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TADALAFIL (CIALIS®) LATEST OPTION FOR THE TREATMENT OF ERECTILE DYSFUNCTION

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Introduction

The National Institute of Health (NIH) has defined erectile dysfunction (ED) as the inability to achieve or maintain an erection sufficiently rigid for satisfying sexual intercourse.[1] Under this definition, it is estimated that greater than 150 million men worldwide suffer from this condition.[2,3] However, some experts question this definition as it may be too broad to truly evaluate the population affected. The definition encapsulates those unable to attain an erection, those unable to maintain an erection, and the subjective judgment of 'satisfactory' intercourse. It is important to keep this in mind as we evaluate the available studies pertaining to ED, in order to appropriately identify the populations being treated which may impact our ability to extrapolate data to our clinical practices.

Tadalafil (Cialis®) is the third phosphodiesterase 5 (PDE5) inhibitor approved by the FDA for the treatment of ED. It is being marketed by Lilly and received approval in December 2003. Unfortunately, there is a lack of head-to-head comparisons between taladafil and the other available PDE5 inhibitors. Therefore, in order to chose the best option for a particular patient, it is important to understand the potential risks and benefits attributed to each medication. In this article we will discuss the safety, efficacy and tolerability of tadalafil. At the same time, we will explore the pharmacokinetic and pharmacodynamic differences that distinguish tadalafil from the other PDE5 inhibitors.

Mechanism of Action and Pharmacokinetics

In the presence of sexual stimulation, nitric oxide (NO) is responsible for initiating a cascade of events that ultimately leads to an erection. Nitric oxide activates guanylyl cyclase, which converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). cGMP is responsible for relaxation of smooth muscle in the corpus cavernosum of the penis allowing the inflow of blood responsible for the erection. Tadalafil selectively inhibits PDE5, which is the enzyme responsible for the catabolism of cGMP, leading to increased concentrations of cGMP in the corpus cavernosum. Since tadalafil has no direct relaxant effect on smooth muscle, it cannot cause an erection in the absence of sexual stimulation-mediated release of cGMP.[4]

Tadalafil reaches its maximum plasma concentration (C_{max}) approximately 2 hours after a single oral dose.[5] Its absorption is not affected by food intake, age, diabetes or mild to moderate hepatic insufficiency.[6] Comparatively, vardenafil and sildenafil achieve lower $C_{max's}$ when administered with a high fat meal, and should be initiated at lower doses in the elderly.[7] This allows for a more convenient administration regimen with tadalafil when compared to other PDE5 inhibitors. Tadalafil's onset of action is between 16 and 45 minutes.[7] Once absorbed, it is widely distributed to the tissues (Vd=62.6L) and protein binding is 94% at therapeutic concentrations. It has a half-life of 17.5 hours, with an effective duration of action of approximately 36 hours,[5] allowing for a for a longer dosing interval than current PDE5 inhibitors. Me-

Table 1. Comparison of PDE5 inhibitors in regards to selected parameters

Parameter	Tadalafil	Sildenafil	Vardenafil
High fat meals	none	C_{max} ? 29%	C_{max} ? 18% to 50%
Half-life (hours)	17.5	4	4 - 5
Metabolism	CYP 3A4	CYP 3A4	CYP 3A4
Active Metabolites	No	Yes*	Yes†
Available doses	5 mg, 10 mg, 20 mg	25 mg, 50 mg, 100 mg	2.5 mg, 5 mg, 10 mg, 20 mg

PDE5=phosphodiesterase 5, C_{max}=peak plasma concentration. *accounts for 20% of activity †accounts for 7% of activity

tabolism is via the CYP3A4 isoenzyme to an inactive metabolite.[8] It is recommended that those taking potent CYP3A4 inhibitors should not exceed a maximum daily dose of 10 mg every 72 hours. Tadalafil is excreted predominantly as inactive metabolites in the feces (approx. 61%) and to a lesser extent in the urine (approx. 36%).[8] A brief profile of the three PDE5 inhibitors is listed in Table 1.

Clinical Trials

Relatively few clinical trials have been completed with tadalafil to date. Some prominent trials include: a general safety and efficacy study of tadalafil versus placebo,[9] a similar study that included only men with diabetes,[10] and a third that evaluated its efficacy at 24 and 36 hours after dosing versus placebo.[7]

Tadalafil versus placebo

Padma-Nathan and colleagues[9] randomized 179 men (mean age 56y) to placebo or tadalafil 2 mg, 5 mg, 10 mg and 25 mg respectively. The International Index of Erectile Function (IIEF) and Sexual Encounter Profile (SEP) were used to measure primary outcomes versus baseline. Both questionnaires were completed after each sexual encounter. All four of the tadalafil groups had significantly greater SEP scores in regards to whether or not they, 'were able to insert their penis into their partner's vagina,' while only the 5, 10 and 25 mg groups reported significantly greater scores in, 'completing intercourse with ejaculation,' (p=0.0005).

As for the IIEF outcomes, all four treatment groups had significant increases in erectile function, orgasmic function, sexual desire and overall satisfaction (p=0.05). Moreover, only the 5, 10 and 25 mg groups had significant increases in overall intercourse satisfaction (p=0.05). Results from this trial are summarized in Table 2. Reported adverse events in this trial were minimal, with only headache, dyspepsia and back pain being reported in > 3% of the men. Only seven subjects withdrew from the study, two of those were related to adverse events. The authors concluded that tadalafil is a safe and effective treatment for ED in doses up to 25 mg.

Porst and colleagues[7] evaluated the safety and efficacy of 24- or 36-hour post dose intervals of tadalafil 20 mg or placebo. This multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 348 men (mean age 57y) used a SEP to record subject's attempts at intercourse and results from intercourse attempts. The authors concluded that both the 24-hour and 36-hour post dose tadalafil groups had more successful attempts at intercourse than placebo (52.9% and 59.2%, respectively). On the other hand, only 29.1% and 28.3% of men were successful in the placebo groups. Adverse events in this trial were similar to others that involved PDE5 inhibitors, with headache (8%), flushing (5.7%), dyspepsia (5.1%) and myalgia (3.4%) occurring more often in the treatment group.

Tadalafil versus Sildenafil

Govier and colleagues[11] conducted a randomized, double-blind, crossover trial of tadalafil versus sildenafil. Two hundred and fifteen men (mean age 49.8y) were randomized to receive either tadalafil 20 mg or sildenafil 50 mg in a four-week interval, before switching to the alternative treatment. This study found that tadalafil was the preferred treatment group in 66.3% of men, while 33.7% of men preferred sildenafil. Patient's prefer-

Table 2. Efficacy outcomes for tadalafil versus placebo[*]

Outcome	Placebo (n=35)	2 mg (n=35)	5 mg (n=37)	10 mg (n=36)	5 mg (n=36)
Ability to insert	(-0.3)	0.6[†]	1.2[‡]	1.0[‡]	1.3[‡]
Ability to complete	0.2	0.8	1.4[‡]	1.7[‡]	1.7[‡]
Erectile Function	1.0	4.1[§]	7.3[‡]	7.8[‡]	9.4[‡]
Orgasmic Function	0.2	1.7[§]	2.0[†]	1.3[§]	2.1[‡]
Sexual Desire	(-0.2)	0.6[§]	0.9[§]	0.9[§]	1.0[‡]
Intercourse Satisfaction	1.3	2.5	3.4[†]	3.2[‡]	4.2[‡]
Overall Satisfaction	0.3	1.8[§]	2.5[‡]	2.5[‡]	3.7[‡]

[*] Figures shown represent mean changes from baseline in SEP and IIEF scores.
[†] $p = 0.005$ vs placebo. [‡] $p = 0.0005$ vs placebo. [§] $p = 0.05$ vs placebo.

ence did not differ between age, duration of treatment, treatment sequence, or previous exposure to sildenafil. It was presumed by the author's that patient preference was probably based on the longer effective window for tadalafil that allowed a more 'natural' sexual encounter, as opposed to a planned encounter, and the fact that taking it without regard of food consumption allows for a simpler administration schedule. This study also showed similar adverse events including headache, dyspepsia, nasopharyngitis and flushing occurring in > 3% of subjects, with no significant differences between the two treatment groups.

Adverse Events

The most frequently reported adverse effects (=2% reported) associated with tadalafil are listed in Table 3. The majority of the events were classified as either mild or moderate in severity. With regards to the myalgias and pain, no underlying cause was elucidated, <5% of all reports were classified as severe, and they were all treated successfully with NSAIDs.

Rare cases of prolonged erection (>4 hours) or priapism (painful erection lasting >6 hours) have occurred in patients taking PDE5 inhibitors. It is important to note that an erection lasting >4 hours can cause irreversible erectile tissue damage, and people with this condition should seek medial attention.[8]

Interactions

Tadalafil is contraindicated in those patients who are concomitantly receiving nitrates or alpha-blockers (excluding tamsulosin 0.4 mg once daily) because it has the potential to greatly increase the hypotensive effects of these agents. It is also contraindicated in anyone with a known hypersensitivity to tadalafil or any of its components. In clinical trials, tadalafil has been co-administered with other classes of antihypertensive agents, with none resulting in a greater than 8/4 mm reduction in blood pressure. None of the changes in these studies were concluded to be of clinical significance.

Patients on potent inhibitors of the CYP 3A4 isoenzyme should limit their tadalafil dose to 10 mg every 72 hours. In clinical trials, the area under the curve (AUC) increased 312% and 124%, with ketoconazole and ritonavir, respectively.

Administration

The recommended starting dose of tadalafil is 10 mg taken one-half to four hours prior to anticipated sexual activity. The dose may be titrated to 20 mg, or decreased to 5 mg on an individual basis, and may be dosed everyday in most populations. Tadalafil may be given without regards to meals, and is not affected by co-administration of antacids or H_2-antagonists.[8]

Patients who have mild to moderate hepatic impairment should be limited to an oral dose of 10 mg daily. For those with severe disease, tadalafil is not recommended. For renal insufficiency, it is recommended that those with a creatinine clearance (CrCl) of less than 30 ml/min should be limited to 5 mg daily. For those with a CrCl between 31 and 50 ml/min, it is recommended to start at 5 mg, with a maximum dose of 10 mg every 48 hours.

Table 3. Number of adverse events with tadalafil versus placebo[8]

Adverse Event	Placebo (N=476)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=394)	Tadalafil 20 mg (N=635)
Headache	5%	5%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back Pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal Congestion	1%	2%	3%	3%
Flushing	1%	2%	3%	3%
Pain in limbs	1%	1%	3%	3%

Cost

The average retail cost for ten comparable doses of the available PDE5 inhibitors is $103 ($95.95-$108.33) for tadalafil, $105 ($102.95-$108.34) for sildenafil, and $96 ($87.99-$103.03) for vardenafil.[12]

Summary

In clinical trials, tadalafil is well-tolerated by about 70% of patients and appears to be a good option for patients who suffer from ED. It has an effective duration of 36 hours, which may provide an advantage over the other available PDE5 inhibitors, allowing it to be given once every 36 hours. More trials are needed before any PDE5 inhibitor is determined to be the drug of choice for ED.

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