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Phosphodiesterase Type 5 Inhibitor Differentiation Based on Selectivity, Pharmacokinetic, and Efficacy Profiles

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Summary: The mechanism of action of the phosphodiesterase type 5 (PDE5) inhibitors (i.e., sildenafil, tadalafil, and vardenafil) involves inhibition of the PDE5 isoenzyme located in penile vascular smooth muscle cells. Sexual stimulation triggers the release of nitric oxide (NO), stimulating the release of guanylyl cyclase, leading to an increase in intracellular cyclic guanosine monophosphate (cGMP) concentrations, a decrease in intracellular calcium, and ultimately relaxation of the vascular smooth muscle in the corpus cavernosum and penile erection. The PDE5 inhibitors have no effect on the penis in the absence of sexual stimulation. Although the various PDE5 inhibitors differ with respect to selectivity and pharmacokinetic profiles, efficacy and safety of these agents are comparable in broad populations of men with erectile dysfunction (ED), including those with diabetes or those taking multiple antihypertensive agents. The most frequently reported adverse events of the PDE5 inhibitors are related to their mild vasodilatory effects and include headache, flushing, dyspepsia, and nasal congestion or rhinitis. Side effects are generally reversible and tend to diminish during continued treatment. Differences in pharmacokinetic properties among the PDE5 inhibitors include the fact that sildenafil and vardenafil have a shorter duration of action (approximately 4 h) compared with the longer period of responsiveness observed with tadalafil (up to 36 h). In addition, in the presence of high-fat food, absorption of sildenafil and vardenafil may be delayed; however, the rate and extent of tadalafil absorption are unaffected by high-fat food.

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Introduction

There are 11 families of cyclic nucleotide phosphodiesterase (PDE) isoenzymes distributed throughout the body. The PDEs are essential for regulating cellular levels of cyclic adenosine 3',5'-monophosphate (cAMP) and guanosine 3',5'-monophosphate (cGMP).[1, 2] Each PDE contains multiple isoforms and has a different level of selectivity for cAMP and cGMP.[1–4] Regulation of these PDE isoenzymes is integral to controlling a host of physiologic functions. For example, PDE3 is involved in the control of cardiac contractility.

Phosphodiesterase type 5 is considered to be cGMP specific and is the main isoenzyme involved in the pathway leading to penile vascular smooth muscle relaxation and erection. It is not localized in the myocytes, endothelial cells, lymphatic cells, or cardiac conduction tissues; it is, however, highly concentrated in the vascular and penile smooth muscle cells. In fact, PDE5 is more concentrated in the penile corpus cavernosum than in the systemic vasculature.

Treatment with oral PDE5 inhibitors is currently considered to be first-line therapy for men with erectile dysfunction (ED). Sildenafil, tadalafil, and vardenafil are currently available and approved by the Food and Drug Administration.

In this article, the mechanism of action by which the PDE5 inhibitors produce an erection will be described in detail. Although there have been no direct comparative studies of the PDE5 inhibitors to date, efficacy and tolerability data from key clinical studies with the various agents will also be discussed.

Phosphodiesterase Type 5 Inhibitors: Clinical Pharmacology

Mechanism of Action

The PDE5 inhibitors enhance erectile function by maintaining sufficient cellular levels of cGMP in both the corpus cavernosum and its contributing vessels to dilate the corporeal sinusoids. This allows the influx of blood that supports penile erection.[2]

During sexual stimulation, nitric oxide (NO) is synthesized and released by endothelial cells and nonadrenergic-noncholinergic (NANC) nerves. Nitric oxide then diffuses into the smooth muscle cells of the penis. There it activates a soluble guanylyl cyclase, which raises the intracellular concentration of cGMP, a secondary messenger of penile erection. The PDE5 inhibition causes a marked elevation of cGMP concentrations in the glans penis, corpus cavernosum, and corpus spongiosum. Cyclic GMP triggers a series of other enzymatic reactions including activation of a protein kinase that ultimately reduces intracellular calcium levels, enhances smooth muscle relaxation, and produces penile erection (Fig. 1).[5] The PDE5 inhibitors have no effect on the penis in the absence of sexual stimulation, when concentrations of NO and cGMP are low.[5]

Phosphodiesterase Type 5 Inhibitors: Pharmacodynamic Properties

Selectivity and Effects on Vision

The PDE5 inhibitors are highly selective for PDE5, but have varying degrees of selectivity for the other PDE isoenzymes in the body.[2] Selectivity is expressed as a value known as the IC_{50}, which is the concentration of drug in vitro that inhibits a given response by 50%.[2] The lower the IC_{50}, the greater the selectivity. A PDE5 inhibitor's selectivity ratio (i.e., the relative affinity of the drug for the PDE5 isoenzyme vs. another PDE) is also based on the IC_{50} value and may have clinical implications for its adverse event profile. For example, sildenafil is a relatively potent inhibitor of PDE6 (localized in the rods and cones of the retina), which may explain the color vision disturbances reported in up to 11% of men receiving sildenafil.[6] Conversely, tadalafil is a weak inhibitor of PDE6 compared with either sildenafil or vardenafil and may account for the rare occurrence of color vision abnormalities (< 0.1%) with tadalafil.[6, 7] Tadalafil is a relatively potent inhibitor of PDE11, which is localized in skeletal muscle and other tissues. However, the physiologic role and clinical relevance of PDE11 inhibition in humans have not been defined.[7]

Effects on Spermatogenesis

Hellstrom *et al.*[8] compared the effects of tadalafil 10 or 20 mg/day for 6 months with those of placebo in a group of healthy men aged at least 45 years who had mild ED. There were no clinically relevant differences noted between tadalafil and placebo with respect to sperm concentration, count, morphology, or motility. In addition, tadalafil did not produce changes in serum levels of reproductive hormones (i.e., follicle-stimulating hormone, luteinizing hormone, testosterone). There was no effect on hormones related to spermatogenesis. Tadalafil was well tolerated; side effects (e.g., headache, dyspepsia, back pain) were the same as those reported for other PDE5 inhibitors.[8] The investigators concluded that daily dosing with tadalafil 10 or 20 mg produced no clinically relevant effect on spermatogenesis.

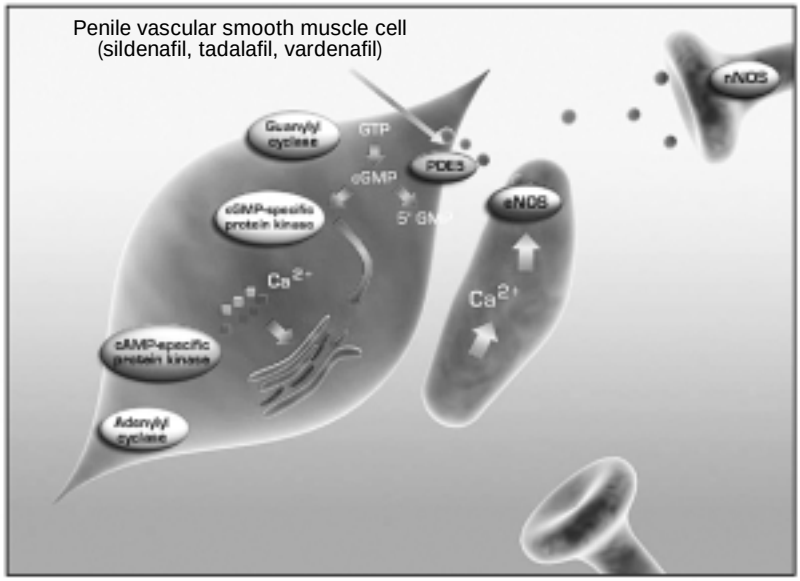

FIG. 1 Mechanism of action of phosphodiesterase type 5 (PDE5) inhibitors. During sexual stimulation, nitric oxide (NO) is synthesized and released by endothelial cells and nonadrenergic-noncholinergic nerves. Nitric oxide diffuses into the penile smooth muscle cells, where it activates soluble guanylyl cyclase. Intracellular concentrations of cyclic guanosine monophosphate (cGMP) increase and intracellular levels of calcium decrease, resulting in increased smooth muscle relaxation and enhanced erection. cAMP = cyclic adenosine monophosphate, cGMP = cyclic guanosine monophosphate, eNOS = endothelial nitric oxide synthase, GTP = guanosine triphosphate, nNOS = neuronal nitric oxide synthase. Adapted from Ref. No. 5 with permission.

TABLE I PDE5 inhibitors: Pharmacokinetics

Parameter	Sildenafil	Tadalafil	Vardenafil
ΔC_{max} with high-fat meal (%)	↓29	No change	↓18–50
t_{max} (h)	1*	2*	1*
$t_{1/2}$ (h)	3–5	17.5	4–5

* = Median.

Abbreviations: PDE5 = phosphodiesterase type 5, ΔC_{max} = change in maximum plasma concentration in fed (high-fat) vs. fasted state, t_{max} = time to maximum plasma concentration, $t_{1/2}$ = plasma half-life. Data from Refs. No. 6, 7, 9, 11, 12.

Phosphodiesterase Type 5 Inhibitors: Pharmacokinetic Properties

Results of pharmacokinetic studies have shown that there are important differences in the absorption and elimination characteristics with the PDE5 inhibitors. Peak plasma concentrations, or C_{max}, may be related to the therapeutic response to a particular drug. Among the variables that can affect C_{max} are the presence of comorbid diseases and concomitant medications or ingestion of food.[2]

Administration of sildenafil with a high-fat meal reduces the C_{max} by about 29%[6] (Table I) and delays the time to achieve peak plasma concentration, or T_{max}, by about 1 h.[6] Clinically, this may result in a delayed onset of action for sildenafil. This drug/food interaction is one of the likely causes for treatment failure of sildenafil in men who are unaware that this medication should be administered on an empty stomach for optimal efficacy. Similarly, taking vardenafil with a high-fat meal decreases the C_{max} ranging from 18 to 50% and delays T_{max} by about 1 h (Fig. 2).[9] However, when vardenafil is administered with a moderate-fat meal, no clinically significant effects on absorption were observed. The manufacturer of vardenafil states that the drug may be taken with or without food.[10] Both the rate and extent of absorption of tadalafil are unaffected by the presence of high-fat food and, therefore, this medication can be taken with or without food (Fig. 3).[6, 11]

The pharmacokinetic profiles of sildenafil and vardenafil are similar (Table II).[10, 12–18] Sildenafil's onset of action has been reported as early as 14–20 min with a median of 60 min, whereas the earliest onset reported with vardenafil is 16 min with a reported median of 25 min. The half-lives of sildenafil and vardenafil are 3 to 5 h and 4 to 5 h, respectively, resulting in a shortened period of responsiveness (about 4 to 5 h) compared with tadalafil.[7, 10, 12, 13] The earliest onset of action for tadalafil has reportedly occurred at 16 min with a median of 45 min. In contrast to sildenafil and vardenafil, tadalafil has a longer elimination half-life of 17.5 h,[7, 14] resulting in an extended period of responsiveness for up to 36 h (Table II).[7, 14–16] Porst *et al.*[15] examined the clinical effects of tadalafil in 348 men and determined that, at 24 h, 53% of intercourse attempts were successful in the treatment group versus 29% for men receiving placebo. The clinical effects of tadalafil continued to be evident at 36 h after dosing, with 59% of intercourse at-

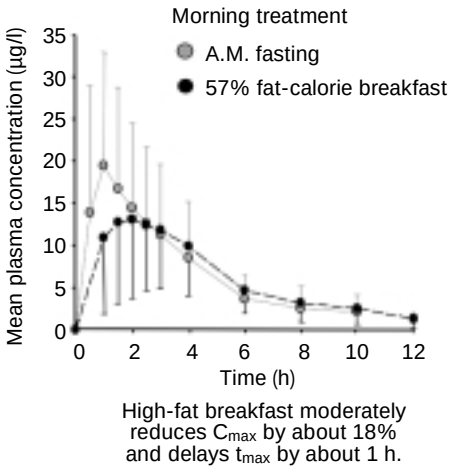

FIG. 2 The effect of food on vardenafil pharmacokinetics. After consumption of a high-fat breakfast, C_{max} decreased and median t_{max} increased. The median t_{max} was 1 h under fasting conditions and 2 h after consumption of a high-fat meal. Adapted from Ref. No. 9 with permission.

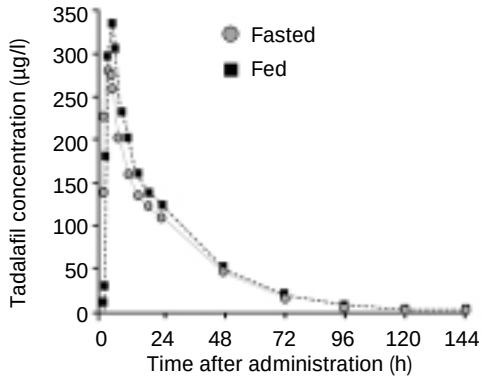

FIG. 3 The effect of food on tadalafil pharmacokinetics. Consumption of a high-fat meal has no clinically relevant effect on the rate and extent of tadalafil absorption in the body. Therefore, tadalafil can be administered without regard to food. Adapted from Ref. No. 11 with permission.

TABLE II PDE5 inhibitors: Onset and duration of activity

PDE5 inhibitor	Onset (min)		Duration (h)
Sildenafil	14–20*	60†	4†
Tadalafil	16*	45†	36‡
Vardenafil	16*	25†	4

* Home setting; stopwatch recording.
† RigiScan®.
‡ SEP Q3
Data from Refs. No. 10, 11, 12, 13, 14, 15, 16, 17, 18.
Abbreviations as in Table I.

tempts being successful in men receiving tadalafil compared with 28% in the placebo group (Fig. 4). The longer duration of action with tadalafil has the potential for increasing flexibility for engaging in sexual intercourse by removing the time constraints associated with the shorter-acting PDE5 inhibitors. This significantly changes the sexual pattern paradigm, in that couples no longer have to plan for intercourse within 4 h of taking a PDE5 inhibitor. In another study, a greater number of men taking tadalafil successfully completed sexual intercourse at 4- to 12-, 12- to 24-, and 24- to 36-h time intervals.[16]

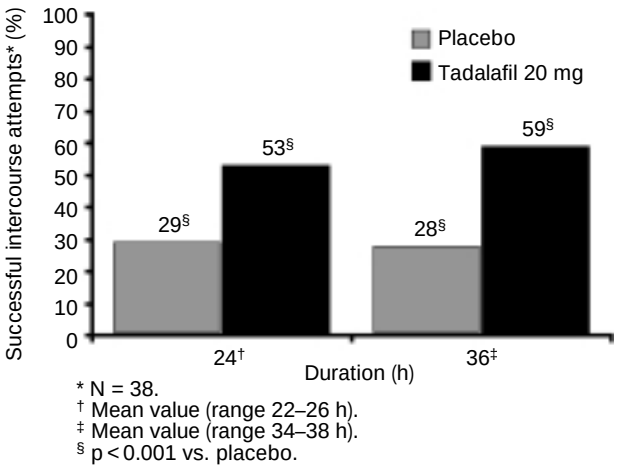

FIG. 4 Percentage of successful intercourse attempts by time interval after tadalafil dosing. At 36 h after dosing, 59% of men were able to have successful intercourse compared with 28% of men receiving placebo. Adapted from Ref. No. 15 with permission.

Efficacy and Tolerability

Efficacy in General Populations

Based on noncomparative clinical study data, efficacy for the three PDE5 inhibitors for the treatment of ED is comparable.[16, 19–21] Because direct clinical comparisons of these agents have not been conducted to date, no conclusions can be drawn about the relative efficacy of the PDE5 inhibitors. In one 12-week, randomized, placebo-controlled study with sildenafil 50 mg, 65% of intercourse attempts were successful in sildenafil-treated patients compared with 20% of men receiving placebo.[19] Results from another 12-week efficacy study with tadalafil showed that successful intercourse rates were 61% with tadalafil 10 mg and 68 to 75% with tadalafil 20 mg, compared with 32% in those receiving placebo.[16, 20] In a clinical study with vardenafil, successful intercourse rates were 65% for both 10 and 20 mg compared with 32% for placebo at 12 weeks.[21] Therefore, clinical evidence suggests that approximately two thirds of men receiving a PDE5 inhibitor will be able to have successful intercourse on a per-dose basis.

Tolerability

Noncomparative clinical data also suggest that tolerability is similar among the three PDE5 inhibitors (Table III).[7, 10, 12, 16, 21, 22] The most frequently occurring adverse effects associated with sildenafil, tadalafil, and vardenafil include flushing, headache, dyspepsia, and nasal congestion or rhinitis. This adverse event profile is typical of agents having vasodilatory action. Back pain and myalgia have reportedly occurred with sildenafil at higher than recommended dosages and with tadalafil at dosages of 10 and 20 mg. In the case of tadalafil, pain associated with these conditions was generally reported as mild or moderate in severity, generally occurred 12 to 24 h after dosing, and typically resolved within 48 h without medical treatment.[7]

In general, very few patients discontinue treatment because of side effects, which tend to dissipate with time; headache, myalgia, or back pain can usually be managed by taking acetaminophen, aspirin, or nonsteroidal anti-inflammatory

TABLE III Tolerability of PDE5 inhibitors*

	Sildenafil†		Vardenafil†‡		Tadalafil†	
Adverse event	Placebo (n = 725)	Sildenafil (n = 734)	Placebo (n = 182)	Vardenafil (n = 188)	Placebo (n = 308)	Taladafil (n = 804)
Headache	4	16	4	21	6	14
Flushing	1	10	0	13	2	4
Nasal congestion/rhinitis	2	4	5	17	4	5
Dyspepsia	2	7	<1	6	2	10

*Based on most commonly reported adverse events. Additional events observed were urinary tract infection (3 vs. 2% for placebo), abnormal vision (3 vs. 0% for placebo), diarrhea (3 vs. 1% for placebo), dizziness (2 vs. 1% for placebo), and rash (2 vs. 1% for placebo) for sildenafil; sinusitis (5 vs. 1% for placebo), accidental injury (4 vs. 3% for placebo), and flu syndrome (2 vs. 1% for placebo) for vardenafil; and back pain (6 vs. 5% for placebo) and myalgia (5 vs. 2%) for tadalafil.

† Figures shown are percentages of patients reporting event.

‡ Based on vardenafil 20 mg/day dose.

Data from Refs. No. 12, 16, 21, 22.

Abbreviation as in Table I.

agents. For all practical purposes, the PDE5 inhibitors are safe for use in the majority of men with ED and the differences in adverse effects among sildenafil, vardenafil, and tadalafil are clinically insignificant.

Efficacy and Tolerability in Special Populations

Men with diabetes: Erectile dysfunction is three times more common in men with than in those without diabetes and affects approximately 50% of men with diabetes during their lifetime.[23] Whether this is related to oxidative stress, tissue fibrosis, or some other factor is unknown. Furthermore, ED occurs 10 or 15 years earlier in men with diabetes than in their age-matched peers without diabetes.[23]

A correlation between HbA_{1C} levels, peripheral neuropathy, and ED in men with diabetes has been demonstrated in one study by Romeo *et al.*[23] The higher the HbA_{1C} levels, the lower the mean erectile function domain score based on the IIEF scale. Low erectile function domain scores were also present in men with peripheral neuropathy, who tended to be relatively young.

Vascular neurologic complications render men with diabetes more resistant to ED treatment. The PDE5 inhibitors, however, appear to improve erections in men with diabetes and ED.[24, 25] In one study by Rendell *et al.*,[26] the percentage of men who responded positively to the Global Assessment Question (GAQ)—Did the treatment improve your erections?—was 56% for the sildenafil group versus 10% for the placebo group. Clinical study results with tadalafil and vardenafil using a more rigorous measurement, the Sexual Encounter Profile (SEP) Question 3—Did your erections last long enough for you to have successful intercourse?—found that the percentage of successful intercourse attempts averaged 44% in men with diabetes receiving tadalafil 10 mg or 51% in those receiving 20 mg compared with 16% in the placebo group.[25] Comparable results have been reported with vardenafil in men with ED and diabetes. The rate of successful intercourse attempts of 49 and 54% was noted in men with diabetes who were taking vardenafil 10 and 20 mg, respectively, compared with the 23% rate observed in the placebo group.[26]

To summarize, the use of sildenafil, tadalafil, or vardenafil in men with diabetes and ED is effective and well tolerated. The tolerability profiles for all three PDE5 inhibitors are generally similar in men with or without diabetes.

Men with cardiovascular disease: The PDE5 inhibitors have mild systemic vasodilatory properties that may result in hemodynamic effects such as transient changes in blood pressure and heart rate. However, oral therapy for ED with PDE5 inhibitors is safe and effective in most patients with established cardiovascular disease or risk factors.[27] Because patients with cardiovascular disease frequently receive multiple drug therapy to control angina, hypertension, and other cardiovascular conditions, potential drug interactions between PDE5 inhibitors and agents used for cardiac management are especially important. For example, the concomitant use of a PDE5 inhibitor with organic nitrates such as nitroglycerin has the potential for producing clinically significant hypotensive effects. Therefore, this combination is contraindicated.[7, 10, 12, 27]

In general, the administration of PDE5 inhibitors causes little or no augmentation of the hypotensive effects of standard antihypertensive agents. Effects are similar in patients receiving single or multiple antihypertensive therapy. According to analysis of data from several placebo-controlled phase 3 studies of interactions, no difference in the incidence of adverse cardiovascular events in patients taking tadalafil with or without commonly prescribed antihypertensive medications was observed.[28] In addition, no statistically significant differences were observed between the tadalafil and placebo groups in mean changes in blood pressure from baseline in patients taking two or more antihypertensive agents.[28]

With respect to efficacy, when sildenafil was given to patients with ED who were taking multiple antihypertensive agents, 71% in the sildenafil group reported improved erections compared with 18% of those in the placebo group ($p < 0.0001$).[29] Similarly, when tadalafil was administered to men with ED who were receiving antihypertensive agents, analysis of seven randomized, double-blind, placebo-controlled trials over a 12-week period showed improved erections based on the IIEF.[30]

Tadalafil also increased the rate of successful intercourse attempts, as assessed by SEP Question 3. At the 20 mg dose, the percentage of successful intercourse attempts was 65% compared with 24% of men in the placebo group.[30] Furthermore, tadalafil was well tolerated in this patient population, with the most frequently occurring side effects being headache, dyspepsia, back pain, and flushing. These occurred about as frequently in men taking multiple antihypertensive drugs as in the general population of men with ED. Limited data are available on the efficacy of vardenafil in patients with ED who are receiving antihypertensive medications.

Conclusions

In response to sexual stimulation, PDE5 inhibitors enhance vasodilation and relaxation of the penile vascular smooth muscle, resulting in improved erectile function. The PDE5 inhibitors (i.e., sildenafil, tadalafil, and vardenafil) are highly selective for the PDE5 isoenzyme. The differences in PDE5 selectivity among these agents suggest that adverse effects may potentially vary according to inhibition of other PDE isoenzymes.

Differentiating properties with respect to pharmacokinetic characteristics are apparent among the PDE5 inhibitors. Because the elimination half-lives of both sildenafil and vardenafil are more rapid than that of tadalafil, the duration of action for tadalafil (up to 36 h) is considerably longer than the duration associated with the other two agents. The extended period of responsiveness associated with tadalafil potentially offers increased flexibility to patients and their partners by minimizing the time constraints associated with planning sexual activity when using the shorter-acting PDE5 inhibitors. Another important pharmacokinetic difference among the PDE5 inhibitors involves the effects on absorption of these agents when administered in the presence of high-fat food. Reports of decreased plasma concentrations and delayed absorption have been associated with sildenafil and vardenafil, potentially re-

sulting in a slower onset of action or reduced efficacy. However, similar effects have not been observed with tadalafil when administered with high-fat food. This lack of drug/food interactions with tadalafil may result in increased dosing flexibility.

The results of noncomparative studies suggest that sildenafil, tadalafil, and vardenafil improve erectile function and the rate of successful intercourse attempts in the general population as well as in men with diabetes and hypertension. Adverse events with these PDE5 inhibitors are generally mild to moderate, transient, and resolve with continued treatment. The most commonly reported adverse events for PDE5 inhibitors include headache, flushing, and dyspepsia. In addition, serious treatment-related cardiovascular effects did not occur with these agents, consistent with their high selectivity for PDE5.

With the introduction of additional PDE5 inhibitors into the therapeutic armamentarium for ED, the differentiating properties of these agents may confer clinical benefits that clinicians as well as couples should consider when selecting a PDE5 inhibitor.

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