PDE5 inhibitors: are there differences?

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The introduction of oral agents for the treatment of erectile dysfunction (ED) has revolutionized the treatment of men with erection problems of all severities and etiologies. Sildenafil, available on the world market since 1998 was joined in 2003 by tadalafil and vardenafil as effective save and reliable oral agents. While these agents share the method of action in common and are all contraindicated with nitrate medications, these are differences among the three agents. Sildenafil has the longest patient experience and the most robust data confirming its activity, safety and tolerability. It has recently been released for use in pulmonary hypertension as well as ED. Vardenafil, the most biochemically potent of the molecules has also been demonstrated to be effective in men with severe ED and in some patients failing sildenafil. Tadalafil is unique in its longer half life and is also tolerable, safe and effective in all severities and etiologies of ED. Tadalafil is also unique in its inhibition of PDE 11, a characteristic of unknown but probably negligible importance. Newer data have also suggested that these agents may be helpful in the treatment of lower urinary tract symptoms.

Since the introduction of sildenafil in 1998, erectile dysfunction has been effectively treated with oral medications. The recent addition of vardenafil and tadalafil to the market has increased the number of phosphodiesterase type 5 inhibitors (PDE5) to three agents used throughout the world. Each of these agents has similar mechanism of action, but has distinct differences. All three drugs in this class have similar pharmacokinetic and pharmacodynamic profiles and each is effective for patients with ED of all ages, severities and etiologies. While there are clear pharmacokinetic and pharmacodynamic differences amongst these agents, clinical differences are somewhat more difficult to identify. Indeed the data of preference trials, head to head clinical trials, and selection trials are few. The differences in pharmacokinetics while having distinct advantages in marketing each drug may be difficult for clinicians and patients to identify. With the lack of data and well done clinical trials, it is difficult for the clinician to differentiate amongst the three agents and to select a PDE5 inhibitor for a specific ED patient or a specific agent to switch to if an initial PDE5 agent is unsuccessful or poorly tolerated. This discussion summarizes some of the current data on PDE5 inhibitors and their efficacy, safety, and use in other conditions.

Key Words: erectile dysfunction, PDE5 inhibitors, penis, sexual dysfunction

Clinical data

The US Food and Drug Administration approved Sildenafil for marketing in March 1998 after extensive clinical trials. Vardenafil was approved in August 2003 while tadalafil was approved in November 2003. Because sildenafil has a 6-year history of safety and efficacy, it has more robust data to demonstrate its use in varied etiologies, populations, and severities of erectile dysfunction. In clinical reviews published in the past 3 years, however, it is apparent that tadalafil and vardenafil have similar efficacies and similar safety profiles to sildenafil.[1-4] The drug side effects are similar with some unique characteristics that will be discussed subsequently. All three agents share a common contraindication for use with nitrate medications.

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Early data for sildenafil include a 12 week randomized, placebo-controlled study of 50 mg that demonstrated 65% of successful intercourse attempts compared with 20% in a placebo group.[5] A 12 week study of vardenafil using mid and high doses of 10 mg and 20 mg reported similar outcomes with 65% of patients recording successful intercourse compared with 32% placebo.[6] A similar design study utilizing tadalafil at both 10 mg and 20 mg demonstrated successful intercourse in 61% with 10 mg and 68% to 75% with 20 mg and only 32% success with placebo.[7] While each of these studies included different populations of patients, had somewhat different inclusion and exclusion criteria, and in the latter two PDE5 inhibitors excluded sildenafil failures, it is clear that all three agents have efficacy in the treatment of erectile dysfunction with all severities and etiologies of erectile dysfunction. In reviewing these studies, however, it is clear that 25% to 35% of patients in these clinical study protocols had inadequate responses to PDE5 inhibitors.[4]

Pharmacokinetics: similarities and differences

Specificity

One classification of differences amongst the three PDE5 inhibitors is that of specificity for phosphodiesterase inhibition. Because phosphodiesterase enzyme is a participant in erectile function, inhibition is a method of facilitating erectile function. Cyclic guanosine monophosphate (cGMP) facilities the relaxation of smooth muscle cells in the corpus cavernosum through the nitric oxide (NO) pathway. Because PDE5 in the corpus cavernosum smooth muscle cells breaks down cGMP, inhibition or blockade of this enzyme will prolong the duration and increase the concentration of cGMP in the smooth muscle cell facilitating erectile function. Currently eleven families of PDEs have been identified in the human. Selectivity of the three currently available PDE5 agents is predominantly for PDE5; however, there is some additional inhibition of other PDE enzymes by the various agents. Table 1. Sildenafil and vardenafil have excellent selectivity for PDE5 versus all PDEs except for PDE6 that has some degree of inhibition from both agents, most significantly for sildenafil. This selectivity for PDE6 produces a dose related impairment of blue green color discrimination and leads to the blue vision that some patients report.[4] This inhibition is not related to the blindness reported with some PDE5 agents. Tadalafil, a weak inhibitor of PDE6, has less 0.1% occurrence of color vision abnormalities.[8] Tadalafil, however, has a higher selectivity for PDE11 than does sildenafil or vardenafil. While the clinical effect of inhibition of PDE11 is unclear, PDE11 is known to exist in cardiac myosites, pituitary gland, and testis.[4] Studies have demonstrated no effect on spermatogenesis or testicular function, more robust long term studies are needed to identify any other effects, if any, of PDE11 inhibition.[9] To date, however, there is no signal that this inhibition is dangerous to patients.

TABLE 1. **PDE5 inhibitors: selectivity for PDE5 versus other PDE isoenzymes***

PDE Isoenzyme	Sildenafil	Tadalafil	Vardenafil
PDE1	80	>4000	690
PDE2	>19000	>4000	62000
PDE3	4628	>4000	40000
PDE4	2057	>4000	47000
PDE6 (rod)	11	188	35
(cone)	10	153	6
PDE7	6100	>14000	>300000
PDE8	8500	>14000	>300000
PDE9	750	>14000	5800
PDE10	2800	>14000	30000
PDE11**	780	6	1620

*Selectivity ratio for PDE5=1 for all inhibitors; higher ratios indicate lower selectivity.

**Physiological role and clinical relevance are not yet known.

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Absorption

Because of differences in gastrointestinal absorption with fatty meals and time of absorption, the three drugs have differences in ultimate peak plasma concentrations based on food intake.[10] Sildenafil, when taken with a high fat meal has a reduction in Cmax of approximately 29% with delays of peak plasma concentration (Tmax) that can be as long as one hour.[11] This interaction may result in delayed onset or reduced efficacy because of a decrease in peak serum concentration. This reduction may result in treatment failure in some patients. Thus, it is important to advise patients taking sildenafil to take it without food or with a reduced fat meal.

Vardenafil, while having less affect of a high fat meal, has some reduction in both Cmax and Tmax. A high fat meal with vardenafil may reduce the Cmax by 18% and delay Tmax by 1 hour. With a moderate fat meal, however, there appears to be no clinically significant affect on gastrointestinal absorption.[12] Indeed clinical Phase III trials did not reduce food

intake other than high fat meals and there appeared to be no change in clinical efficacy with moderate or low fat food intake associated with vardenafil dosing.

Tadalafil because of its longer half-life and absorption, is unaffected by high fat food and can be taken with food intake. While there is some measurable decline in Cmax, because of its long half-life, this change is not clinically significant.[10]

Duration of action

The three available PDE5 inhibitors have some significant differences in half-life ($T_{1/2}$). Sildenafil and vardenafil have similar half-lives of 4 hours while tadalafil's half-life measures approximately 17 1/2 hours for healthy men and 21 1/2 hours for elderly patients. While this change in half-life confers a longer clinical activity period, complete data on the risks of longer half-life are limited. Studies, long-term as well as short-term of tadalafil, however, do not suggest any untoward concern regarding increased morbidity with this longer half-life. The clinician must be aware, however, that emergent treatment with nitrates following ingestion of tadalafil should be delayed for 48 hours compared with 24 hours for sildenafil and vardenafil.[13]

Onset of action

Multiple studies have been performed to evaluate the onset of activity of the three PDE5 inhibitors. Because of the artifical nature of these studies, clinical relevance continues to be in doubt. Indeed the onset of action studies are designed to use stopwatch evaluations by patients or partners following ingestion of the PDE5 agent. Significance in onset of action is measured as first measurement of statistically significant difference in erectile function compared with placebo. While this statistically significant difference may occur as early as 11 minutes with sildenafil and 14 minutes with vardenafil and tadalafil, success at this early time occurs for fewer than 40% of patients treated.[3,7,14] In patients with significant risk factors and co-morbidities for ED, counseling them to begin erectile function trials at 15 minutes or less lead to unsuccessful coitus and may, in the final analysis, create performance anxiety.

Adverse events (AE)

The adverse events of the three PDE5 inhibitors are quite similar. Table 2. Most adverse events are a result of the vasoactive nature of these agents producing vasodilation in vascular beds other than the corpora cavernosa. Additionally, a small number of patients report visual color changes with sildenafil, fewer still with vardenafil and rare reports with tadalafil. Additional AEs include GERD-like symptoms and sinus congestion. All agents are contraindicated with nitrate medications as a result of the risk of additive vasodilation and significant, occasionally catastrophic hypotension. All three agents have similarly adverse events profiles. Indeed long-term studies with sildenafil, vardenafil, and tadalafil have found similar adverse events. Because tadalafil and vardenafil have not been available as long as sildenafil, longer term marketing studies may change these safety profiles, however, after large numbers of prescriptions, no signal to concern appears to be emerging. Adverse events appear to decline over time in studies published with vardenafil and sildenafil.[15,16]

TABLE 2. **Adverse events: PDE5 inhibitors**

	Reported by >2% of patients (%)		
Adverse event	**Sildenafil[1] (Flexible dose)**	**Tadalafil[2] (20 mg)**	**Vardenafil[3] (Flexible dose)**
Headache	16	15	15
Flushing	10	3	11
Nasopharyngitis/rhinitis/ nasal congestion	4	3	9
Dyspepsia	7	8	4
Abnormal vision	3		
Sinusitis			3
Flu syndrome			3
Diarrhea	3		
Myalgia		3	

Safety

Extensive treatment of patients with vascular risk factors using all three PDE5 inhibitors has demonstrated safety with cardiac patients. Indeed sildenafil was originally designed as a cardioprotective agent and studies both clinical and in laboratory has confirmed this safety.[4,17-19] The Princeton Consensus Guideline Conference II carefully reviewed the risks, adverse events, and safety of PDE5 inhibitors in men with cardiac disease.[13] This expert conference with metaanalysis demonstrated no increased cardiac events in patients taking PDE5 inhibitors compared with placebo treated patients or patients in the general, age adjusted population with similar age and risk factor profiles. Indeed in several of the studies reviewed, patients taking regular PDE5 inhibitors were demonstrated to have fewer cardiac events than those not taking PDE5 inhibitors.

In laboratory exercise electrocardiographic studies with sildenafil, vardenafil, and tadalafil have not demonstrated significant risks but, have indeed, demonstrated an improved treadmill time and increased timed cardiac ischemia in patients with stable coronary artery disease.[4, 13]

Based on these and other studies performed in patients taking PDE5 inhibitors, it is apparent that these drugs are safe in patients with various etiologies including cardiac patients not taking nitrate medications. While there is a slight trend of increased QTc noticed with vardenafil this increase remains within a safe range and only those patients with congenital QTc abnormalities should be treated with care when prescribing vardenafil for erectile dysfunction.

Long-term efficacy

With the increasing experience of PDE5 inhibitor treatment for erectile dysfunction, efficacy over time is becoming better documented. Long-term studies including 5 and 6 year data from sildenafil and long-term data from the other two PDE5 inhibitors have demonstrated no clinical evidence for tachyphylaxis with any of these agents. Indeed the long-standing efficacy of sildenafil that is longest on the market, strongly suggests that this class of agents continues to be effective with long-term use. Since these agents are used only on an as needed basis, few patients have taken daily doses for long periods of time. The few long-term daily dosing studies, however, have not demonstrated conclusively any evidence for tolerability or tachyphylaxis.[8,20,21]

Difficult to treat patients

All three PDE5 inhibitors have been demonstrated to be effective in patients with severe erectile dysfunction. Indeed patients with prostate cancer following radiation therapy or radical surgery, patients with severe vascular disease, diabetes, and depression are all treated satisfactorily with these agents. While the efficacy declines in these patients with severe erectile dysfunction, these agents are safe and effective, but consideration in these patients should be given to increasing dosage levels to maximum acceptable dose.

PDE5 failure

Because as many as 30% to 40% of patients will not respond to PDE5 inhibitors alone, strategies must be considered to enhance responses. Most importantly, patients must be counseled in the proper administration of PDE5 inhibitors. For vardenafil and sildenafil, patients should be counseled to avoid high fat meals and for all three agents, patients with significant co-morbidities should be advised to delay sexual stimulation for 1 hour following administration. Similarly, patients should be counseled that sexual stimulation is necessary. Studies with sildenafil have demonstrated an improvement in response after patients have taken sildenafil six or more times. Because many patients have had prolonged erectile dysfunction, they should be counseled that multiple doses may be necessary before optimum response is achieved.[22] If a particular PDE5 inhibitor continues to be ineffective, change to another PDE5 inhibitor may improve response. Indeed a study of sildenafil failures more than 60% of patients responded to vardenafil.

Patients who continue to be poorly responsive to PDE5 inhibitors should be further evaluated for hypogonadism. Indeed, sildenafil has been demonstrated to function poorly in the presence of low testosterone levels. Normalizing testosterone with testosterone gel therapy and maximizing sildenafil dose to 100 mg will increase responses substantially. Indeed Shabsigh et al showed improvement in erectile function domain scores of the IIEF in patients treated with testosterone and sildenafil of 4.4 points compared with sildenafil and placebo of 2.1 points, a statistically significant difference. Additionally those patients treated with a combination had an improvement in ejaculatory function.[23]

Future directions

PDE5 inhibitors were introduced in an effort to improve erectile function. Their efficacy and safety have been well recorded in millions of patients worldwide. These agents, however, should not be confined only to the treatment of erectile dysfunction. The recent approval of sildenafil for

use in pulmonary hypertension has led to the safe, effective, and low morbidity treatment of patients with a severe chronic condition with improvement in their lifestyle and functional status. PDE5s have also been demonstrated to improve lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH). Sildenafil in a small clinical study has demonstrated effectiveness in improving IPSS scores and bothersomeness even though taken only on demand.[24] Recent data from Lilly ICOS has confirmed a significant improvement in LUTS with 5 mg and 20 mg of daily tadalafil in 250 patients undergoing a Phase II study. These patients demonstrated statistically and clinically significant improvement in IPSS scores after 12 weeks treatment. Additional data has demonstrated the importance of chronic dosing of PDE5 inhibitors in patients following radical prostatectomy. Prophylaxis using sildenafil was demonstrated to improve post radical prostatectomy erectile function by sevenfold in a study performed by Padma-Nathan et al. A similar pilot study at our institution has confirmed the effectiveness of tadalafil taken three times weekly beginning one day following radical prostatectomy with improved erectile function at 6 months.[25,26] Finally, early data support the improvement of endothelial cell mediated flow in peripheral arteries suggesting a possible use for these agents as treatment for conditions known to limit endothelial function.

Conclusion

With three effective and safe PDE5 inhibitors, the clinician now has multiple choices in treatment of patients with erectile dysfunction of all severities and etiologies. Based on pharmacokinetics, pharmacodynamics, efficacy and safety, each of these agents can be utilized. Since no well controlled, head-to-head selection or patient preference studies are available, each clinician must choose an agent based on the profile of the patient, his tolerance, risk factors, and side effects. For patients concerned with timing of sexual activity, tadalafil has the longest duration of action with a mean half-life of 17 1/2 hours. In patients concerned with early onset of action, counseling about morbidity and efficacy should be undertaken. Since all three agents have similar onset of action, choices are difficult to make based on early onset. Patients in whom activity is limited because of cardiac disease should be evaluated prior to prescribing PDE5 inhibitors and no PDE5 inhibitor should be prescribed in patients taking nitrate medications. □

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