

Clinical Pharmacology of Phosphodiesterase 5 Inhibitors in Erectile Dysfunction

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Abstract

The drugs active on erectile dysfunction in humans are now mainly phosphodiesterase 5 inhibitors, those that are marketed are Sildenafil, Vardenafil, Tadalafil, and Avanafil. We propose a synthesis of the pharmacological, pharmacokinetic and clinical properties of these derivatives. We have also listed their most common side effects and their potential drug interactions.

Keywords: Phosphodiesterase 5 inhibitors, Sildenafil, Vardenafil, Tadalafil, Avanafil.

Introduction

Phosphodiesterase 5 (PDE 5) inhibitors are a type of targeted therapy used to treat people with pulmonary hypertension (PH) [1]. Targeted therapies slow the progression of PH and may even reverse some of the damage to the heart and lungs. There are two types of PDE 5 inhibitor currently used to treat PH: sildenafil, tadalafil [2].

PDE 5 inhibitors are also used to treat erectile dysfunction [3]. This is because the body has the same type of cells in the blood vessels of the lungs as the blood vessels of the penis. Viagra (sildenafil) has been used to treat erectile problems since 1998.

In case of erectile dysfunction it is essential to determine the cause of the difficulties to obtain or maintain an erection. These problems are common and can be solved effectively by consulting a doctor and following a suitable treatment. Unless there are more serious causes of erectile dysfunction, the recommended treatment will usually be a PDE5 inhibitor. PDE5 inhibitors are a particularly effective type of drug treatment, minimally invasive (oral dosage), with a low risk of side effects.

What is a PDE5 Inhibitor?

PDE 5 inhibitors block a particular enzyme (phosphodiesterase type 5), found in blood vessel walls [4]. PDE5 helps control blood flow to the pulmonary arteries. By stopping PDE5 from working, PDE 5 inhibitors (sildenafil and tadalafil) cause the blood vessels to relax. This increases blood flow to the lungs and lowers blood pressure.

With PDE5 inhibitors, it is possible to restore the natural erectile response in more than 70% of patients with erectile dysfunction. These PDE5 inhibitors can be used to treat all types of impotence, regardless of the cause of the disorder.

Sexual stimulation stimulates the release of NO by the endothelium and non-noradrenergic, non-cholinergic (NANC) parasympathetic fibers (rich in neuronal NOS) [5]. The NO diffuses cavernous bodies through the smooth fibers and binds to the hemic fraction of soluble guanylate cyclase, which stimulates cyclic GMP synthesis (cGMP). This cGMP is an important messenger in calcium signal transduction in the smooth fibers of cavernous bodies. cGMP reduces free sarcoplasmic calcium levels by binding to a cGMP-dependent protein kinase and a cGMP-dependent calcium channel [6]. This decrease in calcium promotes the relaxation of the smooth fibers of the arteries and cavernous bodies, allowing the expansion of sinusoidal spaces and erection. By inhibiting PDE5, the enzyme responsible for cGMP catabolism, sildenafil increases NO. Since sexual stimulation is necessary to initiate NO release, sildenafil is ineffective in the absence of this stimulation [7].

PDE5 is the predominant isoform of phosphodiesterase in the smooth muscle of cavernous bodies. It is found in the smooth muscle fibers of other vessels especially

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pulmonary. The effects of PDE5 inhibition on pulmonary arterial hypertension are under study. The effects on asthma are rather related to PDE4 inhibitors, which are involved in bronchial inflammation and contraction of bronchial smooth muscle fibers

Different Drugs Used to Treat Erectile Dysfunction

The most commonly used PDE5 inhibitor drugs are sildenafil, vardenafil, tadalafil, and avanafil [8]. These medications themselves do not produce erections in men, but allow them to achieve an erection and maintain this erection when there is sexual stimulation. PDE5 inhibitor tablets have no effect in men with decreased libido and unable to produce a satisfactory erection.

Sildenafil

Sildenafil preferentially inhibits PDE5 and to a lesser extent PDE6 (retina) [9] while it has no effect on PDE3 (heart). In vitro studies indicate that sildenafil is only 10-fold more selective for PDE5 than PDE6, while it is 4000 times more selective for PDE5 than PDE3. Sildenafil has no direct muscle relaxant effect on isolated tissue of the human cavernous body. Rather, it enhances the effect of NO by inhibiting PDE5, the enzyme responsible for biodegradation of cGMP in cavernous bodies. During the local release of NO following sexual stimulation, the inhibition of PDE5 by sildenafil produces an increase in the concentration of cGMP in the corpora cavernosa, hence the relaxation of the smooth muscles they contain and the influx of blood into the penis [10]. Sildenafil given at the recommended doses has no effect in the absence of sexual stimulation. In vitro studies have shown that sildenafil has an affinity 10 to 10 000 times greater for PDE5 than for other phosphodiesterase's (including PDE1, PDE2, PDE3, PDE4 and PDE6) and that it acts at least 700 times more on PDE5 than on PDE7 to 11. More precisely, the affinity of sildenafil for PDE5 is more than 4000 times higher than its affinity for PDE3, the cAMP-specific phosphodiesterase that participates at the regulation of cardiac contractility. In addition, the effect of sildenafil is approximately 10 times more potent on PDE5 than on PDE6, an isoenzyme found in the retina. This low affinity for PDE6 may explain abnormalities in color discrimination observed with high doses of sildenafil or in the presence of high plasma concentrations of the drug.

PDE5 is also present in low levels in platelets, smooth vessels and viscera as well as in skeletal muscles. The inhibition of PDE5 by sildenafil in these tissues would explain the increased inhibitory activity of nitric oxide on platelet aggregation observed in vitro, inhibition of platelet thrombus formation in vivo and peripheral vasodilatation in vivo [11].

In eight placebo-controlled, double-blind, placebo-controlled trials using RigiScan® [RigiScan Ambulatory Rigidity and Tumescence Monitor, Dacomed Corp., Minneapolis, USA] (a device to objectively measure penile rigidity and duration of erection), sildenafil is translated by a marked improvement in erections during sexual stimulation compared to taking placebo. Some participants in these trials had established organ dysfunction (spinal cord injury, diabetes, etc.), while others did not. In most of these trials, the efficacy of sildenafil was evaluated approximately 60 minutes after taking the product. In all eight trials, when participants were subjected to visual-type sexual stimulation (VSS), the results consistently showed that,

compared with placebo, sildenafil doses of up to 100 mg resulted in a statistically significant increase in the duration of erections with a degree of rigidity of 60% (stiffness commonly considered sufficient for penetrating sex). In patients who responded to the drug, the median time between oral administration of 50 mg sildenafil and onset of erection (60% stiffness) in response to SSV was 25 minutes. The mean duration of erections with stiffness up to 60% at the base of the penis, in men who received placebo, 25 mg and 50 mg sildenafil, in combination with a 2-hour exposure to SSV, was 3 minutes, 24 minutes and 32 minutes, respectively [12,13].

Pharmacokinetics

Sildenafil is rapidly absorbed. Peak plasma concentration is reached at 30 to 120 minutes (median: 60 minutes) after oral administration in fasted subjects. The average absolute bioavailability is 41% (range 25% to 63%). The pharmacokinetic parameters of sildenafil, when administered orally, are dose proportional when the dose is within the recommended dose range (25 mg to 100 mg). Taking Sildenafil at a high-fat meal resulted in a marked slowing of the drug's absorption rate, which resulted in an average T_{max} prolongation of 60 minutes and an average reduction of 29 minutes. % of C_{max} [14]. In concrete terms, this means that if the patient takes his medication with a high-fat meal, the effect will be longer. Furthermore, even though the amount of drug absorbed was lower (11% decrease in AUC), and this decrease was statistically significant, it was not of clinical significance. The relative bioavailability of the product taken with a meal rather than fasting was 89% (90% CI, 84 to 94%)

The mean steady-state volume of distribution of Sildenafil (V_d eq) is 105 liters, indicating that the product is distributed in the tissues. Sildenafil and its major N-desmethyl metabolite in the circulation both bind to plasma proteins in approximately 96%. This parameter is independent of the total concentration of the drug. Measurement of the amount of sildenafil present in the sperm of healthy volunteers revealed that less than 0.001% of the ingested dose may appear in the sperm of patients 90 minutes after taking the drug.

Sildenafil is primarily removed from the body by two microsomal liver isoenzymes, CYP3A4 (main metabolic pathway) and CYP2C9 (secondary metabolic pathway). The main metabolite present in the circulation is formed by N-demethylation of the N-methylpiperazine part. The metabolite's affinity for PDEs is similar to that of sildenafil, and the potency of its PDE5 inhibitory action in vitro is equivalent to approximately 50% of that of the parent drug. Its plasma concentration is about 40% of that of sildenafil. The N-demethyl derivative is also metabolized, and its terminal half-life is approximately 4 hours.

The total clearance of sildenafil is 41 L / h, and its terminal half-life is 3 to 5 hours. Sildenafil, administered orally or intravenously, is excreted as metabolites, mainly in the faeces (approximately 80% of the administered dose) and, to a lesser extent, in the urine (approximately 13% of the administered dose) [15].

Vardenafil

Studies on purified enzymatic preparations have shown that vardenafil is an inhibitor powerful and selective of PDE5 in humans, its IC₅₀ (concentration that inhibits 50% of the

enzymatic activity) being 0.7 nM. Vardenafil inhibits PDE5 more than others known phosphodiesterases (effect > 15 times greater than on PDE6 [present in the retina], > 130 greater than PDE1 [present in the brain, heart and vascular system] > 300 times larger than PDE11 [present in the testes, penile blood vessels, smooth muscle of the vascular wall, skeletal muscles, prostate and pituitary] and > 1000 times larger only on PDE2, 3, 4, 7, 8, 9 and 10). In vitro, vardenafil produces a rise in the concentration of cGMP in isolated human cavernous bodies, resulting in muscle relaxation. At the conscious rabbit, vardenafil causes a penile erection that depends on the synthesis of monoxide endogenous nitrogen that is potentiated by nitric oxide donors [16].

In patients suffering from erectile dysfunction, erections considered sufficient for penetration (rigidity of at least 60% according to the RIGISCAN® device [RigiScan Ambulatory Rigidity and Tumescence Monitor; Dacomed Corp., Minneapolis, USA]) have been obtained by 64% of men treated with vardenafil 20 mg as soon as 15 minutes after taking, compared with 52% of men taking placebo [17]. The overall erectile response of subjects treated with vardenafil became statistically significant compared with placebo 25 minutes after dosing. In two RIGISCAN® double-blind, placebo-controlled, and cross-over trials of men who had had erectile dysfunction for at least six months, the 10 mg and 20 mg doses of vardenafil significantly improved erections produced by visual sexual stimulation. Objective measures of stiffness at the base and end of the penis (with RIGISCAN®) during visual sexual stimulation revealed that compared to placebo, vardenafil produced significantly better results at all doses and at all times. The average duration of erection sufficient for penetration and produced by visual sexual stimulation was 54 and 67 minutes at the base of the penis and 39 and 45 minutes at the tip of the penis for the 10 mg and 20 mg doses of vardenafil, respectively, compared to 31 minutes at the base of the penis and 17 minutes at the tip of the penis for the placebo [18].

The shortest time between taking the drug and achieving an erection perceived to be sufficient for penetration and achieving full sexual intercourse was assessed in a double-blind, parallel-group and randomized distribution in men with erectile dysfunction. A higher proportion of men who took vardenafil 10 mg or 20 mg than placebo reported full intercourse ($p < 0.025$) at all times after 10 minutes or more and 11 minutes or more, respectively. The interval between taking the drug (flexible dose) and achieving an erection perceived to be sufficient for penetration and achieving full sexual intercourse was assessed in a double-blind, parallel and randomized in men with erectile dysfunction. A higher proportion of men who took vardenafil than those taking placebo reported having had complete sexual intercourse 8 to 10 hours after taking ($p < 0.001$) [19].

Pharmacokinetics

Vardenafil, in the form of a film-coated tablet, is rapidly absorbed. In some patients, peak plasma concentrations are reached just 15 minutes after oral administration. However, in 90% of cases, maximum plasma concentrations are obtained within 30 to 120 minutes (median: 60 minutes) after oral administration in a fasted subject. The absolute oral bioavailability is 15% on average. After oral administration of vardenafil, the increase in AUC and C_{max} is proportional to the dose over the recommended range (5 to 20 mg) [20].

When the vardenafil film-coated tablet is taken with a high-fat meal (containing 57% fat), the rate of absorption is decreased, with a median t_{max} elongation of 1 hour and an average C_{max} decrease of 20%. The AUC of vardenafil is not modified. After a meal containing 30% fat, the absorption characteristics of vardenafil (t_{max}, C_{max}, and AUC) were unchanged compared with fasting administration.

The mean steady-state volume of distribution of vardenafil is 208 L, suggesting a tissue distribution. Vardenafil and its main circulating metabolite (M1) are strongly bound to plasma proteins (approximately 95% for vardenafil or M1). For vardenafil as well as for M1, protein binding is independent of total drug concentrations. In healthy volunteers receiving vardenafil, less than 0.00012% of the administered dose was in the ejaculate obtained 90 minutes after administration.

Vardenafil, in the film-coated tablet form, is metabolised primarily by hepatic metabolism via the cytochrome P450 isoform 3A4 (CYP) with the contribution of the CYP3A5 and CYP2C isoforms.

In humans, the main circulating metabolite (M1) is produced by N-desethylation of vardenafil and is then metabolized; its plasma elimination half-life is approximately 4 hours. Part of this metabolite M1 is found in glucurononjugate form in the systemic circulation. The selectivity profile of this M1 metabolite for phosphodiesterase's is similar to that of vardenafil; in vitro, its inhibitory power against phosphodiesterase type 5 is about 28% that of vardenafil, contributing about 7% to the effectiveness of the drug [21].

In patients receiving vardenafil 10 mg orodispersible tablets, the mean terminal half-life of vardenafil ranged from 4 to 6 hours. The elimination half-life of metabolite M1 is between 3 and 5 hours, and is similar to that of vardenafil.

Tadalafil

The chemical structure of PDE5 inhibitors is similar to that of cyclic guanosine monophosphate (cGMP). The structure of tadalafil is, however, very different from those of sildenafil and vardenafil, which are very similar. cGMP is a mediator of the regulation of several physiological processes, such as relaxation of smooth muscle cells, inhibition of platelet aggregation and adaptation of vision to brightness [22]. The increase in cGMP production produces the majority of non-lytic physiological effects of NO, including penile erection [23].

In addition to its high selectivity for PDE5, tadalafil has a higher selectivity than sildenafil for PDE6, which may account for the greater number of vision problems with sildenafil. Another example of different selectivity between these two molecules, but inverse, is relative to PDE11. PDE11 is the last of the isoforms to have been identified. It is present in many tissues such as the heart, liver, kidneys, testes, brain and pituitary gland [24]. Today, the main benefit or risk related to the inhibition of this enzyme is not known. None of the adverse events reported after more than 4,000 patients treated with tadalafil, regardless of duration or dosage, were related to its inhibition. Tadalafil, as well as sildenafil, have therapeutic effects only observed at free concentrations greater than or equal to 10 times the concentration required to inhibit 50% of the enzyme activity (IC₅₀) for PDE5 inhibition, i.e. 10 nM. Even at the maximum concentration (C_{max}) observed

following a single 20 mg dose of tadalafil in healthy volunteers, the free plasma concentration (74.4 nM) is 5-fold lower than the IC₅₀ for PDE11. PDE inhibition is concentration-dependent and isoform-dependent [24].

Two studies in humans were conducted in which they received 10 or 20 mg tadalafil daily for six months. There was no evidence of decreased or impaired concentration, motility, sperm morphology, or sperm volume under tadalafil at any dose. In addition, no effect was observed on the serum testicular or pituitary hormone levels required for sperm production, irrespective of the dosage of tadalafil administered, for 6 months each day compared to placebo. The duration of 6 months corresponding to 2 cycles of reproduction [25]. The literature shows that the effects of drugs leading to a decrease in sperm production in humans appear 4 to 8 weeks after the start of treatment and culminate at 4 months, which is less than the evaluation time. The clinical cardiovascular tolerance of tadalafil has been specifically evaluated elsewhere [26]. In a recent trial, the results of a stress test showed that there was no statistically significant difference between patients receiving tadalafil 10 mg and those taking placebo on the time to cardiac ischemia [27]. Similarly, administration of 20 mg tadalafil does not affect myocardial perfusion. Another notable point is the frequency of occurrence of myocardial infarction in the population included in the various studies. For patients treated with tadalafil, this rate is 0.28% during randomized double-blind studies and 0.43% for open-label studies, i.e. 0.39% in total. Comparatively, this rate is 1.10% in all placebo-treated populations and 0.60 in the all-male age-adjusted population.

Pharmacokinetics

The time to obtain the C_{max} after oral absorption is 2 hours; the C_{max} is 74.4 µg / l. This concentration is much higher, more than ten times, at the IC₅₀, the assurance of being pharmacologically effective. This point is all the more important because it enables rapid effective concentrations to be reached: a low concentration of tadalafil is sufficient to rapidly inhibit at least 50% of the enzymatic activity, a minimum concentration to obtain a clinical effect [6]. In clinic, tadalafil is significantly effective from the 16th minute [28].

Elimination of tadalafil is relatively slow, with a half-life of 17 hours [26]. It reflects a good diffusion in the tissues. The clinical effectiveness of tadalafil may persist until 24 hours when 80% of patients have a satisfactory erection for successful penetration.

In comparison, the time to obtain the maximum concentration of sildenafil is one hour and its half-life is only 4 to 5 hours. The vardenafil data are close to those of sildenafil.

Avanafil

Avanafil is a reversible, highly selective and potent phosphodiesterase type 5 (PDE5) inhibitor specific for cyclic guanosine monophosphate (cGMP). When sexual stimulation causes local release of nitric oxide, inhibition of PDE5 by avanafil results in an increase in cGMP in the corpora cavernosa of the penis. This results in slackening of the smooth muscles and an influx of blood into the penile tissues, thus producing an erection. Avanafil has no effect in the absence of sexual stimulation [28,29].

In clinical studies, avanafil has been evaluated for its effect

on the ability of men with erectile dysfunction (ED) to achieve and maintain an erection sufficient for satisfactory sexual activity. Avanafil was evaluated in 4 randomized, double-blind, placebo-controlled, parallel-group trials of up to 3 months in the general population of patients with ED in patients with diabetes mellitus type 1 or type 2 and DE, as well as in patients with ED following radical prostatectomy with bilateral nerve preservation. The fourth study evaluated the onset of action of avanafil for two dosages (100 and 200 mg), in terms of the proportion of sexual attempts per patient that resulted in satisfactory sexual intercourse. A total of 1774 patients received avanafil, which was taken on demand at 50 mg doses (one study), 100 mg and 200 mg (four studies), respectively. Patients were asked to take a dose of the study drug about 30 minutes before the onset of sexual activity. In the fourth study, patients were encouraged to attempt sexual intercourse approximately 15 minutes after taking the product, to evaluate the occurrence of the erectogenic effect of avanafil, at the dosage of 100mg and 200mg on demand. In addition, a subgroup of patients was included in an open-label extension study, in which 493 patients received avanafil for at least 6 months and 153 patients for at least 12 months. Patients initially received a 100 mg dose of avanafil and could, at any time in the study, have their avanafil dose increased to 200 mg or decreased to 50 mg based on their individual response to treatment. In all studies, a statistically significant improvement was observed for all the main efficacy evaluation endpoints for the three doses of avanafil compared to placebo [30].

These differences were maintained during long-term treatment (according to studies in the general population of patients with ED, in patients with diabetes and ED, and in men with ED following radical prostatectomy with bilateral nerve preservation, and in an open extension study). In the general population of patients with ED, the average percentage of attempts that resulted in successful sexual intercourse was approximately 47%, 58%, and 59%, respectively, for the groups receiving 50 mg, 100 mg, and 200 mg of avanafil, versus about 28% for placebo. In men with either type 1 diabetes or type 2 diabetes, the average percentage of successful sexual attempts was approximately 34% and 40%, respectively, for the 100 mg groups and 200 mg avanafil, versus about 21% for the placebo group. In men with ED following bilateral nerve-preserving radical prostatectomy, the average percentage of successful sexual attempts was approximately 23% and 26%, respectively, for the 100 mg and 200 mg groups. avanafil, versus about 9% for placebo. In the evaluation study of the onset of action, avanafil demonstrated a statistically significant increase in the primary efficacy endpoint (mean percentage of successful intercourse per patient vs. time after dose - SEP3) versus placebo, having achieved satisfactory sexual intercourse in 24.71% of the attempts for the 100mg dose and 28.18% for the 200mg dose approximately 15 minutes after taking the product, versus 13.78% for the placebo. For all of the pivotal studies conducted with avanafil, the percentage of successful sexual attempts was significantly higher for all avanafil doses compared with placebo, for all attempts at time intervals studied after taking the product [31].

Pharmacokinetics

Avanafil is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes. Its pharmacokinetic properties are proportional to all recommended dose ranges. It is essentially

eliminated via hepatic metabolism (mainly by CYP3A4.) Avanafil has a terminal half-life of approximately 6 to 17 hours, 5 to 0.75 hours after taking place on the occasion of a meal-rich meat; the rate of absorption is reduced, with an average delay to reach Tmax of 1.25 hours and an average reduction of Cmax of 39% (200 mg); significant effect on the intensity of exposure (AUC), minimal clinical significance [32].

Avanafil is nearly 99% bound to plasma proteins. Protein binding is independent of total active drug concentrations, age, and renal and hepatic function. No accumulation of avanafil in plasma was observed for 200 mg twice daily for 7 days. Based on measurements of avanafil in the sperm of healthy volunteers, 45 to 90 minutes after its intake, less than 0.0002% of the administered dose may appear in the sperm of patients.

Avanafil is eliminated mainly by the CYP3A4 (major route) and CYP2C9 (first route) isoenzymes of hepatic microsomes. The plasma concentrations of the major circulating metabolites, M4 and M16, represent approximately 23% and 29%, respectively, of the parent compound. The M4 metabolite has a phosphodiesterase selectivity profile similar to that of avanafil and in vitro inhibition potency for PDE5 equal to 18% compared to that of avanafil. Therefore, the M4 metabolite contributes about 4% of the total pharmacological activity. Metabolite M16 was inactive on PDE5 [29].

Avanafil is highly metabolized in humans. After oral administration, avanafil is excreted as metabolites mainly in the feces (approximately 63% of the administered oral dose) and to a lesser extent in the urine (approximately 21% of the administered oral dose).

Side effects of PDE5 Inhibitors

The use of PDE5 inhibiting drugs, like any drug, causes side effects. Most of the effects are usually mild or moderate and often decrease gradually as the body becomes more familiar with the active substances [33]. It is important to consider the side effects involved and find the right individual dosage. A milder dose will often help reduce side effects [34]. The table below lists the most common side effects, based on a test of the listed tablet forms (Table 1).

Table 1: Common side effects of PDE5 inhibitors.

	Sildenafil	Vardefanil	Taladafil	Avanafil
Headache	16%	16%	14%	15%
Nausea	7%	4%	10%	4%
Back Pain	-	-	6%	-
Nasal congestion	4%	10%	5%	10%
Muscle Pain	-	-	5%	-
Redness	10%	12%	4%	10%
Vision Disorder	3%	-	-	-

Do PDE5 Inhibitors Interact with Certain Drugs?

Although this type of drug is relatively harmless, it is important to note that PDE5 inhibitors are not suitable for everyone. For users who are also taking nitrate-containing medications, treatment with PDE5-inhibiting drugs is contraindicated due to an increased risk of falling blood pressure [35]. Ingesting alpha-blocker inhibitors and PDE5 inhibitors should be separated by

at least 4 hours apart. Users who take cardiac medications can perfectly combine this with PDE5 inhibitors. . The combination of PDE5 inhibitors with nitrates in all its forms is contraindicated due to a risk of sudden hypotension. Association with enzyme inhibitors, including antiproteases and antifungals, calcium channel blockers is not recommended.

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