Phosphodiesterase type 5 inhibitors and erectile dysfunction

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Keywords: erectile dysfunction; PDE5 inhibitors; vascular disease

Abstract

Erectile dysfunction (ED) affects millions of men globally and may adversely affect his, and potentially his partners', quality of life. The introduction, a decade ago, of the phosphodiesterase type 5 (PDE5) inhibitors has revolutionised the management of ED. The PDE5 inhibitors have provided an effective and patient-acceptable therapy for ED. They have had a huge impact on public awareness and understanding of this disease. This article provides an overview of erectile dysfunction and the pharmacology, efficacy, safety and optimal use of the PDE5 inhibitors.

SA Fam Pract 2010;52(3): 207-211

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain an erection for satisfactory sexual intercourse.[1] Erectile dysfunction is prevalent, affecting millions of men throughout the world and, despite increased disease awareness, many men remain undiagnosed. ED can impact negatively on an individual's wellbeing, relationships and quality of life.[2] Successful treatment of ED is associated with improvements in mental health and emotional well-being.[3]

Epidemiology

One of the largest surveys, the 1994 Massachusetts Male Aging Study (MMAS), surveyed 1 709 men aged 40–70 years:

- 52% of respondents reported some degree of erectile difficulty, 10% of whom reported complete ED.[4]

This study also revealed a strong correlation between erectile difficulty and advancing age.[5] This data has subsequently been confirmed by numerous other studies.

Pathophysiology and risk factors

Normal male sexual function is a complex integration of psychological, hormonal, vascular and neurological factors. Risk factors or diseases affecting these systems may have a negative impact on erectile function.[6,7] (Table I)

Historically, most cases of ED were thought to be psychologically based but we now understand that most cases have an organic (physical) or mixed cause.[8] Endothelial dysfunction is now understood to be an important cause of erectile dysfunction.[10] Erection is primarily a vascular phenomenon and vascular diseases are the most common cause of ED, including hypertension, dyslipidaemia, ischaemic heart disease, peripheral vascular disease and the sequelae of diabetes mellitus[9, 11]

Table I: Causes of ED[6–9]

Risk factors	Examples
Aging	
Medication	Antihypertensives, antidepressants, digoxin, spironolactone
Lifestyle	Smoking, obesity, sedentary lifestyle, alcohol and drug abuse
Psychological disorders	Depression, performance anxiety or stress
Vascular disorders	Atherosclerosis, ischaemic heart disease, peripheral vascular disease
Neurological disease	Stroke, multiple sclerosis, spinal cord injury, pelvic trauma or prostrate surgery
Endocrine abnormalities	Low testosterone
Chronic illness	Hypertension, dyslipidaemia, diabetes mellitus, cardiovascular disease, chronic renal failure, heart failure, chronic obstructive pulmonary disease

Erectile dysfunction as a marker of cardiovascular disease

ED and cardiovascular disease share many risk factors and a pathophysiology mediated through endothelial dysfunction.[7] Consequently, patients with cardiovascular disease frequently have ED. Conversely, ED is now considered an early symptom of cardiovascular disease and may be a marker of silent vascular disease.[11] It has been proposed that the smaller penile arteries (1–2 mm) suffer from plaque burden earlier than the large coronary (3–4 mm) arteries.[11] **Any asymptomatic man who presents with ED, without an obvious cause, should be screened for vascular disease.**[11]

Phosphodiesterase type 5 (PDE5) inhibitors

There are three PDE5 inhibitors registered in South Africa: Viagra® (sildenafil), Cialis® (tadalafil) and Levitra® (vardenafil). According to the 2006 American Urological Association (AUA) Guidelines, PDE5 inhibitors are considered to be the first line of therapy in the management of ED, unless contra-indicated.

Pharmacology

PDE5 inhibitors are selective, competitive inhibitors of phosphodiesterase type 5, an enzyme which is responsible for cGMP degradation in the corpus cavernosum. By inhibiting cGMP breakdown, PDE5 inhibitors enhance the vasodilatory effect of nitric oxide (NO) and restore the ability to achieve an erection in a patient with ED.[12] Sexual stimulation is required to initiate NO release, therefore PDE5 inhibitors are ineffective without sufficient sexual arousal.[9]

Pharmacokinetics

Sildenafil and vardenafil have similar molecular structures and similar pharmacokinetic profiles. Tadalafil, however, has a substantially different molecular structure and pharmacokinetics, in particular a long half life of 17,5 hours with a duration of action of up to 36 hours.[8,12] (Table II)

Efficacy

All PDE5 inhibitors have proven effective for the management of ED in the general population and in special population groups such as men with diabetes mellitus, spinal cord injury, post-radical prostatectomy, multiple sclerosis, post-radiation therapy for prostate cancer, and depression. Currently, there are few published, head-to-head trials comparing PDE5 inhibitors and there is insufficient data to support the superiority of one agent over the others.[6–7] As sildenafil was the first available PDE5-inhibitor, it has been the most extensively evaluated for safety and efficacy. In a quantitative meta-analysis of 27 trials in 6659 men with ED, a higher percentage of successful sexual intercourse was achieved with sildenafil compared with placebo (57% vs 21% respectively).[16]

Safety

The safety of the PDE5 inhibitors has been extensively evaluated. In clinical trials, the rate of discontinuation was low (< 5%) for all three drugs, with few or no cases of priapism.[8] Extra caution should be taken in patients with reduced clearance of the drug such as hepatic or severe renal impairment, men over 65 years and taking medication which inhibits cytochrome P450 3A4 enzyme (eg: erythromycin, ketoconazole, cimetidine or the protease inhibitors).[8]

Table II: Pharmacokinetic characteristics of the PDE5 inhibitors[8,9,12,*]

Parameter	Sildenafil	Vardenafil	Tadalafil
Doses available	25 mg, 50 mg, 100 mg	5 mg, 10 mg, 20 mg	5 mg once daily, 20 mg
Administration	Take 60 minutes prior to sexual activity	Take 60 minutes prior to sexual activity	Take from 16 min to 30 min prior to sexual activity
Food interaction	Yes, with high fat foods	Yes, with high fat foods. Not affected by a normal meal.	None
Mean time to peak concentration Cmax (minutes)	60	60	120
$T_{1/2}$	3–5hr	4–5hr	17.5hr
Metabolism	Cytochrome P450 3A4	Cytochrome P450 3A4	Cytochrome P450 3A4
> 65 yrs of age	Half life increased, dose adjustment should be considered	Half life increased, dose adjustment required, recommend lower starting dose	Half life increased, no dose adjustment recommended

* Additional references South African Viagra, Levitra and Cialis package inserts

The most common adverse effects are related to peripheral vasodilation, such as flushing, dizziness, headache, dyspepsia and congestion.[8,9,12] Sildenafil can affect the retina via a weak inhibition of phosphodiesterase type 6. This has been associated with 'blue vision' and is less pronounced or absent with the other PDE5 inhibitors.[9] Back pain has been reported for tadalafil and not with the other PDE5 inhibitors.[8,9]

Cardiovascular safety

Effect on myocardial infarction and death

This has been the area of primary concern due to reports of myocardial infarction and death. These concerns have however been ameliorated as extensive controlled and postmarketing studies have not shown an increased rate of myocardial infarction, ischaemic heart disease or mortality in men taking sildenafil.[8,13] Similar results have been reported with tadalafil and vardenafil.[13]

Treatment of ED in a patient with cardiovascular disease is complicated by a small increase in risk of myocardial infarction related to sexual activity.[7] The First (DeBusk et al 2000) and Second (Jackson et al 2006), Princeton Consensus are valuable guidelines, which have been developed for the safe management of ED in patients with cardiovascular disease and are based on the individual patients' risk. These guidelines identify patients who should be evaluated by a cardiologist prior to initiating PDE5-inhibitor therapy.

The Princeton Consensus guidelines state that sildenafil's short half-life makes it the drug of choice in patients with more severe cardiovascular disease as it allows for the earlier use of supportive therapy if needed.[11]

Effect on blood pressure

PDE5 inhibitors promote vasodilation and may cause small drops in arterial pressure. The degree of drop in blood pressure is small and is rarely a concern in healthy individuals but it may be a concern in patients with cardiovascular disease.[13]

Nitrate interaction

Concomitant use of nitrates with PDE5 inhibitors is contra-indicated. This includes occasional, short-acting sublingual nitrates. PDE5 inhibitors can potentiate the vasodilation of nitrates and result in potentially dangerous hypotension.[7,11,13]

Patients' medication history should be reviewed so as to avoid potential drug interactions.

Antihypertensive interactions

PDE5 inhibitors are generally safe in patients taking antihypertensives. When PDE5 inhibitors are administered to patients on antihypertensive medication, beta-blockers, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, there is usually a small or no additional fall in arterial blood pressure.[11] However, the alpha blockers can induce orthostatic hypotension when taken with PDE5 inhibitors.[11,13] It is recommended to start the PDE5-inhibitor at a low dose in patients who have already adjusted to a stable dose of an alpha blocker.[11,13]

Prolongation of the QT interval

Vardenafil prolonged the QT interval slightly in one study and is therefore not recommended in patients taking type 1A antiarrhythmics (procainamide or quinidine) and type 3 antiarrhythmics (amiodarone or sotalol) or in patients with congenital prolonged QT interval.[11,13]

Other safety concerns

Vision

Rare cases (n = 25) of NAION (nonarteritic anterior ischaemic optic neuropathy) have been reported with PDE5 inhibitors. NAION shares a number of risk factors with ED, such as age over 50 years, hypertension, dyslipidaemia and diabetes. No causative link has been established to date.[15]

Hearing

PDE5 inhibitors have been associated with rare (n = 29) reports of sudden hearing loss. The hearing loss was temporary in approximately one third of patients and on-going in the remaining patients at the time of the report. No causal relationship has been demonstrated.[17]

Optimising PDE5-inhibitor therapy

A number of factors may cause PDE5-inhibitor failure, including doctor, patient, and partner-related causes, as well as disease and drug-related causes. Fifty-five per cent of men who were not previously successful with therapy became successful after re-education and counselling.[14] McCullough AR et al[14] made numerous recommendations for optimising therapy. (Table III)

Once an adequate trial has been completed with one drug and modifiable risk factors have been addressed, the patient may be treated with a different PDE5-inhibitor.[7] Currently, there is insufficient data to counsel patients on the likelihood of success with a different PDE5-inhibitor if they have failed an adequate trial with another drug.

Table III: Recommendations for treatment optimisation with PDE5- inhibitors

Control medical and lifestyle risk factors.
Emphasise the need for sexual stimulation.
Titrate dose if lower doses are not effective.
Counsel patients on how to take the drug properly.
Explain that excessive use of alcohol should be avoided, as this can have a negative impact on erectile function.
Manage expectations and inform patient that most patients respond to treatment after one or two doses; some patients may need seven or eight attempts before they are successful. The first few attempts at intercourse may be emotionally charged for both the patient and partner, especially if patients have not been sexually active for a long time.
Discuss side effects.

Conclusion

ED has a strong association with vascular disease. Therefore, patients diagnosed with ED should be routinely screened for underlying cardiovascular diseases. PDE5 inhibitors are first-line therapy for the management of ED and are effective and well tolerated in the majority of patients. Patients taking nitrates should not take PDE5 inhibitors. In the absence of direct comparative data, pharmacokinetic differences, patient preference and clinical experience could be used to select the most appropriate PDE5-inhibitor.

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Further information

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