. It is generally accepted that, testosterone stimulates the production of NO. Form this elevation erection was achieved. More specifically, androgens are thought to stimulate the synthesis of the neuronal isoform of nitric oxide synthesis (nNOS)1. Although NO is considered to be the predominant vasodilator in the penis, there are other vasodilator pathways in the erectile response that are independent of NO but are androgen regulated. Patients with testosterone and prolactin abnormalities need to take the advice of an endocrinologist before use tadalafil with level monitoring.

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