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Platinum Priority – Collaborative Review – Benign Prostatic Enlargement

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Latest Evidence on the Use of Phosphodiesterase Type 5 Inhibitors for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

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Abstract

Context: Several preclinical reports, randomized controlled trials, systematic reviews, and posthoc analyses corroborate the role of phosphodiesterase type 5 inhibitors (PDE5-Is) in the treatment of men with lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement (BPE).
Objective: Update of the latest evidence on the mechanisms of action, evaluate the current meta-analyses, and emphasize the results of pooled data analyses of PDE5-Is in LUTS/BPE.
Evidence acquisition: Literature analysis of basic researches on PDE5-Is, systematic literature search in PubMed and Scopus until May 2015 on reviews of trials on PDE5-Is, and collection of pooled data available on tadalafil 5 mg.
Evidence synthesis: Latest evidences on the pathophysiology of LUTS/BPE has provided the rationale for use of PDE5-Is: (1) improvement of LUT oxygenation, (2) smooth muscle relaxation, (3) negative regulation of proliferation and transdifferentiation of LUT stroma, (4) reduction of bladder afferent nerve activity, and (5) down-regulation of prostate inflammation are the proven mechanisms of action of PDE5-Is. Data from eight systematic reviews demonstrated that PDE5-Is allow to improve LUTS (International Prostate Symptom Score mean difference vs placebo: 2.35–4.21) and erectile function (International Index of Erectile Function mean difference vs placebo: 2.25–5.66), with negligible change in flow rate (Q_{max} mean difference vs placebo: 0.01–1.43). Pooled data analyses revealed that tadalafil 5 mg once daily allows the clinically-meaningful improvement of LUTS and nocturnal voiding frequency independent of both erectile dysfunction severity and improvement.
Conclusions: PDE5-Is are safe and effective in improving both LUTS and erectile function in appropriately selected men with LUTS/BPE. Data on the reduction of disease progression, long-term outcomes, and cost-effectiveness analyses are still lacking.
Patient summary: We reviewed recent literature on phosphodiesterase type 5 inhibitors in men with lower urinary tract symptoms associated with prostatic enlargement. We found evidence to confirm that phosphodiesterase type 5 inhibitors are a valid treatment option for men affected by bothersome urinary symptoms with or without erectile dysfunction.

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1. Introduction

Lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement (BPE) and erectile dysfunction (ED) are both highly prevalent in elderly men [1]. Although the underlying pathophysiological links between LUTS and ED are not completely understood, both conditions are amenable to therapy with phosphodiesterase type 5 inhibitors (PDE5-Is) [2]. Recently, several studies have suggested that metabolic factors could be important for contributing to both prostate inflammation and enlargement in men with LUTS [3,4]. It has been hypothesized that PDE5-Is could reduce inflammation with the associated fibrosis and improve the oxygenation of the human prostate, with a normalization of prostatic structural anatomy and physiologic activity [5,6].

The aim of this review is to provide an update on the current knowledge on the potential mechanisms of action of PDE5-Is on LUTS/BPE, critically analyze systematic reviews and relevant data from the current literature on the clinical use of all PDE5-Is, and report the latest evidence on pooled-data analyses of tadalafil once daily to provide a definite rationale for the clinical use of tadalafil for the treatment of LUTS/BPE.

1.1. Update on preclinical evidence

The pathways mediating the activity of PDE5-Is: LUTS have a multifactorial pathophysiology and have been discussed extensively [7–9]. Traditionally, the prostate and urethra has been the focus in the pathogenesis of male LUTS. Chalfin and Bradley [10] blocked prostate sensory afferents with lidocaine in patients with detrusor overactivity (DO) and found that overactivity was eliminated in 10/11 patients, but had no effect in four patients with a normal cystometry. Based on these findings, they suggested that sensory stimuli from an anatomically altered prostatic urethra induced DO, and that permanent ablation of sensory stimuli from the prostate in patients with outlet obstruction would be of benefit.

The role of the bladder in male LUTS has been emphasized [9], and much attention has been given to the involvement of the different components of the bladder wall. Changes of the urothelium, afferent nerves, lamina propria, vasculature, and detrusor smooth muscle may initiate LUTS and thus emerge as therapeutic targets [11]. Most probably all of these components are more or less simultaneously involved in the afferent signaling resulting in LUTS, but at least two distinct signaling pathways can be identified: the urothelial and the myogenic pathway [12]. The urothelial pathway is a functional unit consisting of the urothelium, interstitial cells, and afferent nerves (C-fibers) in the lamina propria. The myogenic pathway is activated via in-series mechanoreceptors responding to distention, and via spontaneous contractile activity in units of myocytes generating afferent noise. Urothelial cells have the ability to sense changes in their extracellular environment, and respond to chemical, mechanical, and thermal stimuli by releasing various factors such as adenosine triphosphate, nitric oxide (NO), and acetylcholine. The bladder develops tone during filling and also exhibits nonsynchronized local contractions and relaxations that are caused by a basal myogenic mechanical activity that may be reinforced by the release of acetylcholine from non-neuronal and/or neuronal sources or local mediators, such as prostaglandins and endothelins. It has been suggested that these spontaneous contractions are able to generate activity in afferent nerves that may contribute to LUTS [13]. The central nervous system may be an important initiator of LUTS [14,15]. According to Sakakibara et al [15] there is compelling evidence to suggest that the central nervous system's white matter disease can cause an overactive bladder and incontinence, and in some patients these might be the initial manifestation.

In the pathophysiology of LUTS, the NO/cyclic guanosine monophosphate (cGMP) (NO/cGMP) signaling pathway is believed to play a central role. Since NO signaling occurs via stimulation of soluble guanylate cyclase producing cGMP, it is reasonable to assume that the level of cGMP in different LUT tissues can influence their ability to generate LUTS. One way of modulating cGMP levels is to selectively inhibit cGMP degradation, and it is generally believed that all effects of PDE5Is are mediated by selective inhibition of the degradation of cyclic GMP.

Mechanism of action of PDE5-Is: In several animal species, including humans, the entire LUT expresses PDE5, with a relatively higher abundance within the bladder [16,17]. In human bladder homogenates, vardenafil, sildenafil, and tadalafil inhibited PDE5 activity with IC_{50}s strictly related to those measured in human penile tissue, that is 0.3 nmoles/L, 3 nmoles/L, and 6 nmoles/L, respectively [16].

Although it is well established that PDE5 is expressed and biologically active in LUT, its functional role is still a matter of debate. Clinical studies demonstrated that its inhibition, through all the aforementioned PDE5-Is, resulted in amelioration of LUTS. Several mechanisms of action of PDE5-Is in LUTS have been hypothesized.

1.2. PDE5 inhibition increases LUT oxygenation

Immunohistochemical studies indicate that PDE5 is localized in the endothelial and smooth muscle cells of the LUT blood vessels [17]. In particular, in the human vesicular-deferential artery PDE5 mRNA is higher than in the bladder and as abundant as in corpora cavernosa extracts. In this vessel, PDE5 enzymatic activity was inhibited by tadalafil incubation [19]. In isolated human vesicular-deferential artery rings, tadalafil was able to increase the vasorelaxant response to a NO donor, suggesting an active role of PDE5 in controlling LUT perfusion. In a genetic rat model of OAB and prostate alteration due to LUT ischemia, short-term administration of vardenafil and tadalafil increases bladder and prostate oxygenation [22,23]. Tadalafil effect was even higher after prolonged in vivo administration [22]. A tadalafil-induced decrease in hypoxia-related genes was also reported in a rabbit bladder [24]. Recently, in other rat models of ischemia/perfusion or of partial bladder outlet obstruction, tadalafil was reported to improve impaired