Daily Use of PDE5-Inhibitors: The Road to Happiness?

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The use of phosphodiesterase type 5 inhibitors (PDE5-I) on demand has been established as the gold standard in the treatment of erectile dysfunction (ED), with reported success rates of up to 70%. However, a considerable number of patients suffering from ED do not respond to on-demand treatment with PDE5-I. Therefore, research has focused on strategies to improve ED particularly as a complication of diabetes, cavernous nerve injury following radical prostatectomy, and in those patients who have not responded for various reasons. There is an increasing body of evidence showing that chronic daily dosing may be a treatment option for these “difficult-to-treat” patients; however, our current knowledge of the underlying mechanisms is limited.

It is well known that erectile function is controlled by the degree of corpus cavernosal smooth muscle contraction and relaxation. Among the transmitters leading to relaxation of smooth muscle and dilatation of penile vessels, and thus, erection, endothelial and neurogenic-released nitric oxide (NO) is considered the most important factor [1]. The pathophysiology of diabetes associated with ED is mainly based on endothelial dysfunction leading to the inability of the endothelium to produce vasorelaxing transmitters and to maintain vasodilation. Among the main factors leading to endothelial dysfunction in diabetes seem to be an impaired NO synthesis and release, elevated levels of advanced glycation end-products (AGEs), oxidative stress, and impaired smooth muscle function.

In their article published in this issue of European Urology, De Young et al used a diabetic rat model to analyze the effects of daily dosing with the PDE5-I vardenafil on erectile function and alterations in cavernous protein expression [2]. Apart from an improvement in erectile function, daily dosing of vardenafil for 6 wk improved the diabetes-related reduction of endothelial and smooth muscle content. This was shown by a stronger immunohistochemical staining for CD 31 as a marker for endothelial cells and α-actin as a marker for smooth muscle cells. While the value of quantitative measurements in immunohistochemical observations can always be questioned, the authors also demonstrate stronger expressions of endothelial nitric oxide synthase (eNOS) and α-actin using western blots. These results support recent findings in diabetic rats showing an improved vascular relaxation after treatment with sildenafil for 2 wk, which was explained by a reduction of oxidative stress and enhanced smooth muscle reactivity to exogenous NO [3]. Chronic treatment with a new PDE5-I, SK-3530, leads to a significant improvement in erectile function and, despite persistent hyperglycaemia, suppression of apoptosis of corporal smooth muscle by potentiating Akt signalling [4].

In general, chronic PDE5-I treatment has shown beneficial effects in rats with ED of various aetiologies. In aged rats, long-term treatment with sildenafil facilitated reversal of aging-related cavernosal fibrosis, prevented the loss of corporal smooth muscle, and stimulated NO synthase. In the rat model of cavernosal nerve injury, mimicking the condition of post-prostatectomy ED, it was shown that vardenafil was able to improve smooth muscle function as measured by NOS and smooth muscle content; sildenafil treatment also prevented the...
decrease in the smooth muscle cell-collagen ratio, the increase in apoptosis and reduction in cell proliferation, and partially counteracted the increase in collagen.

The findings observed in these animal models form the basis for the beneficial effects observed in of daily treatment with PDE5-I in vivo. Randomized, controlled, double-blind studies have proven efficacy on erectile function as measured by a change from baseline in the erectile function domain of the International Index of Erectile Function (IIEF). In diabetic patients with ED, there seems to be a synergic effect of propionyl L-carnitine (PLC) and a PDE5-I in reducing monocyte oxidative activity and endothelial dysfunction markers [5–7]. However, studies with longer treatment periods are needed to verify the long-term effects of daily PDE5-I dosing on erectile function.

Similar to ED, lower urinary tract symptoms (LUTS) are highly prevalent in men. The pathophysiological mechanisms leading to LUTS are not fully understood. However, ED and LUTS may have certain cellular alterations in common. As suggested by Andersson et al [8], a reduction in NO-containing nerves is observed in prostate and urethra as a result of bladder outlet obstruction (BOO). ED and LUTS may be part of the metabolic syndrome, sharing common risk factors such as cardiovascular diseases, obesity, and hyperinsulinaemia, leading to autonomic hyperactivity. Finally, there might be an increase in the Rho-kinase activity leading to smooth muscle contraction in prostatic, detrusor, and corporal smooth muscle [9]. PDE enzymes have been demonstrated in different parts of the lower urinary tract. While PDE4 and PDE5 seem to predominate in the prostate, PDE1 and PDE4 are mainly involved in bladder smooth muscle regulation. In the urethra and vasculature, PDE5 may play a major role. Because of their central role in smooth muscle tone regulation, PDEs have become attractive targets in the treatment of LUTS [10].

Beneficial effects have been reported for all three available PDE5-Is. Most recently, Stief et al published the results of a study analyzing the effects of vardenafil on LUTS and quality of life (QoL) in men with or without concomitant ED in a randomized, placebo-controlled study [11]. Following a treatment period of 8 wk with vardenafil 10 mg twice daily, a significant improvement in symptoms (IPSS), erectile function domain score (IIEF-EF), and QoL (Urolife QoL-9) were observed. However, maximum flow rates (Q_max) and post-void residual urine volume (PVR) did not change significantly. These findings are in agreement with randomized, controlled studies looking at the effects of chronic dosing of sildenafil and tadalafil in patients with LUTS. While LUTS, QoL, and erectile function were generally significantly improved following chronic treatment with PDE5-Is, the flow rate was not increased. Why? It can be argued that an improvement in flow rates would have been hard to achieve, because Q_max had been normal at baseline. Apparently, the mechanism and sites of action for the observed positive effects are not completely understood and differ from α1-AR antagonists. Thus, combination therapy of PDE5-Is and α1-AR antagonists may produce additive effects by the combination of both mechanistic principles and, therefore, represent a valid treatment option [12]. Based on preclinical evidence, a relaxant effect on urethral smooth muscle may be partly responsible for the beneficial effects of PDE5-Is. However, the vasculature or mechanisms involved in the afferent signalling pathways of the lower urinary tract, such as afferent nerves, urothelium and suburothelium, and interstitial cells, also cannot be excluded [10].

Chronic treatment with PDE5-Is has been introduced to a variety of other urological and non-urological diseases. Basic research studies as well as clinical studies have been published documenting beneficial effects in premature ejaculation, Peyronie’s disease, priapism, and non-urological indications such as portal hypertension, systemic hypertension, altitude sickness, and Raynaud’s phenomenon [13,14]. While PDE5-Is currently belong to established and approved treatment regimens for some of these conditions—although not as first-line treatments (eg, sildenafil in pulmonary hypertension)—further basic research studies and long-term clinical studies with large numbers of patients are needed to prove the potential benefits in most other indications.

Regardless of its enormous potential to treat various diseases, the concept of PDE5-Is daily dosing will be received with scepticism by the urological community until several key questions have been answered.

Primarily, tolerability and safety remain critical issues among patients who suffer from multiple comorbidities. The long-term use of PDE5-Is is considered safe, showing mild and tolerable adverse effects with no significant cardiovascular safety concerns. The most common adverse effects with PDE5-Is include headache, flushing, dyspepsia, nasal congestion, and back pain (tadalafil). There are no indications of an increase in myocardial infarction or mortality rates in patients taking PDE5-Is; on the contrary, cardioprotective effects have been postulated. However, it has to be emphasized that a thorough screening and diagnosis process for
cardiovascular risk factors are vital before recom-
mending the chronic use of PDE5-Is; according to the
Second Princeton Consensus, patients with ED are to
be stratified into three cardiovascular disease risk
categories: low, intermediate/indeterminate, and
high risk [15]. The proposed causal association
between the occurrence of nonarteritic anterior
ischaemic optic neuropathy (NAION) and treatment
with PDE5-Is does not seem to be established. There
is currently also no proof that tachyphylaxis may
occur with extended use.

In addition, based on current market values, it
seems unlikely that long-term treatment—even with
a low dose—will be affordable for most societies and
most patients. In a recently published Swedish study,
132 men with ED who were receiving treatment with
sildenafil on demand between 1998 and 2000 were
asked about their ongoing treatment in 2003. Of the
men in question, 47% still used sildenafil at least
twice per month. Of those patients who had
 discontinued the use of sildenafil, cost was the most
common reason (48%). Not surprisingly, the expenses
played a far bigger role (86%) in low-income house-
holds than in high-income households (35%) [16].

In conclusion, basic science and clinical studies
have yielded promising results that motivate further
long-term studies to assess the concept of daily
dosing with PDE5-Is in a variety of diseases. Today,
lack of knowledge regarding detailed mechanisms,
safety and tolerability concerns, and costs may
prevent a broad application. However, considering
the potential to treat not only highly prevalent
urological diseases such as ED and LUTS but also
non-urological conditions in which endothelial
function is impaired, pursuing this strategy seems
to be highly justified.

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