Sildenafil: from the bench to the bedside

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Abstract

ERECTILE DYSFUNCTION AFFECTS A LARGE SEGMENT of the male population, and in most cases impaired relaxation of the smooth muscle cells in the corpus cavernosum and the penile arteries is a factor. Sildenafil, a relatively specific vasodilator of the penile circulation, has revolutionized the treatment of impotence. This article describes the biochemistry of erection, outlines the problems that can lead to erectile dysfunction and explains how sildenafil acts to relieve these problems at the cellular and molecular level. Other aspects of therapy, such as potential side effects and absolute and relative contraindications, are also discussed.

Review

Synthèse

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The number of men affected by erectile dysfunction is estimated at more than 100 million worldwide.[1] Although erectile dysfunction is multifactorial, impaired relaxation of the smooth muscle cells in the corpus cavernosum and in the penile arteries is a common denominator in most cases.[1] Most of the effective treatments (except for mechanical and prosthetic devices) exert benefit by relaxing the cavernosal and arterial smooth muscles. The recent introduction of sildenafil, a relatively specific vasodilator of the penile circulation, has revolutionized the treatment of impotence, because it can be taken orally, is effective in 84% of cases and is associated with relatively few side effects.[2] Because several risk factors are common to both erectile dysfunction and cardiovascular disease (such as age, hypertension, atherosclerosis, smoking and diabetes), the two conditions frequently occur together. The clinician should be familiar with the clinical pharmacology of sildenafil and should understand the potential for interaction between sildenafil and other drugs.

Mechanism of action

Blood is supplied to the penis by the cavernosal arteries (branches of the penile artery), which drain directly into the cavernous space (Fig. 1). The cavernous space (corpus cavernosum) contains sinusoids that are surrounded by trabecular smooth muscle. Upon sexual stimulation, the increase in parasympathetic activity results in dilatation of the cavernosal arteries and increased blood flow into these vascular spaces (Fig. 1). At the same time, relaxation of the trabecular smooth muscle increases the compliance of the cavernous spaces, which facilitates entry of the blood. The increase in blood volume and the compression of the relaxed trabecular muscle against the tunica albuginea (a fibrous coat surrounding the penis) results in collapse of the venules and obstruction of venous outflow (Fig. 1). Once this occurs, blood ceases to flow in through the cavernosal arteries, and a rigid erection occurs.

The major mediator of relaxation of the smooth muscle cells in the cavernosal arteries and the trabecular muscle is nitric oxide. This compound is derived from both vascular and neuronal sources. Once sexual stimulation is under way, the nitric oxide required for erection is produced by a nitric oxide synthase in the endothelium of the penile and cavernosal arteries and by an isoform of this enzyme in the nonadrenergic, noncholinergic nerve terminals that densely innervate the corpus cavernosum.

Nitric oxide activates guanylate cyclase, which in turn causes an increase in the levels of cyclic guanomonophosphate (cGMP). This compound then causes smooth muscle relaxation through a variety of mechanisms, including phosphorylation and opening of potassium channels (Fig. 1). The levels of cGMP in the cell reflect a dynamic balance between production of nitric oxide by nitric oxide synthase and degradation of cGMP by cyclic nucleotide phosphodiesterases (PDE).[3] There are 6

subtypes of PDE, each with its own tissue distribution and substrate specificity. PDE5 and PDE6 are relatively specific for cGMP, PDE1 and PDE2 degrade both cGMP and cyclic adenosine monophosphate (cAMP), and PDE3 and PDE4 preferentially degrade cAMP (Table 1).

Sildenafil is a PDE inhibitor. PDE inhibitors are not new to clinical practice. Nonspecific PDE inhibitors, such as theophylline and papaverine, cause smooth muscle relaxation by increasing levels of both cAMP and cGMP. However, the availability of subtype-specific PDE inhibitors is a recent advance. For example, amrinone and milrinone are cardiac inotropes that inhibit PDE3 and possibly PDE1; they have a largely selective effect on cardiac inotropy because they elevate cAMP preferentially in cardiac cells. Sildenafil, a PDE5 inhibitor, was first studied as an antianginal medication. It was soon realized that erection was a common side effect, which could be explained by the abundance of PDE5 in the penile circulation. Sildenafil causes erection by decreasing the breakdown of cGMP and thus prolonging the vasodilatory effects induced in the penile circulation by nitric oxide in response to sexual stimulation (Fig. 1). It must be emphasized that sildenafil can prolong vasodilatation and enhance erection only *after* sexual stimulation and the production of cGMP; it does not spontaneously lead to erection or priapism.

The distribution of possible side effects of sildenafil (dis-

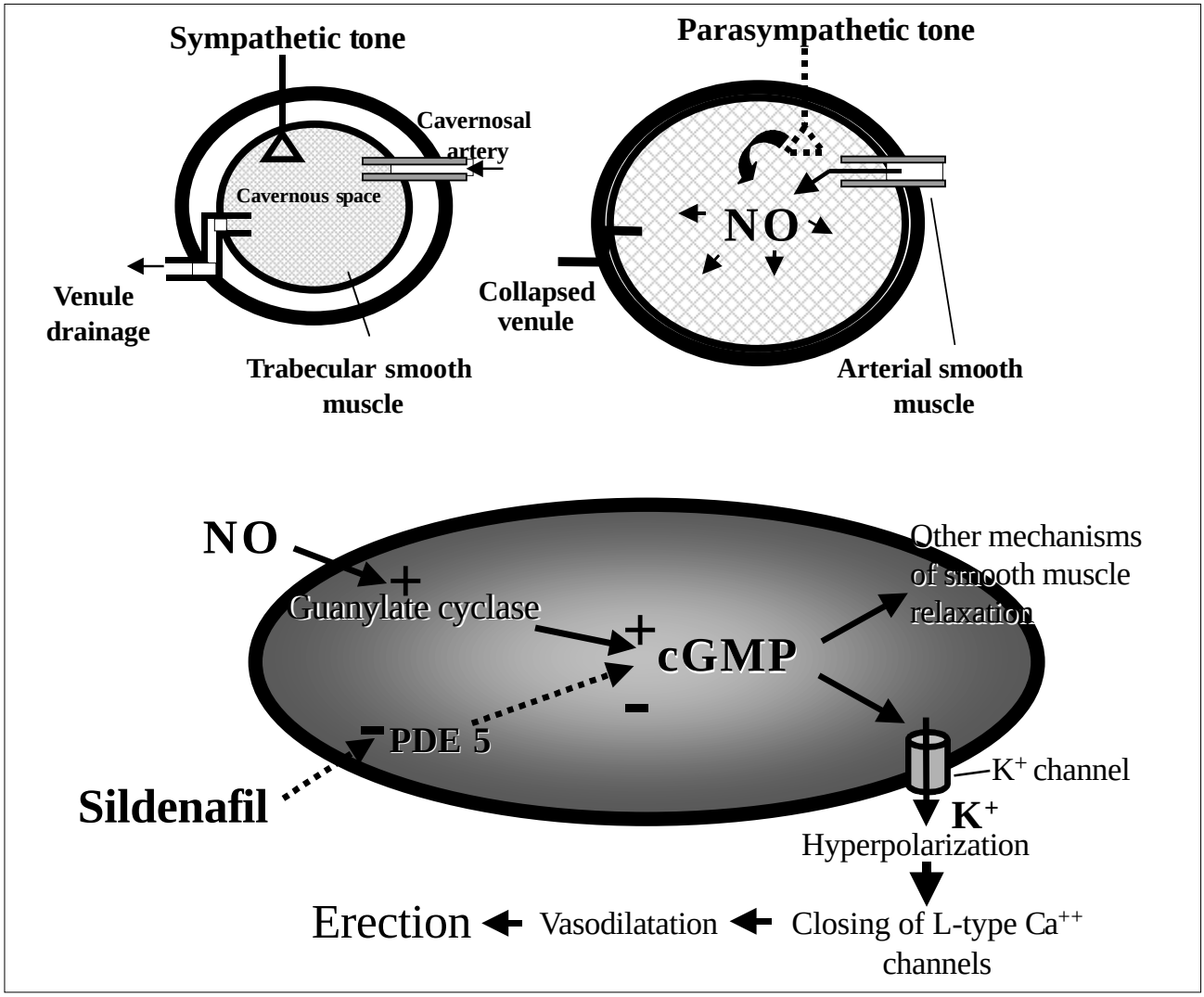

Fig. 1: The mechanism of erection and the role of nitric oxide (NO). The schematics at the top of the figure represent the penis with sympathetic tone (no erection) and parasympathetic tone (erection). Arrows represent direction of blood flow. The schematic at the bottom of the figure represents the intracellular activities within a single smooth muscle cell and the effect of sildenafil on erection. In this schematic, plus symbols and solid arrows indicate activation, and minus symbols and broken arrows indicate inhibition. See text for further explanation. cGMP = cyclic guanomonophosphate, PDE5 = phosphodiesterase 5, K^+ = potassium ion, Ca^{++} = calcium ion.

cussed below) reflects unintended, nonspecific inhibition of other PDE subtypes.[1]

Clinical considerations

The therapeutic dose range for sildenafil is 25 to 100 mg once a day. The drug is metabolized in the liver, so caution is needed when sildenafil is used concomitantly with P_{450} inhibitors such as erythromycin, clarithromycin and ketoconazole.[1] It is excreted in the feces and urine, so the dose must be decreased for patients with cirrhosis or renal failure. The half-life is short (elimination plasma half-life 4 hours).[1]

With the possible exception of impotence after radical prostatectomy, sildenafil improves sexual performance regardless of the cause of erectile dysfunction.[2] In men with this condition, mean scores on the International Index of Erectile Function (IIEF) after sildenafil therapy approach those of age-matched men without erectile dysfunction.[2] The IIEF is a validated, multidimensional, self-administered questionnaire used for the clinical assessment of erectile dysfunction and treatment outcomes in clinical studies.[4] The index is based on 15 questions covering domains such as efficacy of erectile function, sexual desire and satisfaction with intercourse. For example, to assess the efficacy of erectile function patients are asked questions about the frequency of penetration and their ability to maintain erection after penetration. IIEF scores for several domains improved substantially at the end of a 12-week study assessing the effectiveness of sildenafil (intention-to-treat analysis) (Fig. 2).[2]

In the initial drug development studies for sildenafil (which did not include patients with severe cardiovascular disease) the most common side effects were due to the drug's vasodilatory properties (i.e., its effects on PDE5 in vascular smooth muscle). These side effects included headache, flushing and rhinitis (most likely due to nasal hyperemia)[2] (Table 2). Nonspecific gastrointestinal complaints were most likely due to reflux caused by the drug's effects on PDE5 in visceral smooth muscle and relaxation of the lower esophageal sphincter.[2] The selectivity of sildenafil for PDE5 is excellent, although the drug also affects PDE6, which occurs in the retina (where cGMP confers colour vision) (Table 1). Sildenafil is only 10 times more specific for PDE5 than for PDE6 (Table 1). This explains why visual abnormalities (specifically related to blue–green colour vision) occur in 3% of users.[2]

Systemic and pulmonary arterial and venous smooth muscle cells contain PDE5. However, sildenafil causes only a mild and transient decrease in blood pressure (by 8–10 mm Hg for systolic pressure and 5–6 mm Hg for diastolic pressure); peak effects are evident 1 hour after the dose is given and last for approximately 4 hours.[1] Heart rate and cardiac output are not significantly affected. Along with the mild decrease in systemic vascular resistance and afterload, there is also a mild decrease in preload and stroke volume, due to the venous vasodilatation. These effects are not dependent on age or dose (within the range 25 to 800 mg).[1] A small study on patients with severe coronary artery disease also confirmed that the hemodynamic effects of sildenafil — when taken alone — are not associated with clinically significant hypotension.[5]

Because platelets contain PDE5, sildenafil might be expected to affect the function of these cells. Although patients with bleeding disorders have not been studied specifically, no effects on bleeding times have been reported so far. No adverse effects have been reported in patients using acetylsalicylic acid or warfarin, although other antiplatelet agents (such as clopidogrel) have not been studied.[1]

Erectile dysfunction is common in men with cardiovascular disease. This might be explained by the fact that atherosclerosis, which causes endothelial cell dysfunction, can occur throughout the vasculature and may involve several vascular beds, such as the coronary, cerebral and penile circulation. One-third of patients with previous myocardial infarcts and stable coronary artery disease (New York

Table 1: Properties of human phosphodiesterases (PDEs)

Subtype	Substrate	IC_{50} of sildenafil,* nmol/L	Localization†
PDE1	cGMP and cAMP‡	280	Heart, brain, kidney, liver, skeletal muscle, visceral and vascular smooth muscle
PDE2	cGMP and cAMP	68 000	Adrenal cortex, brain, corpus cavernosum, heart, liver, kidney, visceral smooth muscle, skeletal muscle
PDE3	cAMP	16 200	Heart, corpus cavernosum, platelets, vascular and viscera smooth muscle, liver, kidney
PDE4	cAMP	7 200	Kidney, lung, mast cells, heart, skeletal muscle, vascular and visceral smooth muscle
PDE5	cGMP	3.5	Corpus cavernosum, platelets, skeletal muscle, vascular and visceral smooth muscle
PDE6	cGMP	34–38	Retina (cone and rod cells)

Note: cGMP = cyclic guanomonophosphate, cAMP = cyclic adenomonophosphate, IC_{50} = concentration at which 50% inhibition occurs.
*Data from Wallis and colleagues.[3]
†In descending order of concentration.
‡PDE1 has a greater affinity for cGMP than for cAMP.

Heart Association functional class I or II) show electrocardiographic evidence of ischemia during sexual activity, but only 0.9% of myocardial infarcts are triggered by intercourse.[6] If a patient can achieve 5 or 6 METS (metabolic equivalents) on a stress test without electrocardiographic evidence of ischemia, the risk of myocardial ischemia during normal sexual activity is very low.[1] In contrast, in patients who experience exercise-induced ischemia at these workloads, ischemia, both overt and silent, often occurs during intercourse as well. The increase in sexual activity that can be expected after a patient receives a prescription for sildenafil should not be of concern for men with stable coronary artery disease (and negative results on exercise stress testing). The situation is different for patients who are taking nitrates for the treatment of ischemia (indicated by positive results on treadmill tests or angina pectoris), because of the potential for interaction between sildenafil and nitrates.

Although there is no evidence that the effect of sildenafil is additive with those of other classes of antianginal and antihypertensive drugs (including calcium-channel blockers, β-blockers, diuretics and angiotensin-converting enzyme inhibitors), the same does not hold true for nitrates.[1] Concomitant use of nitrates is considered an absolute contraindication to the use of sildenafil[1] (Table 3). Nitrates are prescribed in several different forms, including sublingual nitroglycerin, oral isosorbide mononitrate or dinitrate, nitropatch and nitropaste, all of which have been associated with prolonged decreases in blood pressure when used in conjunction with sildenafil.[1] Nitrates are metabolized in the

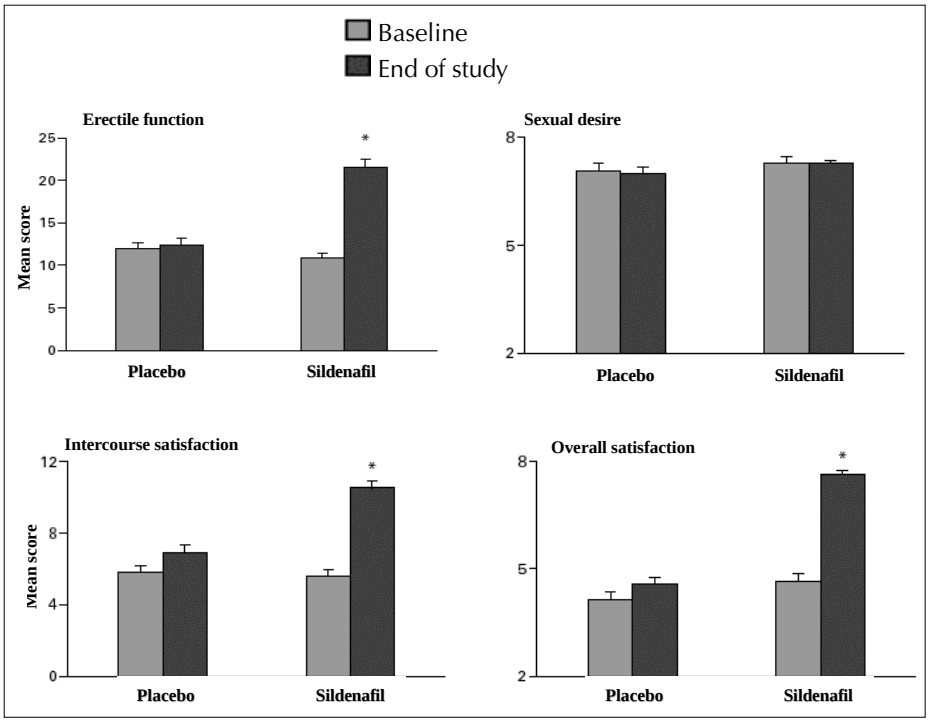

Fig. 2: The efficacy of sildenafil for 4 domains of the International Index of Erectile Function. The bars show mean scores (and standard errors) at baseline and after 12 weeks of treatment with sildenafil (*n* = 137–139 for placebo group and *n* = 134–138 for treatment group). Reproduced, with permission, from Goldstein and colleagues.[2]

Table 2: Noncardiac side effects of sildenafil*

Side effect	% of patients affected
Headache	16
Flushing	10
Nonspecific gastrointestinal problems	7
Rhinitis	4
Abnormalities of colour vision	3

*Source: Goldstein and colleagues.[2]

Table 3: Contraindications to use of sildenafil

Absolute
Concurrent use of nitrates
Relative
Active coronary ischemia (i.e., recent positive result on stress test)
Congestive heart failure and borderline low blood pressure or borderline blood volume status
Multidrug antihypertensive therapy
Any drug that could prolong half-life of sildenafil (e.g., P_{450} inhibitors*)

*See Appendix B in Cheitlin and colleagues.[1]

vessel wall, where they release nitric oxide. Sildenafil prolongs the vasodilatory effects of nitrates by decreasing the breakdown of nitric oxide's main effector, cGMP. It is not known how much time must elapse between administration of sildenafil and administration of nitrates to avoid significant hypotensive effects, although it is prudent to assume an interval of at least 24 hours. Nitroprusside also causes vasodilatation by nonenzymatic release of nitric oxide, and it too is predicted to have a synergistic hypotensive effect with sildenafil.

Relative contraindications to the use of sildenafil include active coronary ischemia (for example, a recent positive stress test), heart failure associated with borderline low blood pressure or low blood volume, complicated multidrug antihypertensive regimens and concomitant use of drugs that can prolong sildenafil's half-life (such as the P_{450} inhibitors mentioned earlier)[1] (Table 3). As of June 1, 2000, 128 deaths associated with use of sildenafil had been reported to the US Food and Drug Administration (FDA) (for more than 6 million prescriptions).[7] Of these deaths, 48 were due to unknown causes, 3 to stroke and 77 to a probable cardiac event. Nineteen of these deaths involved a possible interaction with nitrates. In phase II and III studies conducted before FDA approval of the drug, 28 myocardial infarcts were reported, but this was not significantly different from the number reported in the placebo group.[1] Overall, sildenafil does not appear to increase the incidence of myocardial infarction or death in men with erectile dysfunction.

Future developments

Sildenafil's transition from the bench to the bedside has been rapid. Nitric oxide was discovered in the early 1980s, and the molecular pathways of its actions in the vasculature were described only a few years ago.[8,9] In 1998 the Nobel Prize in Medicine and Physiology was awarded for the discovery of nitric oxide and its molecular pathways, which reflects not only society's tremendous interest in therapies for erectile dysfunction, but also the rapid pace of translational research in the recent years.

As mentioned earlier, one of the major ways by which nitric oxide causes vasodilatation is by activating potassium channels in the plasma membrane of smooth muscle cells. Specifically, nitric oxide activates a family of potassium channels known as the large conductance calcium-activated potassium channels (BK_{Ca}). Although nitric oxide deficiency in the penile circulation (due to endothelial dysfunction) is a major cause of erectile dysfunction, it is possible that the molecular targets of nitric oxide, the BK_{Ca} channels, are also deficient, perhaps through a reduction in expression of these channels with age. An elegantly designed experiment with rats lends support to this hypothesis. Like humans, rats experience erectile dysfunction as they age. In the experiment, complementary DNA for BK_{Ca} channels (which are also known as maxi-K^+ channels) was injected into the corpus cavernosum of rats.[10] Their erections in response to neurostimulation were dramatically better than those of age-matched controls, an effect that was sustained for at least 4 months.[10] This finding suggests that the injected complementary DNA entered the smooth muscle cells of the corpus cavernosum and increased the expression of BK_{Ca} channels, the molecular targets of nitric oxide.

The field of erectile dysfunction is wide open for gene therapy as the distance between the laboratory bench and the bedside is reduced.

Competing interests: None declared.

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