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Pharmacologic strategies in neonatal pulmonary hypertension other than nitric oxide

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ABSTRACT

Inhaled nitric oxide (iNO) is approved for use in persistent pulmonary hypertension of the newborn (PPHN) but does not lead to sustained improvement in oxygenation in one-third of patients with PPHN. Inhaled NO is less effective in the management of PPHN secondary to congenital diaphragmatic hernia (CDH), extreme prematurity, and bronchopulmonary dysplasia (BPD). Intravenous pulmonary vasodilators such as prostacyclin, alprostadil, sildenafil, and milrinone have been successfully used in PPHN resistant to iNO. Oral pulmonary vasodilators such as endothelin receptor antagonist bosentan and phosphodiesterase-5 inhibitors such as sildenafil and tadalafil are used both during acute and chronic phases of PPHN. In the absence of infection, glucocorticoids may also be effective in PPHN. Many of these pharmacologic agents are not approved for use in PPHN and our knowledge is based on case reports and small trials. Large multicenter randomized controlled trials with long-term follow-up are required to evaluate alternate pharmacologic strategies in PPHN.

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Introduction

The fetus is in a state of physiologic pulmonary hypertension with low pulmonary blood flow as the placenta functions as the site for gas exchange. At birth, successful adaptation to extra-uterine life requires a rapid increase in pulmonary blood flow to establish the lungs as the site of gas exchange. Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome in which normal circulatory transition at birth fails to occur, and pulmonary blood flow remains low with right-to-left shunting at the patent foramen ovale (PFO) and/or patent ductus arteriosus (PDA). Pulmonary vasoconstriction, vascular proliferation and remodeling contribute to elevated pulmonary vascular resistance (PVR) in PPHN. The incidence of PPHN has been reported as 1.9 per 1000 live births (range: 0.4–6.8) in the United States and 0.43–6 per 1000

Off-label use: This paper contains information about unapproved use of certain pharmacologic agents (prostaglandins, bosentan, sildenafil, milrinone, riociguat, ciniciguat, and rhSOD are not approved for use in newborn period).

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Bobby Mathew and Corinne Leach declare that they have no relevant competing interests.

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live births in the United Kingdom, with mortality rate ranging between 4% and 33%.[1,2]

Management of PPHN includes supportive therapies, lung recruitment strategies, and pharmacologic pulmonary vasodilation. Inhaled NO (iNO) has been the primary agent studied in large randomized clinical trials, and it is currently the only FDA approved specific pulmonary vasodilator therapy for infants. However, the response to iNO remains suboptimal. A meta-analysis of randomized trials of iNO in newborns with PPHN revealed that almost one-third to half of near-term and term infants with hypoxic respiratory failure/PPHN had a suboptimal response to iNO.[3]

Alternative agents for iNO-resistant PPHN are under active investigation based on their potential physiologic effects and complementary action with iNO. These include systemic and inhaled vasodilators such as PDE 5 inhibitors, prostaglandins, the PDE 3 inhibitor milrinone, and ET-1 receptor antagonists. These promising therapeutic strategies are used by clinicians and centers with expertise in pulmonary vasodilator therapy. In addition, novel areas of investigation include emerging agents such as recombinant human superoxide dismutase (rhSOD), L-citrulline, sGC stimulators and activators, Rho-kinase inhibitors, and proliferator-activated receptor-γ agonists.

Endothelium-derived mediators

The pulmonary vascular endothelium releases vasoactive mediators that play an important role in cardiopulmonary transition at birth. In PPHN, the function of the endothelium is impaired and the balance between vasodilators and vasoconstrictors is altered. There is decreased production of vasodilators such as prostacyclin and nitric oxide (NO) and increased production of vasoconstrictors such as endothelin (Fig. 1).

Many of these mediators and their derivatives or inhibitors are effective pulmonary vasodilators and are beneficial in the treatment of PPHN. These mediators are broadly classified into three categories based on their action via the cGMP, cAMP, and endothelin pathways.

Pulmonary vasodilators acting via the cGMP pathway

Pulmonary endothelial NO production increases markedly at the time of birth. The shear stress resulting from increased pulmonary blood flow and increased oxygenation induces endothelial nitric oxide synthase (eNOS) expression, contributing to NO-mediated pulmonary vasodilation after birth.[4]

Nitric oxide exerts its action through soluble guanylate cyclase (sGC) and the important second messenger, cGMP (Fig. 1). The enzyme phosphodiesterase-5 (PDE 5) breaks down cGMP to inactive GMP. Hyperoxia and superoxide anions may inactivate eNOS, oxidize sGC and decrease cGMP production and stimulate PDE 5 to enhance breakdown of cGMP.[5] Natriuretic peptides (ANP, BNP, and CNP) stimulate particulate guanylate cyclase (pGC) and produce cGMP. Plasma BNP levels are elevated in PPHN[6–8] and may be an alternate source of cGMP. Inhaled NO and PDE 5 inhibitors are commonly used agents in the management of PPHN.

Sildenafil (Viagra®, Revatio®, Pfizer) is the prototype PDE 5 inhibitor. Considerable research in pulmonary arterial hypertension (PAH) and rebranding with a new trade name Revatio® has resulted in sildenafil being a common agent in the chronic management of PAH in adults.[9] Tadalafil (Adcirca®) is also a PDE 5 inhibitor approved for use in pulmonary arterial hypertension in adults. Sildenafil is the most common enteral pulmonary vasodilator used to treat infants, although this has been controversial (http://www.cbsnews.com/news/viagra-for-kids/).

The FDA recently reignited the controversy by issuing a warning and recommending against its use in children (http://www.fda.gov/Drugs/DrugSafety/ucm317123.htm). Subsequent publications by experts[10] and a clarification from the FDA (http://www.fda.gov/Drugs/DrugSafety/ucm390876.htm) have acknowledged that there may be situations in which the risk-benefit profile of sildenafil may be acceptable in individual children, especially when treatment options are limited. It is important to note that sildenafil is not approved in neonates, and the study that triggered this controversy did not enroll any neonates or infants under the age of 1 year.[11] Sildenafil is available in intravenous form, oral tablets and recently as a 10 mg/ml suspension.

Currently, sildenafil is used for the following indications in neonates: (a) as an acute adjuvant to iNO in NO-resistant PPHN or to facilitate weaning of iNO; (b) as an acute primary treatment of PPHN where iNO is not available or is contraindicated; and (c) in chronic primary treatment of pulmonary hypertension in conditions such as BPD and CDH.

There are no large randomized trials evaluating sildenafil in neonates with PPHN. The available evidence from animal models and neonatal reports is summarized below.

Animal models of PPHN

Intravenous sildenafil was noted to be as effective as iNO in piglets with PPHN induced by intratracheal instillation of meconium.[12] Intravenous sildenafil (2 mg/kg) administered to the same model while receiving iNO resulted in systemic hypotension demonstrating that sildenafil-induced vasodilation is not limited to the pulmonary circulation.[13] In a nitrofen-induced rat model of CDH, antenatal sildenafil administration improved lung structure, increased pulmonary vessel density, reduced right ventricular hypertrophy and improved postnatal NO-mediated pulmonary vasodilation.[14] In a rat model of BPD induced by antenatal lipopolysaccharide (LPS) and postnatal hyperoxia exposure, intraperitoneal sildenafil improved alveolarization, and increased vascular distribution in the lung tissue by acting through the hypoxia-inducible factor (HIF) pathway.[15] Exposure to hyperoxia increases PDE 5 expression and activity in pulmonary vasculature and reduces cGMP impairing pulmonary vasodilation.[16,17] Hence, sildenafil may be an effective agent during management of neonates with PPHN with prolonged exposure to hyperoxic ventilation.

Infants with PPHN

A small randomized trial of oral sildenafil in term infants with severe PPHN without access to iNO demonstrated improved survival (6/7) compared to placebo (1/6).[18] A pharmacokinetic trial involving eight different dosing regimens showed that a

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