A review of phosphodiesterase type 5 inhibitors

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Abstract

Currently, three phosphodiesterase type 5 (PDE5) inhibitors are available for clinical use in South Africa; sildenafil, vardenafil and tadalafil. The PDE inhibitors are used in males to treat erectile dysfunction. However, sildenafil is also registered for use in the treatment of pulmonary hypertension. Newer studies are investigating the use of these drugs for other conditions, including hypertension, ischaemia or reperfusion injury, myocardial infarction, cardiac hypertrophy, heart failure and other peripheral circulatory conditions, e.g. Raynaud's disease. The article provides a broad overview of the mechanism of action, indications, pharmacokinetics and side-effects of these agents.

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Introduction

Indications for the use of phosphodiesterase (PDE) inhibitors are not limited to erectile dysfunction (ED) only. They have also showed effectiveness in pulmonary hypertension and other cardiovascular diseases (CVD).[1,2] Their effects on the improvement of cardiac function, exercise capacity and increased cardiac output have been proven by several studies.[3] Also, their vasodilative effects can yield a decrease in arterial blood pressure that can be highly beneficial to patients with CVD.[2] These benefits are made possible by the fact that the enzyme, phosphodiesterase, is present in various parts of the human body, such as the hypertrophied myocardium, and the pulmonary and systemic blood vessels.[4]

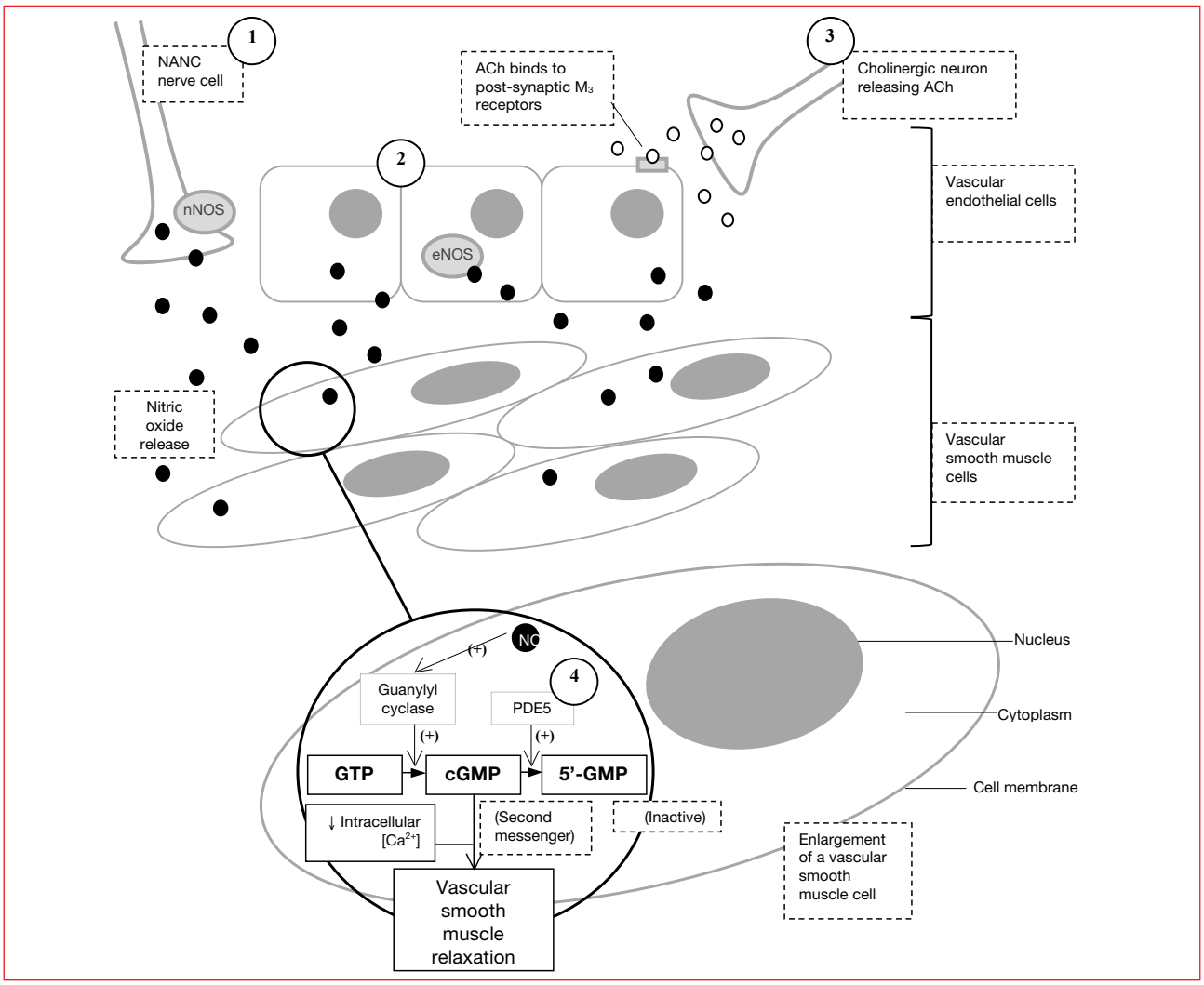
Prior to the roll-out of effective PDE type 5 (PDE5) inhibitors, ineffective and unsafe medications, such as yohimbine, apomorphine, phentolamine and trazadone, were considered for the management of ED. Instead of these medications, invasive therapies, such as penile prosthetic surgery, intracorporeal injectable medication and urethral suppositories, were used in the management of ED.[5,6] These therapies were not only invasive, but also unsafe and deficient because unpleasant techniques were involved.[6]

Although nonselective PDE inhibitors, such as caffeine, proved to have minimal vasculogenic activity, papaverine, an injectable PDE5 inhibitor, was used widely used until its side-effect profile caused the restriction of its use as a monotherapy in ED.[5]

The first oral medication in the PDE5 inhibitor class resulted in an additional choice in ED therapy, and obviously brought about therapeutic outcomes that were desired from the previous forms of treatment.[6] Initially, sildenafil was developed as an antihypertensive and antianginal agent by Pfizer, but was ultimately approved by the US Food and Drug Administration (FDA) for the primary indication of ED because of its lack of efficacy in terms of the original clinical trial outcomes and the "beneficial" side-effect of causing erections. Vardenafil and tadalafil received FDA approval to be used in ED five years after the initial approval of sildenafil.[5]

ED is the persistent failure, for a period of at least six months, to acquire and maintain an erection for the purpose of satisfactory sexual performance.[5,7] More than 150 million men are affected by ED worldwide, which may increase to over 320 million by 2025.[6] Although the prevalence of ED varies among countries, other factors, such as age, poor health and decreased exercise levels, also increase the risk of acquiring ED.[7]

Men have suffered ED as a result of various neurological, neurovascular, endocrinological, psychological and cardiovascular defects. The risks of acquiring ED have increased in smokers and patients with diabetes over the years.[5] Psychological factors that cause ED are stress, depression and anxiety.[5] However, some medicines that are used to manage depression and hypertension, as well as neuroleptics, are known culprits in terms of causing ED.[5,7] Low quality of life, low levels of testosterone, obstructive sleep apnoea syndrome and obesity relate to a higher risk of ED.[7]



5'-GMP: 5'-guanosine monophosphate (inactivated guanosine monophosphate), ACh: acetylcholine, cGMP: cyclic guanosine monophosphate (the second messenger that sets a biochemical cascade in motion, which results in decreased levels of intracellular calcium ions and resultant relaxation of the vascular smooth muscle), eNOS: endothelial cell-derived nitric oxide synthase, GTP: guanosine triphosphate, M_3 receptors: post-synaptic muscarinic receptors of the M_3 subtype, from which receptor stimulation leads to increased production and the release of nitric oxide, NANC: non-adrenergic and non-cholinergic, nNOS = neuronal nitric oxide synthase, NO: nitric oxide, PDE5: phosphodiesterase type 5 (the enzyme that catabolises cyclic guanosine monophosphate)
Nitric oxide is derived from (1) non-adrenergic and non-cholinergic nerves via the action of neuronal nitric oxide synthase, and (2) endothelial cells, via the action of endothelial cell-derived nitric oxide synthase. The production and release of nitric oxide by the endothelial cells is augmented by the stimulation of postsynaptic M_3 receptors (3) by acetylcholine and the site of action of the phosphodiesterase type 5 inhibitors (4)[5,6,8]

Figure 1: The mechanisms involved in vascular smooth muscle relaxation, thereby facilitating normal penile erection

Mechanism of action

PDE5 inhibitors potentiate the vasodilative effect of acetylcholine, which is released from sacral parasympathetic neurons, causing an increase in blood flow to the penis, and thereby facilitating penile erection during sexual stimulation. The penile erection results when the muscarinic receptors in the endothelial cells are activated by acetylcholine. This activation leads to an increased production and release of nitric oxide. The diffusion of nitric oxide into vascular smooth muscle cells activates guanylyl cyclase and the resultant increase in the synthesis of cyclic guanosine monophosphate (cGMP), leading to muscle relaxation and vasodilation of the penis.[8]

PDE5 inhibitors act by hampering the breakdown of cyclic GMP by PDE5, causing an increase in the intracellular concentration of cGMP in the corpus cavernosum of the penis. This action results in vasodilation and an antiproliferative effect on the smooth muscle cells.[8,9]

Figure 1 shows the mechanisms involved in vascular smooth muscle relaxation, thereby facilitating normal penile function.

Both cGMP and cyclic adenosine monophosphate (cAMP), i.e. the cyclic nucleotides, play vital roles in the regulation of cardiovascular functioning in cardiac disorders. cGMP facilitates the effect of nitric oxide, as well as that of atrial natriuretic peptide, while cAMP facilitates the effects of adrenaline on the heart and other tissue.[10] There is a large distribution of PDE5 in the pulmonary tissue, vascular smooth muscle, heart, renal tubules and platelets,[3] hence the vasodilatory effect will not be restricted to the penis, but also to other sites where the enzyme is present. The inhibition

of PDE5 by the highly selective PDE inhibitors catalyses the hydrolysis of cGMP to its inactive form, 5'-guanosine monophosphate, and also facilitates an increase in the vasodilatory effect of endogenous nitric oxide, thereby yielding positive cardiovascular and pulmonary effects in conditions such as hypertension, pulmonary arterial hypertension and coronary artery disease.[1,11]

Indications

Sildenafil, vardenafil and tadalafil are equally efficacious in mild to moderate ED. They are usually considered to be first-line therapy for ED. Nevertheless, the choice of drug is based on side-effect profile and patient requirements.[12,13] Currently, the PDE5 inhibitors are undergoing further investigations beyond ED, including myocardial infarction, cardiac hypertrophy, heart failure, strokes, neurodegenerative diseases, and possibly other circulatory disorders, e.g. Raynaud's disease.[1,3]

Tadalafil might also exert a cardioprotective effect against ischaemia and reperfusion injury in men treated for ED.[14,15]

Pharmacokinetics

Sildenafil and vardenafil have an onset of action of approximately 11-16 minutes after administration. Tadalafil has a 16-30 minute post-dose onset of action, which is delayed compared to sildenafil and vardenafil.[1,16]

Absorption of both sildenafil and vardenafil is delayed by fatty meals. Therefore, the administration of these drugs should occur roughly 1-2 hours after meals, otherwise this may have a negative effect on their efficacy. Alternatively, they should be taken with a reduced-fat meal.[5,8,12] The serum concentration of sildenafil is decreased by 29%, and that of vardenafil by 18%, when co-administered with high-fat meals, and the time it takes to reach serum concentration is extended by an hour.[5] Tadalafil is unaffected by the intake of fatty meals.[5]

The three agents are primarily metabolised by the cytochrome P450 isoenzyme (CYP3A4), and to a lesser extent CYP2C9, and hence every other agent that inhibits the same enzyme will decrease the clearance and increase the plasma levels of these agents. Known inhibitors of both CYP3A4 and CYP2C9, e.g. bosentan, cimetidine, erythromycin, clarithromycin, ketoconazole, ritonavir, saquinavir, fluvoxamine and amiodarone, as well as known inducers of CYP3A4, e.g. rifampicin and carbamazepine, might alter the plasma levels of these agents.[9]

Therefore, it is advised that the dosage of sildenafil and other related agents should be decreased by 50% in men who are taking a CYP3A4 inhibitor as concomitant therapy.[8,13] Concomitant use of PDE5 inhibitors and nitrates potentiate the hypotensive effects of the latter. Therefore, PDE5 inhibitors are contraindicated in patients receiving organic nitrate therapy.[16] The co-administration of PDE5 inhibitors and antihypertensive agents, especially the α-adrenergic blockers, may cause an additional decrease in blood pressure.[16] Vardenafil has resulted in a decrease in systolic blood pressure (SBP) of 7 mmHg, and in diastolic blood pressure (DBP) of 8 mmHg. A mean decrease in SBP of 4.5 mmHg and DBP of 2.5 mmHg were seen for tadalafil. It is recommended that when the combination of sildenafil and an α blocker is absolutely necessary, there should be a four-hour interval between the administration of the two drugs. Concomitant use of vardenafil and the α blocker is contraindicated, and the same holds true for tadalafil and all of the α blockers, with the exception of tamsulosin. The latter agent has a much greater selectivity for the nonvascular α1A-receptor subtype.[16]

Tadalafil is the longest-acting PDE5 inhibitor. Its efficacy lasts up to 36 hours,[13,16] owing to its long half-life of approximately 20 hours. However, the half-lives of both sildenafil and vardenafil are only four hours, much shorter than that of tadalafil by comparison.[5] This allows patients on tadalafil therapy the opportunity to engage in sexual intercourse for up to 36 hours post dose.[16]

Clinical outcome measures

The efficacy of the PDE5 inhibitors is dosage dependent. Table I provides an overview of the PDE5 inhibitors.[12]

Cardiovascular defects could bring about ED. This relates to the drugs used to treat CVD that cause ED, or because both conditions share common risk factors. PDE5 inhibitors cause

Table I: Dosages of the phosphodiesterase type 5 inhibitors and their effectiveness parameters[12,16]

Drug	Indications	Onset of action (minutes)	Half-life (hours)	Dosage (mg)	Effectiveness (%)
Sildenafil (Viagra®, Dynafil®)	Erectile dysfunction (also indicated for pulmonary arterial hypertension under the trade name of Revatio®)	From as early as 11 minutes, with a median time of 36 minutes[16]	3-5	25-100	56-82
Vardenafil (Levitra®)	Erectile dysfunction	From as early as 16 minutes[16]	4-5	5-20	65-80
Tadalafil (Cialis®)	Erectile dysfunction	16-30 minutes[16] (The effects can last up to 36 hours post dosage)	17.5	2.5-20	62-77

an inhibition of platelet activation in patients with coronary heart disease. They also cause dilatation of the epicardial coronary arteries,[16] and improve endothelial malfunction and vascular supply to the penis.[5] This is achieved via the production of nitric oxide by endothelial cells, which then diffuses into the smooth muscle cells to cause smooth muscle relaxation and resultant vasodilatation.[4] Hence, there is no doubt that the positive "side-effects" of the PDE5 inhibitors play a significant role in the management of ED in diabetes and CVD.[4,5]

Tadalafil was found to be the most effective in treating ED, when compared to the other PDE5 inhibitors. All PDE5 inhibitors are considered to be safe in patients with a normal risk profile,[17] despite the mild variation in their efficacy.

To improve the efficacy of the PDE5 inhibitors used to treat ED, it is important to advise patients that the use of these agents must be accompanied by sexual stimulation. Five to eight doses must be taken before the drug is considered to be a failure in patients who do not respond to the first dosage. Treatment of other co-morbidities that may result from ED should be encouraged.[12]

All three agents have proven to increase the return of spontaneous erections in patients who have undergone nerve-sparing retropubic radical prostatectomy.[5,16] The efficacy in treating patients with ED that is caused by diabetes has been proven with all three agents.[5,16] Diabetes has an effect on both the neuronal and vascular supply of the penis, and this makes it challenging to treat.[5,16] All three of the PDE5 inhibitors have undergone clinical trials for this specific indication, and have shown significantly successful outcomes.[5,16]

Side-effects

Sildenafil and vardenafil have caused visual disturbances, such as high sensitivity to light, loss of blue-green colour discrimination in approximately 2-3% of patients and blurred vision because of their inhibitory activity against PDE6. The latter is an isoenzyme found in the retina, i.e. the photoreceptor cells of retinal rods and cones. Tadalafil has not been found to cause visual disturbances because it has little to no effect on PDE6.[5,13]

Although the adverse effects caused by most PDE5 inhibitors are mild to moderate, facial flushing, headaches, dyspepsia, nasal congestion and dizziness have been reported.[12,13]

Figure 2 provides a comparative profile of the most commonly reported adverse effects of the three PDE5 inhibitors.

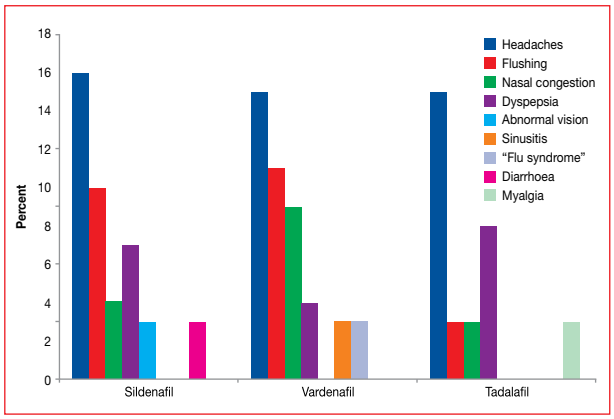


Figure 2: Comparative profile of the most commonly reported adverse effects of the three phosphodiesterase type 5 inhibitors[5]

Patients with refractory erectile dysfunction

More than half of all patients (60-70%) experience treatment success. A smaller percentage (30-40%) does not respond to the use of PDE5 inhibitors alone, and should be counselled on alternative, augmentative treatment options.

These patients should also be assessed according to the following before a diagnosis of treatment failure is made:[5]

- What are their expectations? (Are they realistic?)
- Has the medication been given sufficient time to work? For instance, more than six doses might be required to achieve a satisfactory response with sildenafil.
- Have they taken their medication with a fatty meal? (This is not important with tadalafil).
- Have they undergone a trial with another agent?
- Have they been tested for hypogonadism? (Normalisation with testosterone might significantly increase the response rate to the PDE5 inhibitors).

Conclusion

PDE5 inhibitors are recommended as first-line therapy in patients suffering from ED. However, a small percentage remains refractory to the effects of the PDE5 inhibitors. Sildenafil is also indicated in patients with pulmonary arterial hypertension. Currently, all three of the PDE5 inhibitors are undergoing further testing for other cardiovascular and peripheral vascular conditions.

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