BMC Pharmacology

Oral presentation

Open Access

Soluble guanylate cyclase stimulator attenuates acute pulmonary hypertension and augments the pulmonary vasodilator response to inhaled nitric oxide in awake lambs

Oleg V Evgenov*[1], Fumito Ichinose[1,2], Natalia V Evgenov[2], Mark J Gnoth[3], Kenneth D Bloch[2] and Warren M Zapol[1]

Address: [1]Department of Anesthesia and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA, [2]Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts 02129, USA and [3]Pharma Research Center, Bayer HealthCare AG, Wuppertal, Germany

Email: Oleg V Evgenov* - oevgenov@partners.org

* Corresponding author

from 2nd International Conference of cGMP Generators, Effectors and Therapeutic Implications
Potsdam, Germany, 10–12 June, 2005

Published: 16 June 2005

BMC Pharmacology 2005, **5**(Suppl 1):S28 doi:10.1186/1471-2210-5-S1-S28

Background

Inhaled nitric oxide (NO) is a potent and selective pulmonary vasodilator. NO induces cGMP synthesis by activating soluble guanylate cyclase (sGC) in ventilated lung regions. Carbon monoxide (CO) has also been proposed to modulate smooth muscle tone via activation of sGC. We tested the hypotheses that direct stimulation of sGC by BAY 41-2272 would produce pulmonary vasodilation and augment the pulmonary responses to inhaled NO or CO.

Materials and Methods

In awake lambs instrumented with vascular catheters and a tracheostomy tube, the thromboxane analog U-46619 was administered i.v. to increase mean pulmonary arterial pressure (PAP) to 35 mmHg. In 7 lambs, BAY 41-2272 was i.v. infused at incremental doses of 0.03, 0.1, and 0.3 mg/kg/h. Another 8 lambs received i.v. L-NAME followed by BAY 41-2272 at 0.1 mg/kg/h. In two additional study groups, NO gas at 2, 10, and 20 ppm (n = 8) or CO gas at 50, 250, and 500 ppm (n = 4) was administered via inhalation in a random sequence. Infusion of BAY 41-2272 at 0.1 mg/kg/h was then commenced; the doseof U-46619 was adjusted to maintain PAP at 35 mmHg; and NO or CO was again administered.

Results

BAY 41-2272 reduced PAP and pulmonary vascular resistance and increased transpulmonary cGMP release in a dose-dependent manner. Larger doses of BAY 41-2272 produced systemic vasodilation and elevated the cardiac index. L-NAME abolished the systemic but not the pulmonary vasodilator effects of BAY 41-2272. Furthermore, infusing BAY 41-2272 markedly potentiated and prolonged the pulmonary vasodilation produced by inhaled NO. In contrast, inhaled CO had no effect on pulmonary vasoconstriction before or during administration of BAY 41-2272.

Conclusion

In lambs with acute pulmonary hypertension, BAY 41-2272 is a potent pulmonary vasodilator that augments and prolongs the pulmonary vasodilator response to inhaled NO. Direct pharmacological stimulation of sGC, either alone or in combination with inhaled NO, may provide a novel approach for the treatment of pulmonary hypertension.

Acknowledgements

Supported by grants from the U.S. National Institutes of Health (HL42397), the Research Council of Norway (161151/V40), and INO Therapeutics Inc. (Clinton, NJ).