Pharmacology of phosphodiesterase 5 inhibitors

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The phosphodiesterase enzymes, of at least 11 types, are ubiquitous throughout the body, and perform a variety of functions. Phosphodiesterase type 5 (PDE5) is the predominant enzyme in the corpus cavernosum, and plays a crucial role in penile erection. Inhibitors of PDE5 are the most effective oral agents in the treatment of erectile dysfunction. Sildenafil, tadalafil, and vardenafil are all potent inhibitors of PDE5 and show the same mechanism of action, although they have some pharmacological differences that may translate into varying clinical effects.

Key Words: phosphodiesterase 5 inhibitors, tadalafil

Introduction

The physiology of penile erection has become an important topic for clinicians treating men with erectile dysfunction (ED). Available therapies for ED work at different points in the cascade of neurological, vascular, muscular, and hormonal events that leads to erection, so knowledge of the cascade is crucial for appropriate use of the treatment.

The most effective oral agents for ED are inhibitors of type 5 cyclic guanosine monophosphate-specific phosphodiesterase (PDE5). This article will describe the phosphodiesterase enzymes, examine the mechanism of erection that involves PDE5, and then present pharmacological data on the three PDE5 inhibitors that are either currently, or soon to be, available.

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Phosphodiesterase

The phosphodiesterases are a family of enzymes found throughout the body that act to degrade either cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP).[1,2] In the penile smooth muscle cell, the type 5 phosphodiesterases cleave the cyclic form (cGMP) by hydrolysis to form GMP, which is then recycled by phosphorylation to GTP, then through the actions of guanylate cyclase

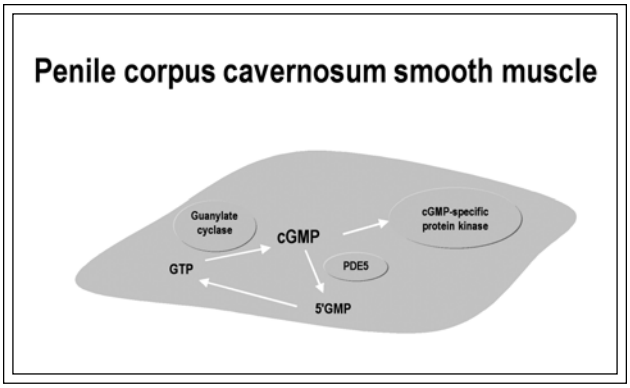

Figure 1. Cyclic guanosine monophosphate and phosphodiesterase.[3]

forms cGMP again Figure 1.[3] The same process, through a different phosphodiesterase, can occur with cAMP, to AMP, ATP, then through the actions of adenylate cyclase to cAMP again. Inhibition of the phosphodiesterase enzyme action results in decreased breakdown of cGMP (cAMP), and thus increased intracellular levels of the cyclic compound.

What are cAMP and cGMP?

These substances, cAMP and cGMP, are ubiquitous second messengers, which act to relay a neuronal, hormonal, or cytokine signal to the target tissue, causing the desired effect.

Phosphodiesterase families

At least 11 different families of phosphodiesterases are found in a range of human tissues. Many of these families also have specific subtypes or isozymes. Table 1 lists the various PDE families that are known and the tissues they target: in discussing ED, PDE5 is the one of crucial interest.[4]

What is an isozyme?

An isozyme, or isoenzyme, is one of various forms or subtypes of an enzyme that shares the same mechanism of action and basic structure, but differs in chemical, physical, or immunological characteristics.[5]

Mechanism of penile erection

The central control of erections is a complex topic, with new neural centres, pathways, and connections being found.[6] The medial preoptic area and the paraventricular nucleus of the hypothalamus are important erectogenic centres, with descending pathways that carry messages through the lumbosacral spinal cord to the penile nerves that control smooth muscle tone in the blood vessels of the penis.[6,7]

TABLE 1. **Phosphodiesterase families**[4]

Name	Substrate	Tissue/organ location
PDE1	cAMP	Brain, lung, heart
PDE2	cAMP, cGMP	Brain, adrenal cortex, liver, goblet cells, olfactory neurons
PDE3	cAMP	Smooth muscle, platelets, cardiac muscle, liver
PDE4	cAMP	Widespread
PDE5	cGMP	Corpora cavernosa, smooth muscle, platelets, kidney
PDE6	cGMP	Retina (rod cells)
PDE7	cAMP	Skeletal muscle
PDE8	cAMP	Testis, ovary, GI tract
PDE9	cGMP	Spleen, GI tract, brain
PDE10	cAMP, cGMP	Brain, testis, thyroid
PDE11	cAMP, cGMP	Smooth muscle, cardiac muscle, testis

At a cellular level in the penis, multiple pathways, messengers, and neurotransmitters are potentially involved in the production of an erection. The most important single neurotransmitter for erection is nitric oxide (NO), and the pathway of interest in this context is termed the NO-cGMP mechanism, illustrated in Figure 2.[3] Nitric oxide is produced by nerve endings and endothelial cells following sexual stimulation. When it crosses the smooth muscle cell membrane,

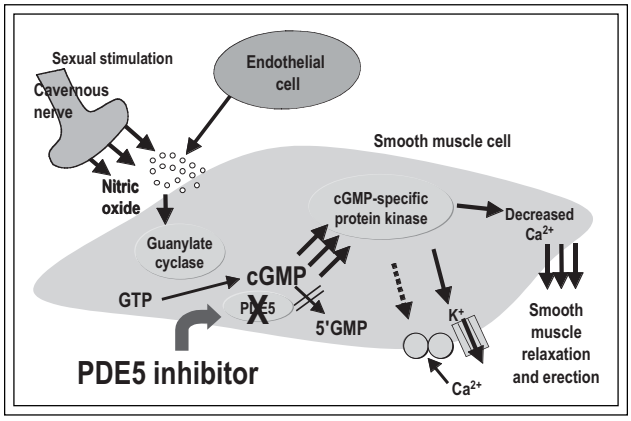

Figure 2. Nitric oxide-cyclic guanosine monophosphate mechanism of erection.[3]

NO causes a change in the conformation of the enzyme guanylate cyclase, increasing its activity, and leading to increased production of cGMP. In penile tissue, elevated levels of cGMP activate a protein kinase, specifically protein kinase G, which affects gap junctions and both potassium and calcium channels (ion channels).[8] The resultant is a reduction in calcium influx which leads to a decrease in cytoplasmic calcium levels, inactivation of myosin kinase, and thus relaxation of smooth muscle cells, a key step in the erectile process. This in turn increases blood flow to the penis, and leads to an erection.[1,9]

What is nitric oxide?

Nitric oxide is a highly unstable free radical that is produced in a number of human tissues from L-arginine by the enzyme nitric oxide synthase. A modulator of various biological processes, NO has an effect on platelet aggregation, endothelial function, cytotoxic activity of macrophages, as well as serving as a neurotransmitter, which is its role in erection. The production of NO requires the presence of oxygen.[10]

Inhibitors of PDE5

Sildenafil, the first PDE5 inhibitor available for the treatment of ED, will soon be joined by tadalafil and vardenafil Figure 3.[4] A review of their molecular structures shows that tadalafil is different than sildenafil and vardenafil. All three drugs share a common mechanism of action: inhibition of PDE5 in corpora cavernosa decreasing the breakdown of cGMP, leading to higher intracellular levels of cGMP and thus more smooth muscle relaxation in the penis, and a better erection Figure 2.[3] These agents do not directly cause erections; rather they all work to enable and improve erections, following appropriate sexual stimulation and release of NO.

The agents also differ in their degree of specificity for PDE5 (a comparison of inhibition of PDE5 with inhibition of other PDE families). The units of measurement in Table 2 are IC_{50}, the nanomolar concentration that reduces the hydrolysis of cGMP by 50%.[11] Selectivity can be assessed by examining the ratio of inhibition of PDE5 to inhibition of other families. When comparing these agents in this manner, it is important to stress that different laboratories may present different findings. This variability may be due to the timing of these studies and the type of assays used in the testing procedure.

TABLE 2. **Inhibition of PDE families/isoenzymes by PDE5 inhibitors (IC_{50}, nM)[11]**

Family	Gene	Sildenafil	Tadalafil	Vardenafil
PDE1	a	290	20 000	630
	b	1100	21 000	5000
	c	110	11 000	460
PDE2	a	19 000	49 000	72 000
PDE3	a	12 000	38 000	7700
	b	17 000	18 000	15 000
PDE4	a	6000	30 000	46 000
	b	5800	22 000	33 000
	c	5200	23 000	34 000
	d	3600	13 000	16 000
PDE5		1	1	1
PDE6		7	780	3
PDE7	a	22 000	47 000	200 000
PDE8	a	19 000	30 000	310 000
PDE9	a	540	19 000	3600
PDE10	a	3100	9000	12 000
PDE11	a	1500	14	640

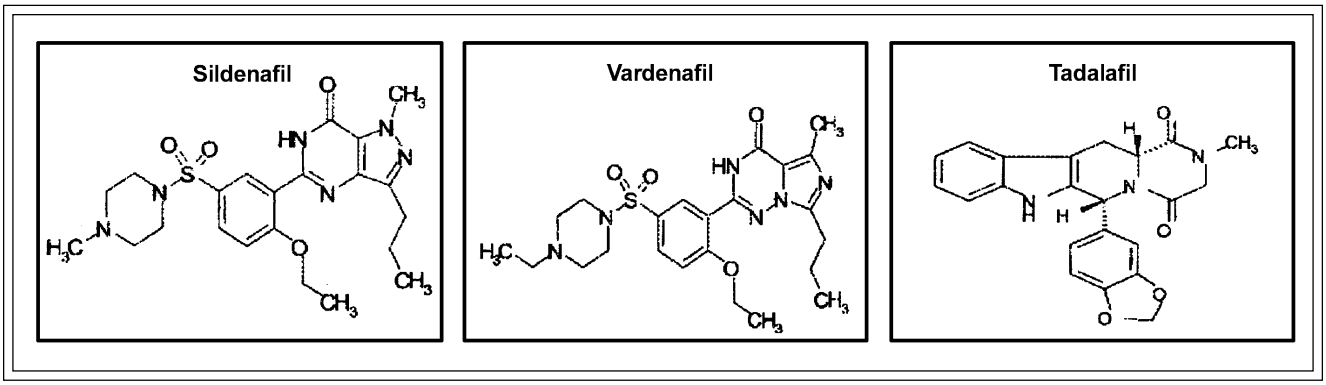

Figure 3. Chemical structures of sildenafil, tadalafil, and vardenafil.[4]

TABLE 3. **Pharmacodynamic characteristics of PDE5 inhibitors**

Characteristic	Sildenafil	Tadalafil	Vardenafil
T_{max}	1.0 h[1]	2.0 h[13]	0.7 h to 0.9 h[12]
Half-life	4 h[1]	17.5 h[4]	4 h to 5 h[12]
Absorption affected by food	yes[1]	no[14]	*
Interaction with alcohol	no[1]	no[14]	no[15]

*Data not available at time of publishing

The principal pharmacological characteristics of the three PDE5 inhibitors are shown in Table 3.[1,4,12-15] The most striking difference between them, also the most likely to show a difference clinically, is the half-life. Tadalafil demonstrates a much longer half-life (17.5 hours versus 4 to 5 hours) than either of the other agents, which translates as reported in clinical trial information by Dr. Brock into an extended period of responsiveness.[16]

Use of PDE5 inhibitors in special populations

Erectile dysfunction typically begins in the fifth decade of life and increases in prevalence with increasing age. Older men with ED frequently have concomitant medical conditions that can alter the pharmacodynamics of drugs. Special attention must be paid in several conditions. The cautions in this section are with respect to sildenafil and are based on clinical trial experience and postmarketing surveillance. The European clinical experience and approvals will likely show the new agents have similar clinical patterns and the cautions will likely be similar in Canada.

In the elderly (over age 65 years), clearance of sildenafil is reduced by roughly 4% for each increase in age by a decade.[1] Patients with chronic stable hepatic cirrhosis have significantly reduced clearance of sildenafil, with an 85% increase in drug exposure.[1] Severe renal impairment (creatinine clearance < 30 mL/min) can reduce the clearance of sildenafil.[1] Clinically, these changes lead to a higher plasma concentration of the drug which is reflected by the recommendation to use a lower starting dose of 25 mg in these patients and increase it gradually.

Adverse effects

The PDE5 inhibitors share a common spectrum of side effects. In the absence of head-to-head trials it is difficult to compare side-effect rates, as different trials enrolled different patient populations, with different inclusion and exclusion criteria, and different side-effect definitions. The most common side effects in all trials of all three drugs have been headache,[1,12] dyspepsia,[1,13] flushing,[12,17] and rhinitis or nasal congestion. Myalgia and back pain have been reported in all of the tadalafil trials, although they have not been associated with discontinuation of the drug. Sildenafil and vardenafil have been associated with myalgia and back pain, although less frequently.[16,18,19] Color vision distortion has been reported with sildenafil mostly in some men receiving 100 mg doses (as a dose-related side effect).[17] These visual changes have not been associated with early discontinuation of the drug. Visual changes have not been significantly associated with either tadalafil or vardenafil.[16,20] Discontinuations due to side effects with all three agents were low across the clinical trial programs for all of these agents.[12]

Cardiovascular safety of PDE5 inhibitors, and their interaction with nitrates, is a concern among men being treated or considered for ED treatment with a PDE5 inhibitor, particularly among men with coronary artery disease. This topic is addressed in detail in the fifth article in this supplement, by Dr. Sender Herschorn.

Conclusion

Phosphodiesterase type 5 inhibitor therapy has become the first-line pharmacologic treatment for erectile dysfunction.[21] The availability of sildenafil has helped to address the needs of men and their partners worldwide in the resumption of sexual activity. New PDE5 inhibitors with different pharmacologic profiles will likely help physicians treating ED and offer those affected with more choice. □

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