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eNeonatal Review

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PPHN: NEW EVIDENCE-BASED APPROACHES

In this Issue...

The gold standard treatment of persistent pulmonary hypertension of the newborn (PPHN) is maximizing ventilation, adding inhaled nitric oxide, and, when those do not work, placing the infant on extracorporeal membrane oxygenation (ECMO). There is a need and desire to have other options in our toolbox to use before adopting ECMO and for centers that do not have inhaled nitric oxide (iNO) and ECMO available to them.

In this issue, we review recent articles involving the safety and efficacy of inhaled and intravenous iloprost (prostacyclin analog), sildenafil, milrinone, and bosentan as potential treatment options for PPHN.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the risks and benefits of aerosolized therapeutic options for the treatment of PPHN when ECMO and iNO are unavailable.
- List the risks and benefits of IV therapeutic options for the treatment of PPHN when ECMO and iNO are unavailable.
- Identify the risks and benefits of oral therapeutic options for the treatment of PPHN when ECMO and iNO are unavailable.

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Guest Faculty Disclosure

Dr. Stoller has disclosed that he has received grant/research funding from Mallinckrodt Pharmaceuticals and Ikaria.

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The authors have indicated that there will be references to the unlabeled/unapproved uses of iloprost, bosentan, milrinone, and sildenafil.

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IN THIS ISSUE

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COMMENTARY

Persistent pulmonary hypertension of the newborn (PPHN) continues to be a potentially deadly disease that is seen in every neonatal intensive care unit (NICU), with an incidence of 2-6 per 1000 live births and a mortality rate of 10%.[1] Current treatment options include the use of inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO). However, many NICUs around the world may not be able to offer expensive and resource-intensive treatment modalities, and while additional pharmacologic therapies are available, they have yet to be proved safe and effective for treating PPHN. Studies have begun to emerge giving hope that additional therapeutic options may be on the horizon.

Iloprost is a synthetic prostacyclin that can be delivered by aerosolization or intravenous routes. Aerosolized iloprost has been shown to improve oxygenation, reverse right-to-left shunt, increase exercise tolerance, and improve quality of life (among other benefits) in children with pulmonary hypertension.[2] The efficiency of drug delivery for inhaled iloprost is highly dependent on alveolar ventilation. This poses a significant challenge, as most studies that showed improvement are among individuals with a stable ventilatory status who are not in acute respiratory distress. For this reason, administration of intravenous iloprost has been explored. Herein we highlight a study that looks at the safety and efficacy of this route. There is no recommendation as to standard dosing for either route of administration at this point; however with future research we should be able to determine the appropriate use of the medication with PPHN.

Sildenafil, a cGMP-specific phosphodiesterase type 5 (PDE5) inhibitor, is FDA approved for treating adult pulmonary arterial hypertension (PAH). Off-label sildenafil use has been expanded to both the pediatric and neonatal population with pulmonary hypertension, even in light of the safety warning from the FDA in the pediatric population. The FDA warning is derived from the results of a sildenafil dose escalation trial in children aged 1–17 years with PAH, in which there was a higher mortality in the high-dose group compared with the low dose group.[3] Although no patients in the study were less than one year old and the survival analysis was confounded and not adequately adjusted,[4-6] it is a very important cautionary tale to keep in mind when prescribing this medication. In the limited studies that have reported on sildenafil in the infant population, no evidence of serious adverse events have been reported.[7] Off-label sildenafil use has been particularly prevalent in areas of the world without access to more proven treatment options for PPHN. In this review we highlight a recent study that looked at the effectiveness of sildenafil in infants with PPHN compared to inhaled iloprost.

Endothelin is a potent vasoconstrictor that has been implicated in the pathophysiology of PPHN. This pathway is specifically targeted by the endothelin-1 receptor antagonist bosentan. Although bosentan is approved for use in adults with PAH, there is a paucity of data regarding the use of bosentan in children and almost no data in neonates with PPHN. Given the existing and more proven therapies for PPHN, the use of bosentan in this population is far from being ready for prime time. Even the most basic data, such as pharmacokinetics, are not yet available. In this review we highlight a small, randomized, placebo-controlled trial of enteral bosentan for the treatment of PPHN in a resource-limited setting. Although this trial has many limitations, the results are encouraging and should prompt additional studies of this medication.

PPHN is not only a disease affecting the pulmonary vasculature, but may also be associated with significant myocardial dysfunction. Milrinone is a phosphodiesterase 3 inhibitor that may improve cardiac function through its action as a positive inotrope and lusitrope (myocardial relaxant), and improve pulmonary hypertension through its vasodilator properties. Relative to the off-label use of some other medications, milrinone has been more rigorously studied in the pediatric population (eg, the PRIMACORP study).[8] Here we review a small, open-label, pharmacokinetics study of intravenous milrinone in outborn neonates with a diagnosis of PPHN. All patients were iNO "nonresponders." This study adds important pharmacokinetics data to the existing literature. Although the authors also include data on pharmacodynamic effects, safety profile, and short-term outcomes, it is not possible to interpret these data fully as no data were collected for infants who did not receive milrinone.

In summary, the manuscripts reviewed in this issue illustrate the important work being done throughout the world to increase our arsenal of tools and our knowledge of how to use them to treat this common and potentially deadly disease in a vulnerable and understudied population of patients.

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IV ILOPROST

Janjindamai W, Thatrimontrichai A, Maneenil G, Chanvitan P, Dissaneevate S. Effectiveness and safety of intravenous iloprost for severe persistent pulmonary hypertension of the newborn. *Indian Pediatrics* 2013;50:934-938.

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Iloprost is a potent vasodilator that is frequently delivered by inhalation, as this route of administration has fewer side effects and does not require long-term central venous access. The challenges with inhalational delivery for acute episodes include delivery methods as well as a potential change in dosing that is dependent on change in lung inflation/ventilation. Intravenous (IV) iloprost is a stable option to ensure consistent delivery of medication while stabilizing a patient's respiratory status.

Janjindami et al sought to explore the use of IV iloprost (IVI) as a rescue therapy for persistent pulmonary hypertension of the newborn (PPHN) and its effect on short-term outcomes of oxygenation and hemodynamic stability. The investigators reviewed the records of 33 infants in their NICU treated with IVI from December 2007 – December 2011. PPHN diagnosis was determined by the presence of a normal heart with suprasystolic pulmonary hypertension and a right-to-left shunt seen on echocardiography. The primary short-term outcomes were an increase in oxygenation and hemodynamic status within 72 hours of initiating treatment. Secondary longer- term outcomes included mortality, duration of ventilation, and diagnosis of bronchopulmonary dysplasia. The most common etiology leading to PPHN in these infants was meconium aspiration syndrome, and care of all infants had already exhausted the usual treatment options, including high-frequency ventilation and inotropic support. ECMO and inhaled nitric oxide were not available at the treating center.

Infants with an OI (oxygen index) of > 20 who did not respond to conventional therapy were considered for IVI at a starting dose between 0.5 and 3.0 ng/kg/min, with a maintenance dose of 1-10 ng/kg/min. The dose was then titrated for clinical response and increased incrementally by 0.5-1 ng/kg/min. Nonresponders were those that did not show

improvement in OI or PaO2 within 12-24 hours of starting IVI therapy. The nonresponders were then placed on another pulmonary vasodilator for combined therapy. The authors did not reveal the secondary agent used or any subanalysis of this group; they only state there was a higher mortality in the IVI nonresponder group.

Their results showed a significant improvement in oxygenation as determined by OI, PaO2 and SpO2 ($P < .05$) for all infants enrolled. There was also a significant increase in the number of infants requiring inotropic support after initiation of IVI ($P < .01$). This study does continue to show the effectiveness of iloprost therapy, while also highlighting the risks we need to be cautious of when determining when to use this therapy and choosing IV over inhaled routes of administration. These are unfortunately the risks and benefits that will have to be weighed at the bedside for each patient, based on their level of hemodynamic stability and adequacy of ventilation. Further, this was a retrospective analysis of records, so the information that can be pulled from it is limited. A head-to-head, prospectively performed trial of IV and inhaled iloprost will be needed before this option could safely be recommended as therapy for infants with PPHN when iNO is not available for use.

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AEROSOLIZED ILOPROST VS SILDENAFIL

Kahvechi H, Yilmaz O, Avsar UZ, et al. Oral sildenafil and inhaled iloprost in the treatment of pulmonary hypertension of the newborn. *Pediatric Pulmonology*. 2014;49(12):1205-1213.

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Kahvechi et al performed a retrospective review of newborns with persistent pulmonary hypertension admitted to their NICU between September 2007 and January 2012 to compare the effectiveness of oral sildenafil and inhaled iloprost. The preferred treatment at this center was inhaled iloprost, with oral sildenafil used only when iloprost was not available. PPHN was a clinical diagnosis combining history, labs, CXR, ABG, and echocardiographic results. Iloprost was administered with a jet nebulizer at a dose of 1-2.5 µg/kg ever 2-4 hours. Sildenafil was dosed by gastric tube at 0.5 mg/kg every six hours, and dosage was doubled if OI did not improve up to a maximum dose of 2 mg/kg. Twenty infants were in the iloprost group and 27 were in the sildenafil group. IV magnesium sulfate was administered as a secondary vasodilator if either primary therapy option was not successful (loading dose of 200 mg/kg over two hours and maintenance dose of 25-50 mg/kg/hr). Eight patients in the sildenafil group and two in the iloprost group received the additional MgSO4 therapy.

Mean airway pressure (MAP), systolic pulmonary arterial pressure (SPAP), OI, arterial/alveolar oxygen gradient (a/AO2) and alveolar-arterial oxygen difference (A-aO2) were tracked at initiation of therapy and on the eighth day of treatment. They showed a statistically significant improvement in all measures from day 1 to day 8 in both treatment groups. However, the difference in mean values between the two groups on day 8 of therapy showed a statistically significant improvement in the iloprost group ($P < .05$). Time to significant response ($P < .03$), duration of mechanical ventilation ($p = 0.000$) and duration of drug therapy ($P = .03$) were all shorter in the iloprost group. From a safety standpoint, more inotropic agents were needed in the sildenafil group ($P = .000$), and there was no difference between the groups in pneumothorax rates or mortality.

This was also a retrospective study with small numbers; thus more research is needed to evaluate safely and effectiveness of these medications in combination as well as in monotherapy in this population.

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MILRINONE AS A TREATMENT FOR PPHN

McNamara PJ, Shivananda SP, Sahni M, Freeman D, Taddio A. Pharmacology of milrinone in neonates with persistent pulmonary hypertension of the newborn and suboptimal response to inhaled nitric oxide. *Pediatr Crit Care Med*. 2013. Jan;14(1):74-84.

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Milrinone inhibits phosphodiesterase 3 (PDE3), an enzyme mediating the degradation of cAMP. By inhibiting PDE3, milrinone acts as a positive inotrope, positive lusitrope (myocardial relaxant), and as a vasodilator. PPHN is associated with high pulmonary vascular resistance and resultant myocardial dysfunction, and thus milrinone has been proposed as a possible treatment for this severe disease. Although milrinone has been well studied in the setting of low cardiac output syndrome after pediatric cardiac surgery, little data is available regarding its use in treating PPHN.

This was a prospective, open-label study to determine the pharmacokinetics of intravenous milrinone in neonates with a diagnosis of PPHN. To be included in this trial, subjects had to born at ≥ 34 weeks and/or have a birth weight of ≥ 1500 grams. They had to be less than 10 days old and have two consecutive OI ≥ 15. The primary objective was to determine milrinone pharmacokinetics in neonates with PPHN. All neonates were given a loading dose and maintenance infusion using doses based on prior pediatric studies.[1] The secondary objectives were to determine pharmacodynamic effects, safety profile, and short-term outcomes. Although not dictated by the trial, all patients were treated with iNO as standard of care. An iNO non-responder was defined by a sustained OI > 25, despite being treated with iNO for a minimum of six hours.

Eleven patients were enrolled in the study. Although all patients were treated with iNO, for inclusion in the study they had to have persistent severe oxygenation failure — thus, by definition, all subjects were iNO non-responders. The authors comment that this failure of iNO may indicate that these patients are either truly iNO non-responders or their nonresponse may be due to difficulty treating these patients in a transport setting. Plasma levels of milrinone were determined after a loading dose, at steady state, and after discontinuation of the study drug to determine the steady state concentration, volume of distribution, half-life, and total body clearance of intravenous milrinone. The authors found that clearance was lower and volume of distribution and half-life were higher compared with existing pediatric and adult data. These results were consistent with prior reports in young children.[2-4]

Over the course of the study all patients had improved markers of oxygenation. Six patients responded to a dose of 0.33 µg/kg/min, three responded to 0.66 µg/kg/min, and two patients did not respond even at the maximum dose of 0.99 mcg/kg/min. All patients were given a normal saline bolus, together with the initial milrinone loading dose. With this treatment protocol, there was no statistically significant decrease in blood pressure. All patients had improvements in echocardiographic measures of pulmonary hypertension, right ventricular function, and systemic blood flow. None of the patients were withdrawn from the study based on the specified safety outcomes.

There are several reasons why changes in clinical practice should not be implemented based on the findings reported in this study until larger, more rigorous trials are performed. At an age of 5-48 hours of life, some of these patients still had extremely high OI despite being treated with iNO. It is not stated what the ECMO criteria were in the study center. A delay in maneuvers to improve oxygen delivery, including ECMO, may be associated with later neurodevelopmental deficits. As there was no control group included in this very small study, it is not possible to determine whether clinical and echocardiographic improvement was attributable to milrinone or simply reflected the natural history of disease in these 11 patients. The pharmacokinetic data, however, may provide a basis for future clinical trials to determine the efficacy of milrinone in iNO non-responders or in areas of the world in which iNO is not available.

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BOSENTAN FOR TREATMENT OF PPHN

Mohamed WA, Ismail M. A randomized, double-blind, placebo-controlled, prospective study of bosentan for the treatment of persistent pulmonary hypertension of the newborn. *J Perinatol*. 2012 Aug;32(8):608-13. doi:10.1038/jp.2011.157.

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Endothelin is a potent vasoconstrictor that has been implicated in the pathogenesis of pulmonary arterial hypertension (PAH) and PPHN. While adults with certain types of PAH have been shown to benefit from treatment with the endothelin-1 receptor antagonist bosentan, very little data is available regarding the use of bosentan in neonates.

This paper reports on a prospective randomized placebo-controlled trial performed at a single center in Saudi Arabia. To be included in this trial, patients had to be less than 7 days old and born at ≥ 34 weeks. They had to have a diagnosis of PPHN and be mechanically ventilated on more than 0.50 FiO2. Patients were randomized to receive either enteral bosentan or enteral placebo (water). Bosentan doses were based on three prior studies comprising four total patients.[1-3] The patients in this center did not have access to iNO, ECMO, or other pulmonary vasodilators. Patients were treated for a maximum of seven days. If there was a sustained improvement in oxygenation at less than seven days with three successive blood gases with an OI < 15, therapy was discontinued. The primary outcome was a favorable response defined as an OI < 15, normal pulmonary artery pressure (< 20mm Hg), and no premature discontinuation of the drug because of lack of efficacy or drug-related toxicity. Secondary outcomes included neonatal death, bronchopulmonary dysplasia, neurologic sequelae, and reactive airways disease six months after treatment.

Twenty-four and 23 patients were enrolled in the bosentan and placebo groups, respectively. Patients were 25.4 ± 1.7 hours old (mean ± sd) in the placebo group and 26.2 ± 1.8 hours old in the bosentan group and had mean OIs of 45.1 ± 3 (mean ± sd) to 43.6 ± 4 in the placebo and bosentan groups respectively at the time of study entry. There was a statistically significant (P < .05) improvement in both OI and SpO2 at six hours and at subsequent time points after study drug administration in the bosentan group compared with the placebo group. The patients in the bosentan group had a statistically significant (P < .0001) decrease in mechanical ventilation time compared with the placebo group (4.3 vs 11.5 days).

The authors reported no clinical (hypotension, gastric intolerance, bleeding or pulmonary hemorrhage) or laboratory adverse effects. There was a statistically significant (P < 0.0001) improvement in the primary outcome in the bosentan group at the end of study therapy. One death occurred in the bosentan group and three deaths in the placebo group, although this difference was not statistically significant. The placebo group had significantly greater incidence of neurologic sequelae compared with the bosentan group (29% vs 0%, P = 0.01).

Treatment options are limited for newborns with PPHN who do not respond to iNO or when iNO is not available. This small trial provides encouraging data regarding the efficacy and safety of bosentan in this population.

This study has several limitations. Approximately one-third of patients in the placebo group were withdrawn from the trial because of "clinical worsening," and the outcomes of these patients were not included in the final analysis. This may have caused artifacts in the

results due to nonrandom attrition of participants. It would have been preferable to perform an intention-to-treat analysis.

Another issue is some heterogeneity in the primary diagnoses. Infants born after premature rupture of membranes may have some degree of pulmonary hypoplasia, which has a very different pathophysiology compared with meconium aspiration syndrome. The size of this study does not allow for subgroup analysis that might allow us to determine diagnosis-specific efficacy. Finally, this study did not report any pharmacokinetics data. Before any larger trials are performed to corroborate these data, it is critical to determine bosentan pharmacokinetics in this population to help ascertain optimal dosing.

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2. Goissen C, Ghyselen L, Tourneux P, Krim G, Storme L, Bou P, Maingourd Y. Persistent pulmonary hypertension of the newborn with transposition of the great arteries: successful treatment with bosentan. *Eur J Pediatr*. 2008 Apr;167(4):437-440.
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- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
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