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Collaborative Review – Benign Prostatic Hyperplasia

Phosphodiesterase Type 5 Inhibitors in the Management of Non-neurogenic Male Lower Urinary Tract Symptoms: Critical Analysis of Current Evidence

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Abstract

Context: A large body of epidemiologic data suggests a causal relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED). Recently reported studies on phosphodiesterase type 5 inhibitors (PDE5-Is) and LUTS have further contributed to the understanding of mechanisms involved in this relationship and of potential treatment options.
Objective: A nonsystematic descriptive review was performed to summarize the literature concerning the role of PDE5-Is in men with LUTS, particularly looking at data derived from clinical trials in relation to the different PDE5-Is or their association with α-blockers.
Evidence acquisition: A comprehensive electronic search was conducted in October 2010 using the Medline database to identify all publications relating to ED and BPH and treatment with sildenafil, vardenafil, tadalafil, udenafil, UK-369003, and combination therapy with alfuzosin and tamsulosin.
Evidence synthesis: In studies in which either ED or LUTS was the entry criterion, sildenafil appears to improve both erectile function and LUTS in subjects with ED. Placebo-controlled trials of tadalafil and vardenafil showed improvement of LUTS secondary to benign prostatic hyperplasia (BPH), but none of the studies showed a significant effect on urodynamic measures. Exploratory studies with UK-369003 showed improvements in LUTS and ED. Sildenafil or tadalafil associated with alfuzosin or tamsulosin showed greater benefits for the combination therapy for both LUTS and ED. The coadministration of udenafil and an α-blocker in patients with BPH and ED also appeared to improve both LUTS and ED severity.
Conclusions: Consistent evidence of improvements in LUTS has been shown with PDE5-Is, either alone or in combination with α-blockers. However, effects on urodynamics or objective measures of urinary flow are lacking. Further areas of research include investigation of mechanism of PDE5-Is, urodynamic studies, identification of new efficacy end points, head-to-head comparison with standard of care, potential benefit of add-on treatment, and long-term outcomes.

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1. Introduction

A large body of epidemiologic evidence supports a causal relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) [1–10] (Table 1), including (1) a consistent dose–response association between increased frequency of LUTS and ED, (2) a significantly higher prevalence of LUTS in men suffering from ED as compared with men with normal erections, and (3) a statistically significant increase on multivariable models of the risk of ED for increasing urinary complaints after adjusting for age and comorbidities.

The association between ED and LUTS also has biologic plausibility given the interrelationships of the known pathophysiologic mechanisms of these disease states [11,12]. The four pathophysiologic mechanisms [13] include the roles of nitric oxide synthase [14,15], autonomic hyperactivity and the metabolic syndrome [16–18], the Rho-kinase activation/endothelin pathway [19], and pelvic atherosclerosis [1]. These processes are not mutually exclusive and may overlap substantially [20,21].

In relation to preclinical data, numerous studies have investigated the effects of phosphodiesterase type 5 inhibitors (PDE5-Is) in the prostate, bladder, urethra, and lower urinary vasculature [22–47]. These agents can be classified according to their preference of affinity for cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP). The 21 human phophodiesterase (PDE) genes are divided into 11 families based on their protein sequences, regulatory considerations, and sensitivity to inhibitors, as well as their cAMP and/or cGMP affinity [22,23]. Alternative splicing of PDE messenger RNAs (mRNAs) occurs at the 50- and/or 30-ends of the transcripts for most of the 21 genes, which yields at least 80 different PDE proteins. Further, at least 6 of the 11 isoenzyme families (PDE types 1–5 and 11) have proved to be of functional importance in the management of LUTS [3]. Francis et al [45] published an excellent review of the effects of cGMP on cellular targets (cGMP-dependent protein kinases, cGMP-gated cation channels, and PDEs). Dorsey et al [46] carried out an extensive review of basic science articles published between 1990 and 2009 examining the pharmacologic effects of PDE5-Is for the treatment of ED.

The objective of this nonsystematic descriptive review was to summarize the literature concerning the role of PDE5-Is in the management of men with LUTS, particularly looking at data derived from clinical trials in relation to the different PDE5-Is or their association with α-blockers.

2. Evidence acquisition

A comprehensive electronic literature search was performed in October 2010 using the Medline database, through either PubMed or Ovid as a search engine, to identify all publications relating to benign prostatic hyperplasia (BPH), LUTS, ED, and PDE5-Is. Both experimental and clinical research studies were considered. English-language articles were included for review, and non-English articles were included if they provided additional relevant information. The search was conducted using a free-text protocol that included the following terms: *lower urinary tract symptoms, benign prostatic hyperplasia, bladder neck, PDE receptors, phosphodiesterase inhibitors, cavernous tissue, erectile dysfunction, sildenafil, vardenafil, tadalafil, udenafil, alfuzosin, tamsulosin,* and *UK-369003*. These terms were arranged by variable combinations of the Boolean operators AND and OR.

Attention was given only to published studies pertaining to the field of urology as based on the journal, authorship, and/or manuscript content. Review articles and case reports were considered if they were relevant. Studies published as abstracts only and reports from meetings were not included unless the interest of the study was considered to be high. Other significant studies cited in the reference lists of the selected papers were evaluated. Publications reporting on the same cohort group from the same institution were limited to the most recent publication. The panel of authors discussed the list of source items, and the articles considered more relevant were selected.

3. Evidence synthesis

3.1. Sildenafil and lower urinary tract symptoms

The most common form of management of ED is pharmacotherapy with PDE5-Is [48]. Table 2 presents a summary of clinical studies of sildenafil and LUTS.

In a prospective open-label study by Sairam et al [49] in 147 men attending an andrology clinic with ED as their main complaint, 112 men used sildenafil on demand before sexual intercourse. Subjects completed the International

Table 1 – Relevant epidemiologic studies of the relationship between lower urinary tract symptoms and erectile dysfunction

Study	Country	Patients	Range,yr	ED,%	LUTS, %	Risk ratio for ED
Braun et al [3]	Germany	4489	30–80	19.2	72.2	2.11
Nicolosi et al [4]	Brazil, Italy, Japan, Malaysia	2412	40–70	16.1	–	2.2–4.9
Rosen et al [5]	USA and six European countries	12 815	50–80	48.9	30.8	3.7–7.6
Vallancien et al [6]	Five European countries	1274	36–92	62	91	1.2–1.9
Boyle et al [7]	Korea and three European countries	4800	40–79	21.1	–	1.1–1.7
Hansen [8]	Denmark	3700	40–65	28.2	39.1	2.3–3.4
Terai et al [9]	Japan	2084	> 40	29.9	27.1	1.5

ED = erectile dysfunction; LUTS = lower urinary tract symptoms.