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Topic
The use of Tadalafil 5mg daily for the treatment of BPH-LUTS

Introduction

Tadalafil 5mg daily is a well established treatment for Erectile Dysfunction. It is now also indicated for the treatment of BPH-LUTS. This report will delineate the evidence for efficacy, safety and proposed mechanisms of action of Tadalafil 5mg daily in the treatment of BPH-LUTS.

The Relationship between BPH-LUTS and ED

Previously BPH-LUTS and ED were regarded as 2 separate diseases and consequently treated separately. The accumulation of data over the years has pointed to the fact that they are related in epidemiology. Men with more severe LUTS, have a lower Erectile Function Score and this relationship is independent of co-morbidities. The severity of LUTS and ED also increases with age[1].

Various studies have shown that the prevalence of ED in men with BPH-LUTS ranges from 47% to 82%[2-6]. Similarly, the prevalence of BPH-LUTS in men with ED ranges between 72.2% and 77.5%[7-9] giving further evidence that both diseases affect similar risk groups.

BPH-LUTS and ED also share similar risk factors including age, diabetes, metabolic syndrome, obesity, sedentary lifestyle, artherosclerotic cardiovascular disease and hypertension[10].

All these evidences elude to perhaps a shared patho-physiologic mechanism between BPH-LUTS and ED.

A shared Patho-Physiologic Mechanism between BPH-LUTS and ED

It is well understood that the various risk factors mentioned above (i.e. age, diabetes, metabolic syndrome, obesity, sedentary lifestyle, artherosclerotic cardiovascular disease and hypertension) result in Insulin Resistance, Chronic Inflammation and Steroid Hormone Changes. These then result in patho-physiological changes that can contribute to the patho-physiology of both ED and BPH-LUTS.

Reduced NO-cGMP Signaling

Nitric Oxide is involved in many essential biological functions both directly and via its induction of the c-GMP second messenger pathway[11]. People with Diabetes have a lower Nitric Oxide level. This is because the Nitric Oxide Synthase which produces Nitric Oxide is Insulin Dependent. Diminished Nitric Oxide leads to vascular damage including endothelial dysfunction as well as vascular inflammation. This alters smooth muscle relaxation and contractility leading to arterial insufficiency. This in turn can lead to neuropathy and hypoxia-related tissue damage.

The NO-cGMP pathway is very well understood in how it causes ED. A drop in NO and consequently cGMP levels lead to failure of the Cavernosal smooth muscles to relax resulting in poor arterial flow and therefore ED. Tadalafil and other drugs in its class inhibit the enzyme Phosphodiesterase Type 5 which selectively metabolizes cGMP. This results in an up-regulation of cGMP leading to relaxation of the Cavernosal smooth muscle.

Reduction in the NO-cGMP signalling also leads to pelvic artherosclerosis. This consequently results in chronic ischaemia in the prostate and reduced prostatic blood flow. This in turn leads to an increase in oxidative stress and inflammation. This induces stromal proliferation and transdifferentiation and extracellular matrix production in the prostate by up-regulating TGF-ß1 and bFGF. Which in turn will lead to BPH[12].

Increased RhoA-ROCK Signaling

Penile detumescence is a complex process. A well studied pathway is the G Protein Ca^{2+} dependent pathway (Phospholipase C). Recently, the RhoA/Rho-Kinase pathway involved in Ca^{2+} sensitization has also been shown to play an important role in penile detumescence. Rho-Kinase causes smooth muscles contraction by changing the MLCP:MLCK ratio leading to impaired contractility of the corpus cavernosum. NO is known to inhibit RhoA/Rho-Kinase activity. This same pathway has been postulated to be involved in the development of hypertension and diabetes[13].

The RhoA/Rho-Kinase pathway has also been shown to play an important role in the regulation of bladder smooth muscle tone. An aberration of this pathway may be one of the factors in causing the irritative symptoms of BPH-LUTS.

Autonomic Hyperactivity

Insulin resistance can lead to sympathetic nervous system activation via an up regulation in IGF-1 and cytosolic-free calcium in smooth muscles and neuronal cells. This leads to an increase in prostate smooth muscle tone and blockage of the bladder outflow tract resulting in LUTS.

Norepeneprhine derived from the sympathetic system is the chief neurotransmitter in penile flaccidity and detumescence. An up regulation on the sympathetic pathway can therefore lead to ED[14].

Current Treatment Options for BPH-LUTS

- 5 α Reductase Inhibitors

5 α Reductase converts Testosterone to DHT which has a strong trophic effect on the prostate. The prostate is very rich in this enzyme. Inhibiting the 5 α Reductase will result in a reduction in DHT levels and subsequent reduction in prostate size. Because DHT is also involved in various sexual functions, this treatment may lead to side effects such as loss of libido, reduction in semen volume and ED. An often desired side effect is the reversal of androgenic alopecia[15].

- α1 – adrenoceptor antagonist (α blockers)

The prostate is rich in α1 adrenergic receptors which receive signals from the sympathetic nervous system resulting in smooth muscle contraction of the prostate. Blocking these receptors will lead to relaxation of the smooth muscle and subsequent relief of LUTS. Depending on the selectivity of the α blockers, they may lead to side effects such as dizziness and hypotension. α blockers have also been linked to sexual side effects of ED, ejaculatory dysfunction (especially retro-grade ejaculation) and decreased libido[15].

Mechanism of Action of PDE5I on BPH-LUTS

PDE5I increases cGMP by inhibiting PDE5 which selectively breaks down cGMP. This leads to better perfusion and less signalling on the prostate to enlarge. This also increases pelvic perfusion leading to reduced ischaemia. This may lead to less oxidative stress on the prostate and a reduction in signalling for the prostate to enlarge. An increase in NO also inhibits the RhoA/Rho-Kinase pathway which will reduce the contractility of bladder musculature leading to a decrease in LUTS. PDE5I also reduces autonomic hyperactivity by reducing the inflammation and oxidative stress caused by the metabolic syndrome[16].

Efficacy of Tadalafil 5mg daily for the treatment of BPH-LUTS

Tadalafil 5mg once a day resulted in statistically significant improvement in LUTS secondary to BPH compared with placebo on IPSS. Tadalafil 5mg demonstrated further benefit compared to 2.5mg. 10mg and 20mg provided minimal further improvement over 5mg[17].

Tadalafil 5mg once daily improved IPSS and Quality of life scores for men both with and without ED. This is evidence that Tadalafil does not cause symptomatic improvement of BPH-LUTS just by improving the erection[19].

Tadalafil 5mg daily is just as effective as Tamsulosin 0.4mg in improving IPSS scores and Qmax. However, only Tadalafil improved Qol and IIEF scores[20].

Tadalafil/Finasteride co-administration provides early and significant LUTS improvement (compared to placebo/finasteride) in men with prostatic enlargement secondary to BPH[22].

Safety of Tadalafil 5mg daily

In a 1 year open label trial of Tadalafil 5mg daily, most adverse events were transient and episodic. They were mild or moderate in severity. The most commonly reported adverse events were dyspepsia, back pain and headache[18].

Adverse events profile in men with ED and LUTS on Tadalafil 5mg daily and men with LUTS but no ED were similar[19].

There are no additional haemodynamic adverse events during co-treatment of Tadalafil with an α1 adrenergic receptor antagonist[21].

Summary

ED and BPH-LUTS affect the same patient population and share similar patho-physiology. Tadalafil 5mg OAD is an effective and safe treatment option for patient with ED, BPH-LUTS of both conditions simultaneously.

Practice Pointers

1. Always screen patients who present with ED for LUTS and vice versa.
2. Offer patients with both ED and LUTS Tadalafil 5mg OAD as monotherapy.
3. Consider Tadalafil 5mg OAD for patients presenting with ED who are 50 years or older because of the high prevalence rate of BPH and because many patients may not report bothersome symptoms.
4. Consider Tadalafil 5mg OAD for patients presenting with ED with co-morbidities such as Diabetes, Obesity or Hypertension because Tadalafil might tamper the oxidative stress caused by these diseases.
5. Consider Tadalafil 5mg OAD for patients who fail PRN therapy with Tadalafil 20mg or other PDE5Is.
6. When discussing PDE5I options with patients, bear in mind the advantages of Tadalafil 5mg OAD:
    a. Reduction in dosage errors
    b. Ease in patient education
    c. Efficacy in relieving possible BPH –LUTS
    d. Possible mechanism in reducing chronic inflammation effects from chronic diseases
    e. Possible mechanism in reversing endothelial dysfunction

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