



Literature Reviews

Effect of BAY 41-2272 in the pulmonary hypertension induced by heparin-protamine complex in anaesthetized dogs.

Freitas CF, Morganti RP, Annichino-Bizzacchi JM, de Nucci G, Antunes E. *Clin Exp Pharmacol Physiol* 2007 Jan-Feb;34(1-2):10-4.

Reviewer:

Theodore A. Alston, MD, PhD
Harvard Medical School

Abstract

Bayer 41-2272 activates soluble guanylate cyclase without the need for nitric oxide. Experimentally, the vasodilator reduces systemic and pulmonary hypertension and improves congestive heart failure. Because the drug was valuable in animal models of chronic pulmonary hypertension, researchers in Brazil tested it against protamine-induced pulmonary hypertension.

Anesthetized dogs received femoral artery and Swan-Ganz catheters. A bolus of heparin (500 IU/kg) was followed in 3 min by protamine (10 mg/kg). The heparin had little hemodynamic effect, but the large dose of protamine was followed in 2 min by an increase of mean pulmonary artery pressure from about 10 to about 30 mmHg. Pulmonary resistance, heart rate, and wedge pressure rose while systemic pressure, systemic resistance, cardiac output, and SpO₂ decreased. Substantial recovery occurred within 15 min.

When BAY 41-2272 (10 mcg/kg/h) was started 10 min before the heparin, there was an increase in heart rate, cardiac output, and plasma level of cyclic-GMP. Furthermore, the drug nicely blocked the pulmonary hypertension expected of the heparin-protamine. On the other hand, the drug did not block the reversal of heparin anticoagulation by protamine.

The vehicle for the experimental drug was the solvent dimethylsulfoxide. The vehicle tended to lower SpO₂. The drug more than compensated for the effect of the vehicle and blunted the drop in SpO₂ caused by heparin-protamine.

Comments

The enzyme guanylate cyclase within vascular smooth muscle is the receptor for nitric oxide, whether the NO is derived from endothelial cells or from drugs metabolized to NO (such as nitroprusside or nitroglycerin). The enzyme carries a regulatory molecule of ferrous heme that binds NO. The change in the shape of the heme upon combining with NO causes the enzyme to be activated for production of cyclic-GMP, which then triggers vasodilation. Elucidation of this system earned Furchgott, Ignarro, and Murad a 1998 Nobel Prize (<http://nobelprize.org/>).

BAY 41-2272 is one example of many experimental drugs which have been selected in vitro for the ability to activate guanylate cyclase in lieu of NO. BAY 41-2272 probably interacts with the regulatory heme à la NO, but other examples can activate the enzyme even when the ferrous (reduced) heme has been inactivated by oxidation by nitric oxide or by reactive oxygen species (superoxide radical and hydrogen peroxide) that are generated in excessive quantities in inflammatory states (Evgenov OV. *Nat Rev Drug Discov* 2006;5:755).

Neither BAY 41-2272 nor its present congeners are selective for pulmonary vessels over systemic ones; though an inhaled preparation could potential mimic inhaled NO. They will most likely come to clinical fruition as nitrate alternatives that do not suffer tachyphylaxis. Like nitrate activators of guanylate cyclase, they are likely to cause profound hypotension when administered with ordinary doses sildenafil and other inhibitors of the phosphodiesterase for inactivation of cyclic-GMP. Since sildenafil has value in chronic pulmonary hypertension, BAY 41-2272 might find use against chronic pulmonary hypertension as well as against acute conditions such as that of the present paper.