Cialis (tadalafil): a new treatment for erectile dysfunction

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Oral phosphodiesterase inhibitors have become the mainstay of treatment for erectile dysfunction. A novel and potent phosphodiesterase inhibitor, tadalafil, known as Cialis, has been introduced in the UK as an alternative to the other currently available phosphodiesterase inhibitors for the treatment of erectile dysfunction.

Erectile dysfunction (ED) is defined as the inability to achieve and maintain a penile erection adequate for satisfactory sexual intercourse (National Institutes of Health, 1992). It is estimated to currently affect approximately 2.3 million men in the UK, however, this is projected to more than double by the year 2025 (Aytac et al, 1999).

Men with cardiovascular disease and diabetes mellitus appear to be more prone to this condition, with up to 75% of diabetic men suffering from ED. Data from clinical trials suggest that drugs such as sildenafil (Viagra, Pfizer, Sandwich, Kent) have reduced efficacy in men with diabetes and vasculogenic ED compared to those with other medical conditions (Rendell et al, 1999). Therefore the search has been on to find a more potent, selective and efficacious phosphodiesterase type 5 (PDE-5) inhibitor to treat male ED.

THE PHYSIOLOGY OF ERECTION

In the erectile process, a cascade of events leads to the production of the chemical messenger cyclic guanosine monophosphate (cGMP). cGMP allows blood vessels in the penis to relax, increasing blood flow and thereby promoting an erection. An enzyme called PDE-5 breaks down cGMP, thus reducing blood flow, which in turn reverses or prevents an erection.

In the penis the predominant phosphodiesterase type is the PDE-5 isoform, although 11 isoforms of the enzyme have been described in mammalian tissues. Oral ED treatments, known as PDE-5 inhibitors, block the breakdown of cGMP by the PDE-5 enzyme. In this way they reinforce the erectile process, helping men with ED to attain and maintain an erection.

As competitive inhibitors of PDE-5 drugs including sildenafil and vardenafil (Levitra, Bayer, Newbury) have a similar chemical structure to cGMP. The chemical structure of tadalafil (Cialis, Lilly-Icos, Indianapolis, USA) is different to the other competitive PDE-5 inhibitors (*Figure 1*).

POTENCY AND SELECTIVITY

The ideal PDE inhibitor for the treatment of ED should be potent and have a high selectivity for PDE-5. Potency is most commonly expressed as the IC_{50} of the drug, i.e. the concentration of a drug in vitro required to inhibit 50% of a measured response, e.g. enzyme activity.

In the case of PDE-5 inhibitors, the lower the IC_{50} the more potent the drug is in vitro and therefore less of the drug is required to inhibit PDE-5. However, this does not always mean that a more potent drug will have greater efficacy. Efficacy of a drug is a measure of its clinical or in-vivo effects and therefore does simply depend on the potency of a drug in vitro but also its pharmacokinetic profile, i.e. its absorption, distribution and metabolism within the body.

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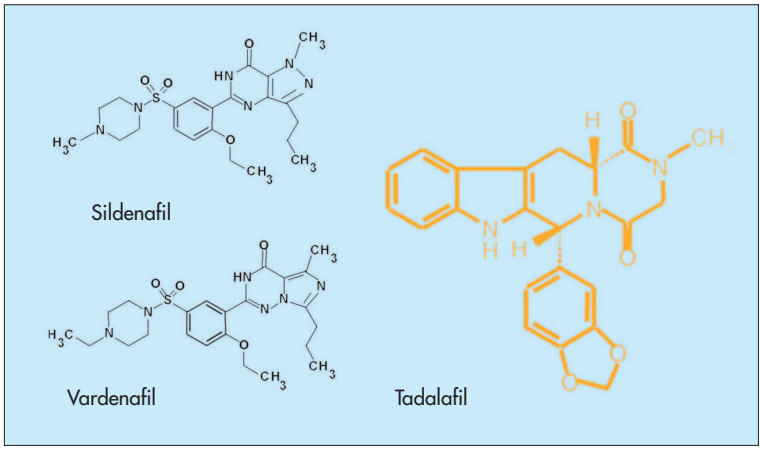
Figure 1. The chemical structures of the phosphodiesterase type 5 (PDE-5) inhibitors.



The selectivity of a drug is the relative activity of a drug between different receptor types or isoenzymes. For competitive antagonists such as the PDE inhibitors, selectivity can be expressed by the ratio of IC_{50} values for each PDE isoenzyme. Selectivity is the main factor determining the side-effect profile of a drug. Therefore, PDE inhibitors used for ED should have a high selectivity for PDE-5, thereby minimizing their side effects on other PDEs present in the body.

TADALAFIL IN MALE ED

Tadalafil is a potent, reversible and selective PDE-5 inhibitor, which has been available in the UK from February 2003.

Potency and selectivity

In-vitro studies show that tadalafil has an IC_{50} of 0.9 nM for inhibition of PDE-5 (Angulo et al, 2001) (*Table 1*). Although this is lower than comparative values for sildenafil, there appears to be considerable variation in reported values of IC_{50} for currently available PDE-5 inhibitors (Corbin and Francis, 2002). However, tadalafil has a 780-fold greater selectivity for human PDE-5 over the retinal or PDE-6 isoenzyme. Furthermore, greater concentrations of tadalafil are needed for any appreciable inhibition of other human PDEs (it is over >10 000-fold more selective for PDE-5 than for PDEs 1–4 and 7–10) (Angulo et al, 2001). This suggests that the side-effect profile of tadalafil may be less extensive than that of sildenafil.

Pharmacokinetics

In pharmacokinetic studies in healthy volunteers, tadalafil 20 mg was found to be rapidly absorbed with a mean time to maximum drug concentration (T_{max}) of 2 h and a half life ($t_{1/2}$) of 17.5 h (Patterson et al, 2001b) (*Table 2*). The mean plasma concentrations are sufficient to exceed the IC_{50} of tadalafil within 30 minutes of taking the drug. The drug appears to be effective up to 24–36 hours post dosing (Patterson et al, 2001b) and is consistent with rigiscan studies (a quantitative measure of penile rigidity). The mean plasma concentration in one study was 113 mg at 1 hour compared to 69 mg 24 hours post dosage, suggesting that the duration of action of tadalafil may be prolonged compared to other PDE inhibitors (the duration for sildenafil is up to 8 hours, and the duration for vardenafil is not known yet).

Tadalafil is predominantly eliminated by the liver, but studies have suggested no significant effects of hepatic/renal impairment, age or gender on its pharmacokinetics. Alcohol and food had no clinically significant effect on the pharmacodynamic data for tadalafil (Patterson et al, 2001a).

TABLE 1.
In-vitro IC_{50} values for phosphodiesterase type 5 inhibitors

	IC_{50} values (nM)
Sildenafil	3.5
Vardenafil	0.7
Tadalafil	0.9

TABLE 2.
Pharmacokinetic profiles of currently available phosphodiesterase type 5 inhibitors

	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$(h)
Sildenafil	560	0.8	3.7
Vardenafil	209	0.7	3.9
Tadalafil	378	2.0	17.5

modified from Corbin and Francis (2002). C_{max} = maximum plasma concentration; $t_{1/2}$ = half life; T_{max} = time to maximum concentration.

Clinical trials

Two phase III multicentre drug trials have been published assessing the efficacy of tadalafil. In one study, 179 men were randomized to receive placebo or tadalafil in doses of 2, 5, 10 or 25 mg (Padma-Nathan et al, 2001). The study took place over a 3-week period. Men with a history of untreated endocrine disease, premature ejaculation, radical prostatectomy, significant cardiovascular and neurological disease and diabetes mellitus were excluded from the study. Efficacy was evaluated by recording changes in International Index of Erectile Function (IIEF) scores, Sexual Encounter Profile (SEP) and post-treatment global assessment question (GAQ) on the impact of treatment on their erections.

Tadalafil significantly increased IIEF question 3 (penetration) at all doses and question 4 (maintenance of erection after penetration) at all doses except the 2 mg dose. Overall treatment increased the mean percentage of intercourse attempts and lead to an improvement in quality of erections compared to placebo.

In a larger five centre randomized, double blind, placebo-controlled drug trial, a total of 1112 men with mild-to-severe ED of various aetiologies received placebo or tadalafil at fixed daily doses ranging from 2.5 to 20 mg (Brock et al, 2002). Men with unstable cardiovascular disease, ED following radical prostatectomy, pelvic surgery, cerebrovascular accident and spinal cord trauma were excluded from the study. Patients were instructed to administer treatment before sexual activity, without restrictions on food or alcohol intake.

Compared with placebo, tadalafil at doses from 5 to 20 mg significantly enhanced erectile func-

tion as measured by IIEF, SEP and GAQ (*Figure 2*). Dose escalation with tadalafil improved all major efficacy variables compared to placebo. Overall mean IIEF increased by 7.9 with tadalafil 20 mg, with 59% of patients reporting normal erectile function (erectile function domain greater than 26) compared to 11% of controls (*Figure 3*).

There was also a significant improvement in the proportion of affirmative responses to SEP question 2 (ability to penetrate) and SEP question 3 (ability to maintain erection and complete intercourse) in tadalafil-treated men compared to placebo. Treatment with tadalafil 20 mg led to successful intercourse as early as 30 minutes, but even when attempted up to 36 hours after dosage. Tadalafil was equally efficacious irrespective of the primary aetiology of ED or the patient's age.

Some PDE inhibitors appear to be less efficacious in patients with diabetes mellitus. A prospective placebo-controlled trial has assessed the efficacy of tadalafil 10 and 20 mg in 216 patients with type 1 and 2 diabetes mellitus. Primary efficacy was indicated by an improvement in the ability to engage in sexual activity as assessed by GAQ (question 1 and 2) and increasing the percentage of patients with positive responses to SEP (question 2 and 3) with both doses compared to placebo (Saenz De Tejada et al, 2001). Furthermore, both doses increased IIEF erectile function domain score by 6.4 and 7.3 with tadalafil 10 and 20 mg respectively (*Figure 4*). This was compared to a placebo increase of 0.1.

Interestingly, IIEF erectile function domain scores increased independent of the type of diabetes, diabetic therapy or level of glycaemic control. Although these initial results suggest that tadalafil is efficacious in men with ED secondary to diabetes mellitus, clinical efficacy has to be further assessed in phase IV longitudinal studies.

Similarly, men with hypertension appear to be more prone to ED. In hypertensives tadalafil 2.5–20 mg improved primary efficacy parameters of sexual function as assessed by GAQ, IIEF and SEP over a 12-week on-demand treatment period. Tadalafil appeared equally efficacious in men with or without hypertension, regardless of whether or not they were taking concomitant antihypertensive therapy. The incidence of adverse events was no different in men with a history of hypertension.

Clinical safety

Sildenafil potentiates the effects of nitrates, with significant reductions in blood pressure occurring in volunteers and for this reason is contraindicated in patients taking organic nitrates, e.g. those with angina (Padma-Nathan et al, 2001). Patients with cardiac disease are also warned of the potential risks of exercise on the heart and case reports have been described of myocardial ischaemia occurring after use of sildenafil (Jackson et al, 2002).

In a randomized placebo controlled trial 80 healthy volunteers taking tadalafil 20 mg for 10 days experienced no statistically significant differences in blood pressure or heart rate compared with placebo. The incidence of myocardial infarction and cardiac death was low (six deaths) and similar to that of patients treated with placebo (Hutter et al, 2002).

Furthermore, tadalafil has been used to safely treat ED in men with stable cardiovascular conditions, indicating it is safe to use in this subgroup. Tadalafil appears to be safe in men with concurrent cardiovascular disease (Hutter et al, 2002). A total of 1328 patients in phase III clinical trials with at least one cardiovascular risk factor were analysed, including those with

Figure 2. Percentage of positive responses to global assessment question: 'has the treatment you have been taking improved your erections'. Modified from Brock et al (2002).

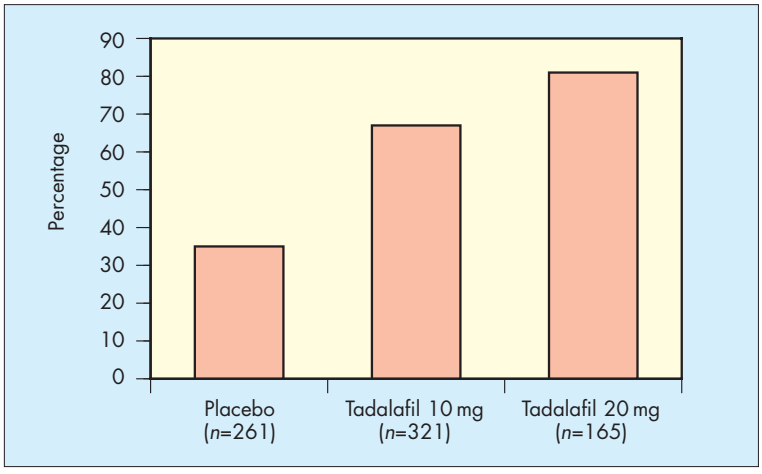
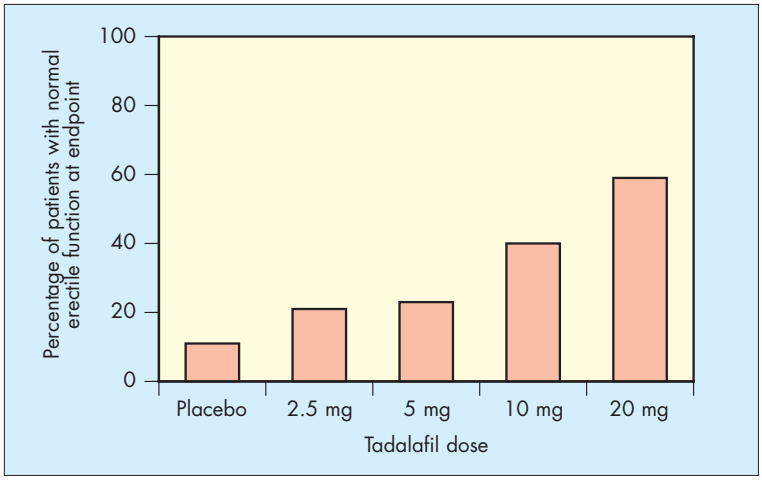


Figure 3. Percentage of patients with normal erectile function at endpoint. Normal defined as International Index of Erectile Function erectile function domain score > 26.



hypertension, diabetes mellitus and hyperlipidaemia. The incidence of cardiovascular events was not statistically significantly different from those receiving placebo (Hutter et al, 2002).

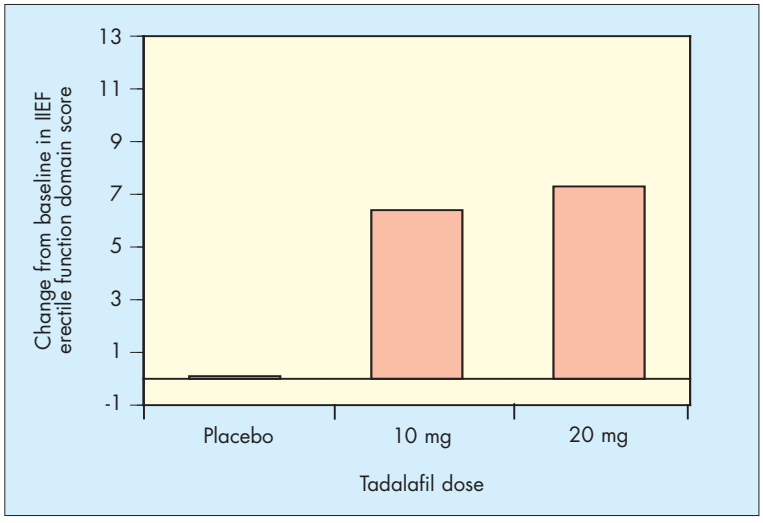
A pharmacodynamic study reports the interaction of nitrates with tadalafil (Kloner et al, 2002). In this double-blind, randomized, three-way, cross-over study the haemodynamic effects of co-administration of sublingual nitroglycerin or isosorbide mononitrate with tadalafil 5 or 10 mg was assessed in patients with chronic stable angina. Although there were no serious adverse events in this study group related to hypotension, there were some patients in whom tadalafil augmented the decrease in blood pressure induced by nitrates. For this reason co-administration of nitrates with tadalafil is contraindicated.

Adverse effects

PDE-5 is found in most vascular and visceral smooth muscle cells. Consistent with this the reported side effects of tadalafil are related to the distribution of PDE-5 within the body. The commonest adverse events reported are headache and dyspepsia followed by back pain, nasal congestion, myalgia and flushing (Brock et al 2002) although only 2.1% of patients discontinued therapy as a result of adverse events compared to 1.3% in the placebo group.

Tadalafil-related side effects decrease in frequency with continued administration and, consistent with available in-vitro data, tadalafil exerted no clinically significant effects on vision.

Figure 4. The effect of tadalafil on the International Index of Erectile Function (IIEF) erectile function domain score in diabetic patients. Modified from Saenz De Tejada et al (2002).



KEY POINTS

- Tadalafil is a potent, selective novel phosphodiesterase type 5 inhibitor.
- It is safe and well tolerated in a wide spectrum of men with erectile dysfunction.
- Tadalafil has a rapid onset and prolonged duration of action of up to 24 hours.
- It has no interactions with food.
- It is highly effective in improving erectile function across a broad range of aetiologies including diabetes mellitus.

CONCLUSIONS

Tadalafil is a novel PDE-5 inhibitor, which is safe and well tolerated in a wide spectrum of men with ED, including those with diabetes mellitus and stable cardiovascular disease. It has a relatively rapid onset of action and a prolonged duration of action of up to 24 hours in clinical practice.

Although clinical studies suggest that tadalafil is a highly efficacious oral pharmacotherapy for the treatment of male ED, phase IV clinical drug trials are needed to fully determine this. Furthermore, comparative studies are needed to assess if the in-vitro data supporting the role for tadalafil are replicated in clinical studies, ideally with head to head studies with the other currently available PDE-5 inhibitors. HM

Conflict of interest: none.

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