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Erectile Dysfunction Drug as Efficacious In Heart Failure Treatment

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Abstract

Erectile dysfunction is a common in men with cardiovascular disease, as there is impairment of hemodynamic mechanisms in the penile and ischemic vasculature. Erectile dysfunction is the condition in which mainly the blood supply is improper to penis so it also leads to cardiac related problems. Tadalafil citrate, an orally active, selective inhibitor of phosphodiesterase type 5 (PDE5), has demonstrated excellent efficacy and safety profiles in men with erectile dysfunction of various aetiologies. In erectile dysfunction mainly the blood supply is improper to penis so it also leads to cardiac related problems so Tadalafil is a potent drug which selective inhibits specific phosphodiesterase type 5 (PDE5) which then lead to erection and this may help in Heart Failure Treatment majorly in systolic heart failure where heart is not able to pump properly. Viagra-type drugs were initially developed as potential treatments for heart disease before they were found to have unexpected benefits in the treatment of erectile dysfunction.

Keywords: Erectile dysfunction , Heart Failure, PDE5 Inhibitor, Tadalafil.

Introduction

Erectile dysfunction (ED) is also known as impotence, is a type of sexual dysfunction characterized by the inability to results in an erection of the penis during sexual intercourse. ED is a physical and psychological condition which occurs when a man in unable to keep a penis intake enough for sexual activity.

In about 80% patients ED occur by physical condition which include cardiovascular disease, diabetes mellitus, neurological problems such as following prostatectomy, hypogonadism, and drug side effects. While in 10% of patients ED result from psychological impotence is where erection fails due to the thoughts or feelings; mainly due to strong response to placebo treatment.

In the past, the build-up of plaques in the arteries of your body (atherosclerosis) was believed to be the reason why erectile dysfunction often introduces heart problems. The object was that plaque build-up reduces blood flow in the penis, making an erection difficult. However, experts now believe that erectile dysfunction introduce heart problems is more often due to the dysfunction of the inner lining of

the blood vessels (endothelium) and smooth muscle. Endothelial dysfunction causes insufficient blood supply to the heart and impaired blood flow to the penis, and aids in the development of atherosclerosis.[1]

ED is characterized by systematic or constant inability to develop an erection of sufficient rigor to experienced sexual activity. ED often has an influence on the psycholocial well being for both men and their partners. Around 75% of diagnosed cases of ED goes untreated, as men do not pursue treatment because of feeling of embarrassment.

Causes[2]

Prescription drugs (e.g., Selective Serotonin reuptake inhibitors, beta blockers (Atenolol), alpha-2 adrenergic receptor agonists, hormone modulators, and Neurogenic disorders (e.g., diabetic neuropathy, temporal lobe epilepsy, multiple sclerosis, Parkinson's disease) Cavernosal disorders (e.g., Peyronie's disease) Hyperprolactinemia (e.g., due to a prolactinoma, tumor in pituitary gland) Psychological causes: stress, and mental disorders Surgery (e.g., radical prostatectomy)

Aging: It is seen four time less in the common aged men in their 40s than the 60s

Renal failure

Lifestyle habits: smoking, which plays an important role in risk factor for ED as it advances arterial narrowing.

Pathophysiology

Arousal of penis happens by two mechanism; the reflex erection, which is procure by directly touching the penile shaft; act by peripheral nerves and the lower parts of the spinal cord and the psychogenic erection, which is achieved by sexually stimulating; act by the limbic system of the brain. In both cases, an entire neural system is required for a complete erection. The secretion of nitric oxide (NO) is conducted by the stimulation of the penile shaft by the nervous system which results relaxation of smooth muscles of corpora cavernosa (the main erectile tissue of penis), and eventually penile erection. Further, sufficient levels of testosterone (produced by the testes) and an entire pituitary gland are involve in the development of a healthy erectile system. From above mentioned mechanisms of a normal erection, ED may occur due to lack of adequate penile blood supply or psychological problems hormonal deficiency, disorders of the neural system. Injury in spinal code causes sexual dysfunction including ED. Depletion of blood flow can decrease endothelial function due to the usual causes associated with coronary artery diseases, and elongate exposure to bright light.[3]

Treatment[4]

The general treatment for the ED, particularly the aerobic type exercise is used for the prevention of ED in the midlife.[1] The first line treatments for the ED includes the medications by mouth and vacuum erection devices, [1] followed by injection in the penis as well as penile implants.

Pharmacological

The drug administrated by the orally route or mouth are falls in the category of PDE5 inhibitors, sildenafil(Viagra), vardenafil (Levitra) and tadalafil (Cialis).

Penile injections is given which contain medication such as papaverine, phentolamine, and prostaglandin E1, referred mainly as alprostadil.In addition to this, alprostadil suppository is available which can be inserted through urethra, which give effect within 10 min result in the erection which last up to an hour. Priapism is often seen as a side effect.

Low levels of testosterone in male can experience ED. Taking testosterone may help maintain an erection. Men with type 2 diabetes are twice as likely to have lower levels of testosterone, and are three times more likely to experience ED than non-diabetic men.

Non-Pharmacological

Pumps

The device used in the ED as a pump is known as penis pump or vacuum erection device. A pump, applies a negative pressure by the mean of vacuum erection device helps draw blood into the penis and can be use just prior to sexual intercourse. Vacuum therapy devices are available under prescription, is approved by various type of FDA. In case, pharmacological activity is failed, external vacuum pump can be use to attain erection; to maintain the erection of the penis a separated compressing ring is shaped at the base. The temporary treatment is achieved by the penis pump which can be distinguished from the vacuum erection device, due to absence of compressing ring in the penis pump. Penis pump are claimed to increases the penis length is used regularly and a vibrate as an aid for masturbation.

Surgery

If all the above mentioned treatment is failed, the surgery is often used which is relied on the prosthetic implants, involves the insertion of artificial rods into the penis.Vascular reconstructive surgeries are applicable for some people.

Discussion

Tadafafil

Pharmacodynamics

Tadalafil is used to cure male ED (impotence) and pulmonary arterial hypertension (PAH). Physiological process of erection demands the release of nitric oxide (NO) in the corpus cavernosum. This then triggers the enzyme guanylate cyclase which cause in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation in the corpus cavernosum, resulting in increased influx of blood and an erection. Tadalafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degeneration of cGMP in the corpus cavernosum. This means that, with tadalafil on board, normal sexual stimulation results increased levels of cGMP in the corpus cavernosum which conduct to superior erections. Without sexual stimulation there is deactivation of the NO/cGMP system, tadalafil should not results an erection.[5]

Mechanism of Action

Penile erection throughout sexual stimulation is attain by the relaxation of penile arteries and corpus cavernosal smooth muscles, results increased blood flow to the organ. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which raise the synthesis of cGMP in smooth muscle cells. Cyclic GMP results smooth muscle relaxation and increased blood flow into the corpus cavernosum, and is degenerated by the cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum located around the penis. Tadalafil blocks PDE5 and thereby increases erectile function by increasing the amount of cGMP available.[6]

Pharmacokinetic

Absorption**:** Single oral dose of administration

Distribution: Plasma Protein Binding (PPB) 94%

Metabolism: Tadalafil is mainly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes methylation and glucuronidation to form methylcatechol and methylcatechol glucuronide conjugate, respectively. In vitro data recommend the metabolites are not expected to be pharmacologically active at distinguish metabolite concentrations.

Excretion**:** Tadalafil is excreted mainly as metabolites, majorly in the feces (Approximately 61% of the dose) and to a minimal extent in the urine (approximately 36% of the dose).

Half life: 17.5 hours

Toxicity: Oral, Rat LD50 = 2000 mg/kg, no deaths or toxicity.

Affected Organism: Humans and other mammals.

Side-effects:

- Headache
- upset stomach
- back pain
- muscle aches
- flushing (reddish skin)
- stuffy or runny nose
- diarrhea
- Priapism (in men). Symptoms can include: a painful erection that won't go away
- Vision changes. Symptoms can include: seeing a shade of blue when looking at objects or an entity difficulty in telling the difference between the colors blue and Green a sudden decrease of vision in one or both eyes Hearing loss. Symptoms can include: a sudden loss or decrease in hearing ringing in the ears dizziness
- Low blood pressure. Symptoms can include: feeling lightheaded or dizzy fainting Angina (chest pain)

Interaction with tadalafi:

Angina drugs (nitrates)

If you take tadalafil with nitrates, your blood pressure could suddenly drop to dangerously low levels. This could make you dizzy or cause you to faint. Examples of nitrates include:

- Nitroglycerin
- isosorbide dinitrate
- isosorbide mononitrate
- amyl nitrite
- butyl nitrite

High blood pressure or prostate drugs (alpha blockers)

If you take tadalafil with certain alpha blockers, your blood pressure could suddenly drop to low levels that are dangerous. This could make you dizzy or cause you to faint. Examples of these drugs include:

- terazosin
- tamsulosin
- doxazosin
- prazosin
- alfuzosin

Certain HIV drugs[7]

Taking tadalafil with certain HIV drugs could enhance tadalafil levels in your blood. This can lead to low blood pressure, dizziness and fainting, and vision problems. In men, it can also lead to priapism. These drugs are protease inhibitors and include:

- ritonavir
- lopinavir/ritonavir

Oral antifungal drugs

Taking certain antifungal drugs with tadalafil may increase levels of tadalafil in your blood. This can lead to low blood pressure, dizziness and fainting, and vision problems. In men, it can also lead to priapism. Examples of these drugs include:

- ketoconazole
- itraconazole

Antibiotics

Taking certain antibiotics with tadalafil may raise the level of tadalafil in your blood. This can lead to low blood pressure, dizziness and fainting, and vision problems. In men, it can also lead to priapism. Examples of these drugs include:

- clarithromycin
- erythromycin
- telithromycin

Other types of antibiotics may lower the level of tadalafil in your blood. This could prevent tadalafil from working well. These drugs include:

- rifampin

Other erectile dysfunction (ED) drugs

These medications work in the same way as tadalafil. If you take them with tadalafil, it increases your risk of side effects. Examples of these drugs include:

- sildenafil
- vardenafil

Other pulmonary arterial hypertension (PAH) drugs

If you take tadalafil with other types of PAH drugs, your blood pressure could suddenly drop to dangerously low levels. Examples of these drugs include:

- riociguat
- Stomach acid drugs

Taking these medications with tadalafil may keep your body from absorbing tadalafil well. Examples of these drugs include:

- magnesium hydroxide/aluminum hydroxide

Epilepsy drugs

Taking certain anti-epileptic drugs with tadalafil may lower the level of tadalafil in your blood. This could prevent tadalafil from working well. Examples of these drugs include:

- carbamazepine
- phenytoin
- phenobarbital

Doses and administration

Tadalafil Use For Erectile Dysfunction

Starting dose of Tadalafil for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients. Tadalafil use to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of Tadalafil, this should be taken into consideration.

Tadalafil For Once Daily Use for Erectile Dysfunction

Starting dose of Tadalafil for once daily use is 2.5 mg, taken at approximately the same time every day, without regard to timing of sexual activity. The Tadalafil dose for once daily use may be increased to 5 mg, based on individual efficacy and tolerability.

Tadalafil For Once Daily Use For Benign Prostatic Hyperplasia

Starting dose of Tadalafil for once daily use is 5 mg, taken at approximately the same time every day.

Tadalafil For Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia. Starting dose of Tadalafil for once daily use is 5 mg, take at approximately the same time every day, without regard to timing of sexual activity.[8]

Uses

Tadalafil is used to treat male sexual dysfunction (impotence). In combination with sexual stimulation, tadalafil works by increasing blood flow to the penis to keep erect.It is also used to treat the symptoms of an enlarged prostate (benign prostatic hyperplasia-BPH). It helps to relieve symptoms of BPH such as difficulty in beginning the flow of urine, weak stream, and the need to urinate frequently or urgently (including during the middle of the night). It is thought to work by relaxing the smooth muscle in the prostate and bladder. [9]

Use of Tadalafil in Heart failure

The study of Tadalafil -- which is in the same class as Viagra -- proves that the drug is biologically efficacious as a treatment for heart failure in sheep. However, effect is likely to also be shown in humans. Heart failure is a lethal situation, occurring when the heart is too weak to pump enough blood to fulfil the body's needs.

It also leads to build-up of fluid that backs up into the lungs, resulting in breathlessness as well fluid retention, resulting in swelling of different parts of the body. Most current treatments are inefficacious."This discovery is

significant advancement in lethal condition which causes distress for thousands of people across the UK, India and beyond," "We do have limited evidence from human trials and epidemiological studies that show Tadalafil can be efficacious in treating heart failure."This demonstrates that Tadalafil could now be a possible therapy for heart failure."It's completely possible that some patients taking it for erectile dysfunction also have a casual protective effect on their heart."[10]

Sheep were used as the physiology their hearts is similar to human hearts. When the animals had heart failure -- induced by pace makers -- which was moderately advanced to need treatment, the team administered the drug. Within a short period the gradually worsening of the heart failure was stopped and, considerably the drug reversed the effects of heart failure. The biological cause of breathlessness in heart failure- the inability of the heart to counter to adrenaline was almost completely reversed. The dose the sheep received were comparable to the dose humans are given when being treated for erectile dysfunction (ED).

Tadalafil blocks an enzyme called Phosphodiesterase 5 or PDE5S for short, which synchronize how our tissue counters to hormones like adrenaline. The research found that in heart failure, the drug adjusts the series of chemical reactions in the body -- to restore the hearts potential to respond to adrenaline. That increases the potential of the heart to force blood around the body when working harder."This is a widely used and very safe drug with lesser side effects."However it is not advisable to public to treat themselves with the drug and should always speak to their doctor if they have any concerns or questions."Tadalafil is only acceptable as a treatment for systolic heart failure -- when the heart is not able to pump properly -- and there may be interactions with other drugs patients are taking."[11]

Conclusion

The PDE-5 inhibitors have new treatment of ED; however their role in the treatment of cardiovascular diseases has yet to be determined.PDE-5 inhibitors are safe and effective therapy for ED in patients with mild to moderate heart disease and who have low cardiac risk.Tadfalil is effective in improving the the life, activity of Heart Failure patients, especially patients with pulmonary hypertension. The exact mechanism by which PDE-5 inhibitors improve Heart Failure is unknown but may be related to improved endothelial function, reduced preload, reduced after load or some direct effect on the diseased myocardium. Tadalafil is effective in treating pulmonary hypertension. Tadalafil is mainly treated in ED but it is also shows its efficacy in treatment of Heart Failure.

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