

The new horizons of pharmacotherapy. Unexpected pharmacological actions and a new therapeutic strategy of phosphodiesterase–5 inhibitors

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Article history

Submitted: May 28, 2014

Accepted: June 26, 2014

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Introduction Benign prostate hyperplasia and erectile dysfunction affect a significant subset of men. BPH and ED may have the same promoting conditions and are the strong predicting risk factors to each other. A significant number of these patients are bothered by lower urinary tract symptoms (LUTS). Direct correlation of age, sexual dysfunction and LUTS severity has been well documented. Many sexually dysfunctional patients with concomitant BPH receive alpha–adrenergic antagonists and any Phosphodiesterase–5 (PDE5) inhibitor simultaneously. PDE5 inhibitors relieve LUTS symptoms in the course of BPH and reduce independent detrusor contractions. This paper presents the results of clinical trials on the efficacy of PDE5 inhibitors on LUTS, new perspectives on its use and newly–identified side effects.

Material and methods The review is based on an internet search of PubMed and Medscape databases. The search terms were as follows: LUTS and ED, BPH and phosphodiesterase–5 inhibitors, LUTS clinical trials, phosphodiesterase–5 inhibitors mechanisms.

Results Clinical trials show an epidemiological and pathophysiological relationship between BPH, LUTS and ED. Numerous studies reveal the alleviating effect of phosphodiesterase–5 inhibitors on LUTS, expressed as the reduction of IPSS score, but not followed by a change in Qmax. Opponents raise a link of PDE5 inhibitors with increased risk of melanoma. New studies reveal that phosphodiesterase–5 inhibitors are effective in the treatment of neurological disorders.

Conclusions Researches reveal the efficacy of phosphodiesterase–5 inhibitors in LUTS along with an improvement of erectile function. The molecular mechanism of action of such drugs suggests imminent novel applications. Potential benefits will be multidimensional. Unfortunately, interfering with particular molecular mechanisms may alleviate some diseases, but may lay groundwork for others – new and even more devastating.

Key Words: BPH/LUTS and phosphodiesterase–5 inhibitors ◊ PDE5I mechanisms ◊ PDE5I side effects

INTRODUCTION

For sure, each of us remembers the excitement when the first phosphodiesterase–5 (PDE5) inhibitor – sildenafil – entered the markets. It created a great stir, many women flickered eyelids tellingly, ...or even got filmy eyes. Now it is rumoured that things may go even further. New papers have kept pace with this trend [1]. Coexistence of benign prostate hyperplasia and erectile dysfunction

Benign prostate hyperplasia (BPH) affects a significant subset of men in their sixties. Additionally, erectile dysfunction is not uncommon at this age. Epidemiological data clearly shows that over 30% of 50–year–old men are affected by symptoms of BPH. Apart from obvious symptoms related to dynamic and static components of prostate enlargement, a significant number of patients are bothered by symptoms related to detrusor muscle dysfunction. Nearly 50% of men at the age of 70 or above experience at least

moderate lower urinary tract symptoms (LUTS) [2]. Patients with prostate hyperplasia are usually treated successfully pharmacologically. Now, pharmacology gives a plethora of different possibilities. Among them, long-acting alpha-adrenoceptor antagonists and 5-alpha-reductase inhibitors are the mainstay of therapy, used either separately or in combination [3]. The irritative (nocturia, urinary urgency, frequency) and obstructive (weak stream and incomplete bladder emptying) symptoms of LUTS resolve after successful treatment of BPH alone or with the help of antimuscarinic drugs regulating bladder dysfunction. Of course, other causes of LUTS exist, like urinary stones, tumours, systemic diseases or infections [4]. Beside prostate hyperplasia, a considerable proportion of elderly men is affected by erectile dysfunction (ED). The co-occurrence of BPH and ED is not uncommon, both may have the same promoting conditions and are strong predicting risk factors for each other [5]. Direct correlation of age, sexual dysfunction degree and LUTS severity has been well-documented [6, 7, 8].

Possible mechanisms of ED and LUTS convergence

Where do these afflictions come from? While risk factors seem to be numerous, many patients consider ED as a common aspect of ageing. Provided that erectile dysfunction and LUTS symptoms are statistically interrelated, the exact mechanisms of this phenomenon are still unclear, though they may have common risk factors [9, 10, 11]. For sure, cardiovascular and endocrinological diseases are the dominating causes: 47% of men over 55 yrs have some symptoms of ED. Of the remaining 53% fully sexually-functional men, 57% will report any of the ED symptoms after the next 5 year period. A strong statistically significant correlation (with hazard ratio 1.46) of ED and cardiovascular events has been documented [12]. Moreover, endocrine disorders, which often affect elderly patients, significantly contribute to the incidence and severity of erectile dysfunction. Both cardiovascular and endocrinological disturbances are elements of the metabolic syndrome, also recognised as groundwork for BPH development. It is known that sexual function deteriorates along with obesity [13]. Due to the growing popularity of PDE5 inhibitors, many ED patients with concomitant BPH receive alpha-adrenergic antagonists and any PDE5 inhibitor simultaneously. Different sources of data like the patients personal impressions, observational evidence and laboratory experiments suggest that phosphodiesterase-5 inhibitors may affect bladder, prostate and urethra function to relieve bothersome symptoms related to LUTS caused by prostate hyperplasia. More-

over it has been presented that PDE5 inhibitors may reduce independent detrusor contractions [14]. The abundance of neural nitric oxide synthase has been demonstrated mainly in the bladder neck and the urethral wall. This localization proves that nitric oxide plays a decisive part in the micturition reflex [15, 16]. Indeed, in rats, the suppression of NO synthase activity leads to bladder hyperactivity [17]. Possible pathways explaining the alleviating effect of PDE5 inhibitors on LUTS symptoms have been proposed:

1. Bladder, urethra and prostate smooth muscle relaxation, through the nitric oxide pathways, are similar to those of the penile cavernosal bodies. At this point it would be helpful to remind ourselves some facts. Neural and endothelial origin nitric oxide (NO) stimulates guanylate cyclase, which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP lowers the plasmatic calcium level. Through several enzymatic steps this leads to the detachment of myosin from actin and consecutively to muscle relaxation. cGMP is degraded by several types of enzymes – phosphodiesterases, of which the type 5 is the most important in genital tissues. However, in the prostate, PDE type 4 is the predominant form and prevails over PDE5. The presence of nitric oxide synthase, NO and the different phosphodiesterases has been shown all over the lower urinary tract [13, 18]. Therefore PDE5 inhibitors are the main topic of this review. In comparison to the normal gland, the hyperplastic prostate contains significantly lower levels of NO [19]. Next, cGMP by itself exerts an antiproliferative effect on smooth muscle cells, where the NO-cGMP pathway may be involved in decreasing of volume of the prostate stroma [20]. Therefore, inhibition of PDE5 activity is likely to reduce the bulk of the prostate.
2. Disabling of autonomic hyperactivity (an element of the metabolic syndrome) by inhibiting the activity of noradrenaline and endothelin pathway modulation [13]. Both phenomena contribute to LUTS development [14].
3. Inhibition of Rho-kinase activation: the mechanism is particularly interesting as this pathway is responsible for calcium-independent contractions of smooth muscles and also for smooth muscle proliferation [21]. Concurrently Rho-kinases prevent the activation of NO synthase, which diminishes intracellular NO level and hinders smooth muscle relaxation [21].
4. Pelvic ischemia secondary to atherosclerosis and narrowing of pelvic arteries. Atherosclerosis impairs blood inflow and oxygenation of the bladder wall. Hypoxia contributes to the hyperplasia of connective tissue in the bladder and subsequent impairment of its compliance [13, 22, 23]. Because of its vasodilatory effect, PDE5 inhibitors improve blood flow.

Clinical studies on phosphodiesterase-5 inhibitors efficacy for the treatment of LUTS

A number of interesting findings originate from recently published trials conducted in men suffering from BPH. Research analysed the efficacy of phosphodiesterase-5 inhibitors and presented statistically significant alleviation of LUTS symptoms expressed by the International Prostate Symptom Score (IPSS) scale, along with improvement of erectile function. The clinical studies are mentioned below. The results are in line with expectations based upon results of laboratory experiments on isolated cells and tissues and animals as well. Yet, some “experimenter bias” must be excluded.

One research team found that from a group of 20 patients with co-occurring LUTS and ED after 12 week-long treatment with sildenafil, 32% reported improvement in IPSS scale and LUTS-specific quality of life [24]. Another study on 62 patients with LUTS and ED investigated the efficacy of alpha-blockers (alfuzosin) combined with a PDE5 inhibitor (sildenafil) versus monotherapy over a period of 12 weeks. The greatest improvement of IPSS parameters was noted with combination therapy, while for monotherapy individually the results were similar and worse than in the former [25]. A much larger group of patients (366) was assessed over a 12 week-long sildenafil-monotherapy. In the initial course, patients received 50 mg daily for 2 weeks, and further 100 mg daily for 10 weeks. The final analysis shows a significant reduction in IPSS scale (of 6.32 points). The advantageous effect was particularly significant for severe LUTS symptoms [26].

The use of other PDE5 inhibitors to decrease LUTS accompanying BPH has been investigated in large randomised clinical trials. These trials also showed a decrease in severity of bothersome symptoms. The efficacy of Tadalafil in LUTS was estimated in a large (281 men) study. Similar to previously cited studies, some decrease on the IPSS scale was noted as compared to placebo (of 3.8 points at 12 week) [27]. Vardenafil at a dose of 10 mg two times daily during a period of 8-weeks resulted in a 5.9 point-reduction in IPSS score (a group of 222 men in randomised trial) [28]. However, one should note that the improvement reflected by the IPSS score (subjective measure) was not followed by any change in Qmax (objective measure) [29].

Perspectives of phosphodiesterase-5 inhibitors in the treatment of premature ejaculation

Recently, some authors have debated the use of PDE5 inhibitors as a novel treatment of premature

ejaculation (PE). PE is regarded as the most prevalent sexual disorder [30, 31]. Undoubtedly, the mechanism of PE is multifactorial, but still remains unclear and treatment is based mainly on behavioural methods [32]. However, a few pharmacotherapies have emerged lately: topical anaesthetics, selective serotonin re-uptake inhibitors and alpha-adrenergic antagonists are the most commonly prescribed remedies. Now, phosphodiesterase-5 inhibitors have emerged as a potential medication in PE therapy. This concept results from experimental data demonstrating that NO/cGMP pathway is involved in sexual behaviour centrally and peripherally (not only on penile tissues) alike [32]. The former is supported by experiments on rats which present that nitric oxide in the medial preoptic area induces erection and inhibits ejaculation. The activity in the latter consists of relaxation of smooth muscles of the vas deferens, seminal vesicles, prostate and urethra, then inhibiting emission and ejaculation. Additionally, PDE5 inhibitors reveal direct anti-adrenergic activity on urogenital tissues. Thereby, these drugs may prolong intravaginal ejaculatory latency time [32]. Other proposed mechanisms include: analgesia of the glans sensory receptors, decrease of the central sympathetic tone and support of sexual self-assessment and confidence [30, 32, 33]. Despite such promising assumptions, clinical trials on the efficacy of PDE5 inhibitors in PE treatment provide equivocal, if not conflicting, results [33, 34]. Chen and co-workers reviewed available data and presented that placebo-controlled studies did not reveal the supposed efficacy of PDE5 inhibitors alone in PE, while one paper presented some behavioral/mental benefits [32]. These conclusions stay in concert with another publication [34]. A survey by Chen’s team found that combination therapy with a selective serotonin re-uptake inhibitor (paroxetine) is more efficient than with either substance alone [32]. Their own results presents that sildenafil prolongs intravaginal ejaculatory latency time, but yet to be reflected in the subjective visual scale [32]. Some encouraging data on PDE5 inhibitor in the treatment of PE concerns the combination with topical analgesia of the penile glans [35].

The dark side of phosphodiesterase-5 inhibitors

Does the cons prevail the pros?

Beyond all doubts, administration of very expensive medicines like PDE5 inhibitors over a three month period will be a heavy financial burden on the health care system, particularly in our times of cost constraints. If the health-service should cover these expenses, then how extensible is that duvet?

Furthermore, researchers did not precisely assess a prolonged, pro-erectile effect of a 3-month regimen with PDE5 inhibitors. Indisputably, sometimes there can be too much of a good thing. We don't know much about the long-term effects of such stimulation. Fundamental objections raise a proved link of PDE5 inhibitors with an increased susceptibility to melanoma. Laboratory data confirm epidemiological observations that sildenafil may contribute to an increased risk of melanoma, and may promote melanoma invasiveness, especially in patients with a genetic predisposition like the BRAF gene mutation. It is known that PDE5 inhibitors promote melanin synthesis – a factor for melanoma development – and low phosphodiesterase-5 activity propagates melanoma cells invasiveness [36].

A very recently published paper should turn heads. A 10-year-long study on 25,848 men from the Health Professionals Follow-Up Study revealed that the risk of melanoma development was significantly elevated for sildenafil users when compared to non-users (hazard ratio 1.84). Data stratified for 1000,000 individuals, indicate 216.4 melanoma cases in the sildenafil subgroup and 135.4 melanoma cases in the non-sildenafil subgroup. In addition, the investigators found an increased risk of melanoma for men taking sildenafil occasionally [36]. The association of melanoma with other inhibitors was not tested in that research, but it does not exclude such a relation. The study did not show a correlation between sildenafil use and other skin cancers. The foregoing remarks cast doubts on potential long-term use of PDE5 inhibitors in LUTS.

New areas of application for phosphodiesterase-5 inhibitors. A hope for victims of devastating diseases.

Fortunately, new researches have brought to light really good news about unexpected pharmacological actions and new therapeutic strategies of PDE5 inhibitors, beyond their known use in pulmonary hypertension. Clinical data from tests of tadalafil and sildenafil reveal that

phosphodiesterase-5 inhibitors may be effective in the treatment of muscular dystrophies. Studies revealed that impaired muscular blood flow with subsequent oxygen depletion in Duchenne and in Becker muscular dystrophies results from the loss of nitric oxide in vessels wall [37, 38]. Similar to its use in penile tissues, PDE5 inhibitors should, and do, protect NO in skeletal muscles. A randomised trials revealed that even single, standard doses of PDE5 inhibitors restore weakened muscular blood inflow, correct tissue oxygenation and subsequently result in significant improvement of exercise capacity and muscular strength [37, 38]. Another beneficial effect was described for spinal-cord injury patients. Here, PDE5 inhibitors enhanced the relaxation of the bladder wall in a neurogenic bladder [39].

Closing remarks

The remarkable efficiency of phosphodiesterase-5 inhibitors in the treatment of erectile dysfunction is well-known. Novel potential use for treatment of other diseases has emerged. Thanks to its vasodilatory activity, the applications may be manifold. Up to now, besides ED treatment, PDE5 inhibitors have been used for the treatment of pulmonary hypertension in adults and neonates. The molecular mechanism of action of such drugs suggests that other, new applications are very probable and diverse. By acting on NO-cGMP, Rho-kinases pathways and on adrenergic activity, potential benefits will be multidimensional – the use of PDE5 inhibitors in the treatment of muscular dystrophies is an example. A lack of effective treatment of numerous diseases and the huge financial burden of scientific research on entirely new drugs, calls for urgent scrutiny of existing medicines. For example, old drugs like metformin have found many new applications. Yet, one of the major challenges of this approach is that we do not know whether interfering with particular cellular molecular mechanisms alleviates diseases or creates groundwork for others – new and even more devastating. Melanoma risk related to phosphodiesterase-5 inhibitors is an example of the latter.

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