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Effects of sildenafil citrate on human hemodynamics

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DOI: http://dx.doi.org/10.1016/S0002-9149(99)00043-0

Abstract

Nitric oxide (NO) induces the formation of intracellular cyclic guanosine monophosphate (cGMP) by guanylate cyclase. Sildenafil, which selectively inhibits phosphodiesterase type 5 (PDE5) found predominantly in the corpora cavernosa of the penis, effectively blocks the degradation of cGMP and enhances erectile function in men with erectile dysfunction. The NO–cGMP pathway also plays an important role in mediating blood pressure. It is, therefore, possible that the therapeutic doses of sildenafil used to treat erectile dysfunction may have clinically significant effects on human hemodynamics. Three studies were undertaken to assess the effects of intravenously, intra-arterially, and orally administered doses of sildenafil on blood pressure, heart rate, cardiac output, and forearm blood flow and venous compliance in healthy men. A fourth study evaluated the hemodynamic effects of intravenous sildenafil in men with stable ischemic heart disease. In healthy men, significant ($p < 0.01$) decreases in supine systolic and diastolic blood pressures were observed with intravenous sildenafil (20, 40, and 80 mg) at the end of the infusion period when plasma levels of sildenafil were highest (mean decreases from baseline of 7.0/6.9 and 9.2/6.7 mm Hg, for the 40- and 80-mg doses, respectively). These changes were transient and not dose related. Modest reductions in systemic vascular resistance also were observed (maximum decrease 16%), although heart rate was not affected by sildenafil administration when compared with placebo. Single oral doses of sildenafil (100, 150, and 200 mg) produced no significant changes in cardiac index from 1–12 hours postdose between placebo- and sildenafil-treated subjects. The approved dosage strengths of sildenafil citrate are 25 mg, 50 mg, and 100 mg. The 80-mg intravenous dose and the 200-mg oral dose of sildenafil produced comparable plasma levels at twice the maximum therapeutic dose (recommended range, 25–100 mg). After brachial artery infusion of sildenafil (up to 300 μg/min), there was a modest vasodilation of resistance arteries and a reversal of norepinephrine-induced preconstriction of forearm veins. These hemodynamic effects were similar to but smaller in magnitude than those of nitrates. In a small pilot study of men with ischemic heart disease, decreases from baseline in pulmonary arterial pressure (−27% at rest and −19% during exercise) and cardiac output (−7% at rest and −11% during exercise) were observed after 40-mg intravenous doses of sildenafil. Sildenafil was well tolerated by subjects and patients in all studies, with headache and other symptoms of vasodilation the most commonly reported adverse effects of treatment. Modest, transient hemodynamic changes were observed in healthy men after single intravenous or oral doses of sildenafil even at supratherapeutic doses. In men with stable ischemic heart disease, sildenafil produced modest effects on hemodynamic parameters at rest and during exercise.

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