BMC Pharmacology

Oral presentation

NO-cGMP signaling in the pathogenesis and treatment of persistent pulmonary hypertension of the newborn

Steven H Abman*[1] and Philippe Deruelle[2]

Address: [1]Pediatric Heart Lung Center, University of Colorado School of Medicine, Denver CO USA and [2]Department of Obstetrics, Faculte de Medecine, Universite de Lille, Lille cedex, France

Email: Steven H Abman* - steven.abman@uchsc.edu

* 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):S30 doi:10.1186/1471-2210-5-S1-S30

Persistent Pulmonary Hypertension of the newborn (PPHN) is the clinical syndrome that is characterized by the failure to achieve or sustain pulmonary vasodilation at birth, leading to severe hypoxemia due to extrapulmonary right-to-left shunting of blood across the foramen ovale and ductus arteriosus. As a potent and selective pulmonary vasodilator, inhaled NO (iNO) has been shown to be an effective therapy for PPHN. However, some infants have limited or no response to iNO therapy, leading to the need for ECMO therapy or death. Mechanisms that contribute to poor responses to iNO in some infants with PPHN are incompletely understood, but are partly related to impairment of NO-cGMP signalling in the hypertensive neonatal pulmonary circulation. Based on past studies that demonstrated impaired production of endogenous nitric oxide (NO) in PPHN, we hypothesized that BAY 41-2272, a direct soluble guanylate cyclase (sGC) activator, may be a potent pulmonary vasodilator in the perinatal pulmonary circulation, thereby providing a novel treatment strategy for severe PPHN.

To test this hypothesis, we performed a series of experiments in chronically–prepared, late gestation fetal sheep (between 128 – 135 days; term = 147 days). At surgery, catheters were placed in the main pulmonary artery (MPA), aorta (Ao), and left atrium to measure pressures, and a flow transducer was placed on the left pulmonary artery (LPA) to measure blood flow. An additional catheter was placed in the LPA for selective intrapulmonary drug infusion. After at least 2 days recovery from surgery, we infused BAY 41-2272 (0.1 – 2.5 mg x 10 min) into the LPA. We found that BAY 41-2272 caused a very potent (up to 5-fold) increase in pulmonary blood flow and fall in PVR. During prolonged (2 hr) infusions, BAY 41-2272-induced vasodilation was sustained throughout the study period. Pretreatment with nitro-L-arginine, a NOS inhibitor, did not attenuate pulmonary vasodilation. When compared with sildenafil, a cGMP-specific type 5 phosphodiesterase (PDE5) inhibitor, the fetal pulmonary vasodilator response to BAY 41-2272 was more prolonged.

To determine the effects of BAY 41-2272 in a model of severe PPHN, we performed similar experiments in chronically instrumented fetal sheep after ligation of the ductus arteriosus (DA) ("experimental PPHN"). In this model, DA ligation causes progressive increases in PAP and PVR over several days, which remain elevated even during ventilation with hyperoxia after birth. In this model, we compared the pulmonary vascular effects of BAY 41-2272, acetylcholine (an endothelium–dependent agonist), and sildenafil. Despite the early loss of acetylcholine-induced vasodilation, BAY 41-2272 and sildenafil continued to cause potent fetal pulmonary vasodilation. After 9 days of intrauterine pulmonary hypertension, sheep were delivered, intubated and ventilated with supplemental oxygen. At birth, BAY 41-2272 dramatically reduced PVR and augmented the vasodilator response to iNO. Sildenafil also caused pulmonary vasodilation and enhanced the response to inhaled NO. We conclude that BAY 41-2272 causes potent pulmonary vasodilation in normal sheep and in an experimental model of severe PPHN, and that these effects were at least as potent as sildenafil. In addition, BAY 41-2272 enhances iNO-induced pulmonary vasodilation in experimental PPHN after birth. We speculate that BAY 41-2272 may provide a novel treatment strategy for severe PPHN, especially in newborns with partial or poor responses to inhaled NO therapy.