Sildenafil: desired and undesired effects

About 50% of men aged between 40–70 years have some degree of erectile dysfunction, and 30% report moderate to severe impotence (Goldstein and Beavo, 1998). Vascular disease, diabetes, prostate surgery, psychiatric disorders and concomitant drug therapy may predispose to impotence, and psychological factors exacerbate the problem. Sildenafil (Viagra, Pfizer) is the first orally active treatment for impotence, and has attracted much attention in the lay and professional press. This article describes some of its wanted and unwanted effects.

MECHANISMS

Most doctors were taught that the neurogenic control of penile erection is neatly divided into the two branches of the autonomic nervous system — parasympathetic and sympathetic. Activation of parasympathetic fibres causes arteriolar vasodilatation, and thereby increases blood flow to the penis to engorge the corpus cavernosum. In contrast, activation of the sympathetic nervous system is important in the process of ejaculation and leads to arteriolar vasoconstriction which ends erection.

However, this view is overly simplistic and wrong. There is a third branch of the autonomic nervous system which is involved in relaxation of a wide variety of smooth muscle — the non-adrenergic non-cholinergic (NANC) nervous system. NANC nerves in the penis release a powerful dilator substance which relaxes the corpus cavernosum and the small arteries and arterioles supplying the penis. This dilator substance released by NANC nerves is nitric oxide (NO), and the nerves have been re-classified as nitrergic (NO-releasing).

Unlike classical neurotransmitters NO is not stored in vesicles but is synthesized on demand by the action of NO synthase. It is a small, reactive and diffusible gaseous mediator (Bhagat and Vallance, 1996).

Stimulation of nitrergic nerves leads to generation of NO which activates the enzyme guanylyl cyclase present in smooth muscle. Guanylyl cyclase converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), an intracellular messenger which relaxes the smooth muscle. Once nerve stimulation ceases, NO generation stops and the cGMP is rapidly metabolized by cGMP phosphodiesterase.

Sildenafil inhibits phosphodiesterase type 5 (PDE5), the isoform found in the smooth muscle of the corpus cavernosum and blood vessels of the penis. Thus, in the presence of sildenafil, cGMP levels tend to be higher and return to baseline more slowly following nerve activation. Sildenafil acts as an amplifier, enhancing the effectiveness of normal neurogenic stimuli for erection.

EFFICACY

There is good evidence that the drug works in humans — a number of well-controlled clinical trials have demonstrated its efficacy in men with erectile impotence (e.g. Goldstein and Beavo, 1998), and it would appear to be as effective as alternative approaches such as intracavernosal injections. Unlike these other approaches, sildenafil should not have the same propensity to cause priapism, since once the neural stimulation has ended, the erection should fade. Full review of the efficacy data is outside the scope of this article and is described in detail elsewhere (Drug and Therapeutics Bulletin, 1998).

UNWANTED EFFECTS

At the highest dose of sildenafil about 10% of individuals experience headache, flushing or dyspepsia, and the drug causes a small drop in arterial blood pressure (UK data sheet for Viagra, 1998). These effects may all be explained by its mechanism of action. NO and the guanylyl cyclase/cGMP system are important mediators of smooth muscle relaxation throughout the body, and PDE5 is the major enzyme that degrades cGMP in a wide variety of smooth muscles, not just in the genital tract.

Thus sildenafil enhances endogenous NO-mediated dilatation in systemic blood vessels (flushing and a small fall in blood pressure) and in intracranial vessels (headache). Furthermore, the oesophageal sphincter is densely innervated with nitrergic nerves and the dyspepsia may well be the result of relaxation of the sphincter leading to acid reflux.

Visual disturbance has also been reported. About 2% of patients report a colour tinge to vision, or altered perception of light. The reported incidence is greater at the highest dose of the drug (100 mg), with about 10% of individuals experiencing visual disturbance. This effect can also be explained by the drug's action. There are 7 families of PDEs and sildenafil is about 4 000–10 000-fold more selective for PDE5 compared to types 1–4 and type 7. However, it is only about 10-fold selective for PDE5 compared to type 6. In other words, at clinically effective doses sildenafil is likely to inhibit PDE type 6 (PDE6) to some degree. This isoform is important for phototransduction in the retina. Genetic defects in PDE6 are the cause of autosomal recessive retinitis pigmentosa and autosomal dominant night blindness, and experimental lesions in

PDE6 cause retinal degeneration in mice (Beavo, 1995). Clearly it will be important to have an active pharmacovigilance programme to monitor retinal integrity in long-term regular users of the drug.

There have also been reports of cardiac deaths following sildenafil use but it is difficult to know whether these are related to the drug itself. As predicted, sildenafil amplifies the effects of NO donors, including glyceryl trinitrate and amyl nitrite (poppers), and co-administration of these drugs is potentially dangerous. However, enhancement of endogenous NO in the vasculature might be expected to have vasodilator and antiplatelet effects and protect against acute coronary events rather than precipitate them. Further studies will be required to determine whether there is any causal relationship between sildenafil use and coronary events.

USE IN PRACTICE

Sildenafil seems as effective as alternative treatments for impotence, is probably safer (at least in terms of immediate unwanted effects), is undoubtedly more convenient and costs about the same. It clearly is an advance and will form a useful part of treatment in individuals with proven erectile dysfunction. There is no evidence that it enhances sexual performance in those with normal erectile function or that it acts as an aphrodisiac. In those for whom it is indicated we should all be on the look out for unexpected, unwanted effects and for any long-term effects on the retina. Nitrergic nerves are also present in the corpus cavernosum of the clitoris and the vaginal wall, and so there is a good scientific rationale for expecting an effect in women. Clinical trials are underway to explore such potential effects. HM

KEY POINTS

- Sildenafil is an orally active treatment for impotence.
- Sildenafil enhances nitric oxide-mediated relaxation of corpus cavernosum and penile blood vessels.
- Unwanted effects of the drug are accounted for by its mechanism of action.
- Retinal effects are the result of cross-inhibition of phosphodiesterase type 6. It is not known whether they will cause problems in the long term.

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