



HOWARD S. BUSH, MD

Chairman, Department of Cardiology,
Cleveland Clinic Florida, Fort Lauderdale

Safe use of sildenafil in patients with coronary artery disease

ABSTRACT

Despite isolated reports of myocardial infarction and sudden cardiac death in men taking sildenafil for erectile dysfunction, clinical evidence shows the drug to be safe, effective, and well tolerated in most men with coronary artery disease. Nevertheless, caution is advised in specific instances.

DESPITE REPORTS OF myocardial infarction and sudden cardiac death in men taking sildenafil (Viagra) for erectile dysfunction,¹ evidence indicates that the drug is safe, effective, and well tolerated in most men with coronary artery disease (CAD). In some patients with CAD, however, sildenafil is either contraindicated or to be used with caution.

This brief report evaluates the data relating to sildenafil and the risk of cardiovascular events and makes recommendations for its safe use in men with CAD.

HEMODYNAMIC EFFECTS OF SILDENAFIL

Sexual stimulation causes parasympathetic nerves to release nitric oxide (NO), leading to the production of cyclic guanosine monophosphate (cGMP), which causes smooth muscle relaxation in the corpora cavernosa, which in turn allows arterial blood to flow into the corpora and produces an erection.² Phosphodiesterase 5 (PDE5) breaks down cGMP, causing smooth muscle to resume its usual contracted state.

Sildenafil works by promoting vasodilation. More specifically, it inhibits the action of PDE5, allowing cGMP to accumulate in the corpora cavernosa and thereby potentiating and maintaining the erection.

Sildenafil plus nitrates increases risk of severe hypotension

Since sildenafil and nitrates both increase levels of cGMP in the systemic circulation, taking them together can potentiate the vasodilatory effects of both drugs, resulting in severe hypotension. A 1998 consensus statement from the American College of Cardiology and the American Heart Association³ recommended that sildenafil not be prescribed to patients receiving any form of nitrate therapy. Specific recommendations are discussed below.

ERECTILE DYSFUNCTION: A SIGN OF VASCULAR DISEASE

Erectile dysfunction is often a manifestation of generalized vascular disease. In addition, erectile dysfunction and CAD share several common risk factors, including hypertension, tobacco use, depression, diabetes mellitus, and older age. Therefore, when a new patient presents for evaluation and management of erectile dysfunction, one should consider performing a cardiovascular evaluation before addressing his sexual dysfunction. This evaluation may include a physical examination of the circulatory system, a fasting lipid profile, a hemoglobin A_{1c}, and an electrocardiogram.

EVIDENCE THAT SILDENAFIL IS SAFE IN CORONARY ARTERY DISEASE

We have considerable evidence that sildenafil does not aggravate CAD. For example, a 12-week study⁴ of 224 men with erectile dysfunction and documented CAD, multiple cardiac risk factors, or both who were not taking nitrates found that sildenafil treatment led to a significant improvement in achieving and

Despite reports of sudden death, evidence indicates sildenafil is safe in men with CAD



maintaining erections. The most common adverse events were mild or moderate flushing, headache, and dyspepsia. The investigators concluded that oral sildenafil is effective and well-tolerated in men with CAD who are not taking nitrates.

In a retrospective analysis of double-blind, placebo-controlled studies of sildenafil vs placebo in patients with erectile dysfunction and ischemic heart disease who were not taking nitrates,⁵ the incidence of cardiovascular adverse events in patients taking sildenafil was no different than that in patients taking placebo. Additional reviews confirmed this.³

Sildenafil in severe coronary artery disease

Researchers at the University of Pennsylvania⁶ demonstrated that oral sildenafil had no direct adverse cardiovascular effects in 14 men with severe coronary artery disease. After the men took the drug, their systemic and pulmonary blood pressure decreased by a small but consistent amount (< 10%). In addition, the double product, a measure of myocardial oxygen consumption (heart rate \times systolic blood pressure), fell significantly ($P = .02$). This drop would be expected to result in a parallel decrease in coronary blood flow. However, coronary blood flow, coronary vascular resistance, and coronary-artery diameter did not change significantly, nor did pulmonary capillary wedge pressure, right atrial pressure, heart rate, cardiac output, or cardiac index. Relative coronary flow reserve was also unchanged ($P = .90$).

Reports of cardiac death with sildenafil

Deaths have been reported among men using sildenafil¹; however, isolated case reports such as these are of limited use for drawing conclusions about the drug's safety.⁷ Furthermore, the number of deaths reported is well below what

would be expected statistically, considering the number of men taking sildenafil, their age, and their cardiovascular risk factors.

RECOMMENDATIONS

The following recommendations are based on the ACC-AHA consensus statement³ and on evidence from clinical trials:

- Evaluate CAD risk before treating erectile dysfunction: erectile dysfunction may be a sign of generalized vascular disease
- Although sildenafil is safe and effective in most men with CAD, do not prescribe it to those who are taking any form of nitrate therapy, since it may potentiate vasodilation and lead to severe hypotension
- Be cautious about prescribing sildenafil to patients with active coronary ischemia (eg, frequent angina), to patients with congestive heart failure, borderline low blood pressure, and borderline low-volume status, or to patients with hypertension who are on complex antihypertensive drug regimens
- Because sexual activity carries a small but measurable risk of a cardiac event, discuss this risk with heart disease patients before prescribing any treatment for erectile dysfunction
- In men with erectile dysfunction and documented CAD, consider exercise treadmill testing to determine if they can safely achieve the physiologic workload (4 to 6 metabolic equivalents) associated with sexual intercourse.

Although patients with documented CAD are theoretically at higher risk for a cardiac adverse effect from taking sildenafil, the actual risk is quite small, and most patients can benefit from the improved quality of life that this treatment can offer. Close interaction between the urologist and the cardiologist is recommended.

Sildenafil and nitrates taken together may cause severe hypotension

REFERENCES

1. Food and Drug Administration Web site. Postmarketing safety of sildenafil citrate (Viagra). Available at: www.fda.gov/cder/consumerinfo/viagra/safety3.htm. Accessed February 14, 2001.
2. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med* 1998; 338:1397-1404.
3. Cheitlin MD, Hutter AM, Brindis RG, et al. Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol* 1999; 33:273-282.
4. Rohenhok R. Efficacy and safety of Viagra (sildenafil citrate) in men with cardiovascular and erectile dysfunction. American College of Cardiology Scientific Session 2000. Day 3, March 14, 2000.
5. Conti CR, Pepine CJ, Sweeney M. Efficacy and safety of sildenafil citrate in the treatment of erectile dysfunction in patients with ischemic heart disease. *Am J Cardiol* 1999; 83(5A):29C-34C.
6. Hermann HC, Chang G, Klugerherz BD, et al. Hemodynamic effects of sildenafil in men with severe coronary artery disease. *N Engl J Med* 2000; 342:1622-1626.
7. Baum C, Kweder S, Anello C. The spontaneous reporting system in the United States. In: Strom B, editor. *Pharmacoepidemiology*. 2nd ed. Philadelphia: John Wiley & Sons; 1994:125-137.

ADDRESS: Howard S. Bush, MD, FACC, Chairman, Department of Cardiology, Cleveland Clinic Florida, 3000 West Cypress Creek Road, Fort Lauderdale, FL 33309; e-mail bush@ccf.org.