Tadalafil

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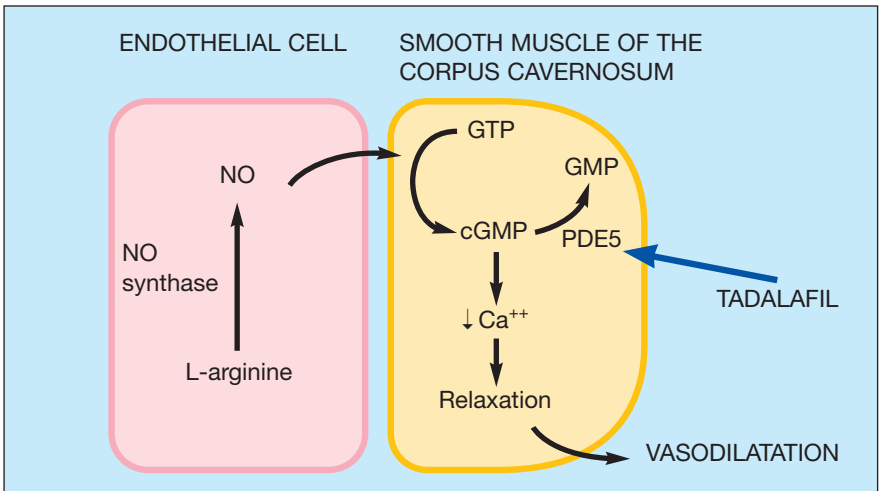
Introduction

Erectile dysfunction affects a significant percentage of men with diabetes, often with mixed aetiology and associated decrease in quality of life. The launch of sildenafil in 1998 and its subsequent widespread clinical use has made a significant impact on the treatment of erectile dysfunction. Phosphodiesterase 5 (PDE5) inhibitors were initially studied as antihypertensive and anti-anginal agents, but it became clear in early healthy volunteer studies that the drug had a potentially greater clinical use in erectile dysfunction, with the first major trial of sildenafil in erectile dysfunction reporting improved erections by 77–84%. Competition to sildenafil followed with the approval of vardenafil, a more selective inhibitor of PDE5 enzyme, and tadalafil, a longer acting PDE5 inhibitor which was first approved for clinical use in 2003.

Figure 1. The pharmacological action of tadalafil (see 'Notes' below the diagram)



NOTES. Nitric oxide (NO) causes an increase in cyclic guanosine monophosphate (cGMP) which reduces the amount of Ca^{++} (calcium) in vascular smooth muscle of the corpus cavernosum in the penis, resulting in vasodilatation and an erection. Tadalafil, like other PDE5 inhibitors, works by blocking the breakdown of cGMP to the inactive GMP. (GTP: guanosine-5'-triphosphate.)

Pharmacology

Figure 1 outlines the pharmacological action of tadalafil. Like all PDE5 inhibitors it potentiates the effect of nitric oxide (NO) released in response to sexual stimuli. NO causes vasodilatation within the corpus cavernosum in the penis, thereby achieving erection. The effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is broken down by PDE5. Blockade of PDE5 thus potentiates NO-mediated erectile response. The longer duration of action of tadalafil (up to 36 hours) and prolonged half-life (17.5 hours) with onset of action within one hour makes it suitable for once daily dosing. The drug is excreted by the kidneys and dosage therefore has to be reduced in renal impairment. Pharmacological interactions can occur with other medications metabolised by the cytochrome P450 enzyme such as the azole antifungals and erythromycin. As the duration of action of tadalafil is around eight times longer than the other PDE5 inhibitors, adverse effects with concurrent nitrate use can be prolonged.

Trials of safety and efficacy

The efficacy and safety of tadalafil in men with erectile dysfunction were first assessed in a multicentre, double-blind, placebo-controlled study published in 2001.[1] A total of 179 men (mean age 56 years) were randomised to receive placebo or tadalafil at doses of 2, 5, 10 or 25mg, taken on demand over a three-week period. Significant improvement was noted in responses to the International Index of Erectile Function (IIEF) questionnaire. No significant changes in laboratory values, ECGs, or blood pressure were observed.

In a subsequent trial of 1112 men with a mean age of 59 years (range 22–82 years) and mild to severe erectile dysfunction of various aetiologies randomised to placebo or tadalafil, the drug was consistently efficacious across disease severities, aetiologies and all age profiles.[2] Tadalafil was well tolerated, with headache and dyspepsia the most frequent adverse events. Efficacy and safety data have been reproduced in various ethnicities including Japanese, Eastern European, Western European, South East Asian and North American men.

Clinical trials of tadalafil have excluded patients with unsuccessful

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prior treatment with sildenafil, raising questions about its superior efficacy. A retrospective analysis of pooled data from 14 tadalafil clinical trials examined the effect of this exclusion by comparing efficacy results in 1349 sildenafil naïve patients with efficacy results in 1440 patients previously responsive to sildenafil.[3] For most efficacy outcomes, responses in the naïve group (probable mix of responders and non-responders) were not statistically different from responses in the prior-responder group. The similar responses of these two patient groups observed in this *post-hoc* analysis suggest that exclusion of sildenafil non-responders in previously reported tadalafil clinical trials may not have substantially affected efficacy outcomes.

Specific evidence for use in diabetes

A recent Cochrane review evaluated eight studies with 976 men randomised to PDE5 inhibitor therapy.[4] All but one of these studies, which lasted for 16 weeks, had a duration of 12 weeks. Six studies used sildenafil, one study vardenafil and one study tadalafil. Compared to placebo, these agents showed favourable effects in scores estimating the quality of sexual life. This review concluded that PDE5 inhibitors comprise a valuable treatment option for erectile dysfunction in men with diabetes, but recognised that there were no head-to-head comparisons between the three available PDE5 inhibitors, and no trials comparing them with other available therapeutic options.

In the study of tadalafil used as part of the aforementioned Cochrane review, treatment with the drug significantly improved responses in men with type 1 or type 2 diabetes and a minimum three-month history of erectile dysfunction who were randomly allocated to one of three groups: placebo (n=71), tadalafil 10mg (n=73), or tadalafil 20mg (n=72).[5] The improvements were regardless of baseline HbA_{1c} level and treatment with tadalafil did not alter mean HbA_{1c} levels. Tadalafil was well tolerated, with headache and dyspepsia being the most frequent adverse events with active treatment.

Discussion

Prospective trials comparing tadalafil with sildenafil have shown patient preference for the longer acting tadalafil, thought to be related to the flexibility with timing of intercourse. However, analysis of prescription data from the UK has shown that patients on sildenafil were less likely to switch their PDE5 inhibitor than those on tadalafil. Giving patients with erectile dysfunction the opportunity to try all three available PDE5 inhibitor drugs has been shown to improve long-term treatment adherence. Tadalafil is one of three PDE5 inhibitors available. The choice of agent and response are likely to be influenced by the individual patient. However, PDE5 inhibitors as a class of drug have not been shown to be effective in men with diabetes and severe erectile dysfunction, where alternative strategies may be preferred.

Interestingly, there are also some emerging data that suggest PDE5 inhibition with tadalafil may improve beta-cell function. This, along with ongoing work looking at the potential use of tadalafil in idiopathic pulmonary hypertension (where sildenafil is currently used), means that tadalafil may have an interesting future ahead with indications outwith erectile dysfunction.

Key points

- Erectile dysfunction is a common problem in patients with diabetes
- PDE5 inhibitors may have a therapeutic benefit for men with diabetes and erectile dysfunction
- Tadalafil is a long acting PDE5 inhibitor which has theoretical advantages over its competitors because it has a fast onset of action but a sustained effect; however, there are no head-to-head trials comparing the efficacy of the three available PDE5 inhibitors

Conflict of interest statement

There are no conflicts of interest.

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