More Potential for Sildenafil Than Potency

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Sildenafil (Viagra) has the reputation of a typical lifestyle drug. Already, Philip Roth has introduced it to the American literature as such in his novel, The Human Stain, in which the hero, Coleman Silk, a 70-year-old retired college professor, takes his regular Viagra before meeting his girlfriend, who is half his age.1 Given that we are being bombarded by spam e-mail messages advertising sildenafil and other drugs in its group for cheap but uncontrolled sale, one is pleased to find a serious trial on a new indication for this substance in the current issue of Circulation.2

Sildenafil was applied to patients with therapy-resistant Raynaud’s phenomenon (ischemic finger attacks) in a randomized, placebo-controlled study for 4 weeks in a dose of 50 mg twice daily. The authors report their results on 16 patients with severe secondary Raynaud’s phenomenon (mean age 49 years, range 22 to 74 years, 15 females) associated with either systemic sclerosis or mixed connective tissue disease. These patients showed not only an increase in the surrogate parameter of Doppler anemometric flow velocity in finger nail-fold capillaries but also a clinical improvement in Raynaud attacks in terms of severity, number, and duration. Moreover, the 6 patients with chronic ulcers at the fingertips exhibited a clear tendency for healing.

It is noteworthy that all of these patients were pretreated without success by other drugs such as nitroglycerine, calcium channel blockers, ACE inhibitors, prostanoids, bosentan, and pentoxifylline. Even though all patients showed a positive effect in the reported series, as always, there appear to be exceptions. In a separate publication by the same group of authors, 1 case with Raynaud’s phenomenon due to chemotherapy did not respond to sildenafil but did respond later to tadalafil.3

As opposed to primary Raynaud’s phenomenon, a discomforting but benign affection that occurs in up to 8% of the male and 17% of the normal female population in an English general practice,4 the secondary form represents a less frequent but serious clinical problem. It often may be a complication of connective tissue diseases that leads to the disablement of the patients. It is difficult to treat, and of all the recommended remedies, including surgical approaches such as thoracic sympathectomy, none has shown great efficacy or durability.5 So, if the clinical efficacy of sildenafil can be corroborated, it would fill in an important gap in peripheral vascular therapy. The effect of sildenafil may even be potentiated by its combination with other vasodilating measures,6 and it may be speculated that other peripheral vascular beds might be influenced favorably by this drug.

No serious adverse events were observed in this series of patients despite regular use of 100 mg/d for 4 weeks, a dose that probably exceeds by far that applied with regard to satisfactory intercourse. However, of the 20 patients initially recruited, 2 had to be excluded because of side effects, and other minor side effects, such as headache, nausea, or mucosal swelling, were frequently seen. If applied to larger numbers of patients, adverse events may possibly occur. Cardiovascular events due to pressure drops (especially together with nitroglycerin preparations), visual disturbances, or other symptoms must be observed with great care. In addition, the patients must be warned that headaches may occur at least transiently.

The mechanism of action of sildenafil is well known. By inhibition of phosphodiesterase type 5, the effect of endothelial NO on cGMP is increased and leads to enhanced vasodilation that lasts considerably longer than the short half-life of the drug would suggest. This effect can be shown not only in epicardial coronaries but also in brachial arteries.7 It was also demonstrated that sildenafil lowers mean pulmonary and wedge pressure, lowers epicardial coronary artery tone, and improves coronary and brachial artery flow-mediated dilation in patients with coronary artery disease and in healthy subjects. There are reports on the positive effects of sildenafil in pulmonary hypertension associated with systemic sclerosis8 and in pulmonary artery hypertension due to high altitude.9 Moreover, a positive effect on cutaneous microcirculation by increased finger nail-fold flow velocity was shown experimentally.10 There have been, in fact, quite a few additional case reports11–14 on Raynaud’s phenomenon not quoted in the present study that would clinically confirm the findings by Fries et al.3

Thus, the effect of sildenafil is not restricted to the corpora cavernosa. Because the report in this issue of Circulation describes data based on a randomized, controlled, double-blinded crossover study, it appears that sildenafil has now finally made its entrance into circulatory therapy by more than 1 sound indication.

References

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