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Sildenafil Therapy for Bronchopulmonary Dysplasia: Not Quite Yet

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Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy and complicates the course of up to one-third of extremely preterm babies. BPD results in poor long-term pulmonary outcomes and increases the risk of neurodevelopmental delay. As a result, a significant amount of research has sought to better define the population most at risk, as well as to develop prevention strategies. (1, 2) We now understand that the risk for BPD increases with younger gestational age, intrauterine growth restriction, presence of chorioamnionitis, and delay in time to full enteral feeds. (2, 3) However, the ability to identify populations of at risk infants has not improved our ability to prevent BPD. While prenatal steroids and postnatal surfactant have diminished the impact of respiratory distress syndrome, they have not diminished the frequency or severity of BPD in the extremely low birthweight population. (2, 4) In recent years, various strategies such as hydrocortisone, recombinant human superoxide dismutase, vitamin A, caffeine, and most recently, inhaled nitric oxide have all been tested as BPD-prevention strategies, but with a variable degree of success. (5–12) To date, there is no absolute therapy to prevent BPD other than to prevent preterm birth.

As smaller and younger babies survive with BPD, the complication of BPD-associated pulmonary hypertension has gained recognition. BPD-associated pulmonary hypertension (PH) occurs in 30–45% of infants with moderate to severe BPD (as defined by the NIH consensus criteria). (13–16) The exact etiology of this pulmonary hypertension is poorly understood, although recent evidence from both animal and human studies suggest that intrauterine growth restriction increases risk for BPD-associated PH.(14, 17, 18) Early injury to the developing lung impairs both alveolarization and angiogenesis, and emerging evidence indicates that preterm birth at an early stage of lung development produces a developmental arrest of pulmonary vessel formation.(19) Other factors, such exposure to supraphysiologic oxygen levels, lead to remodeling and pruning of the remaining small pulmonary vessels, producing vascular dysfunction and pulmonary hypertension. Over time, this pulmonary hypertension contributes to ongoing hypoxemia, which induces further vascular remodeling and eventually leads to right ventricular hypertrophy.(20) In the most severe cases, right ventricular hypertrophy progresses to right ventricular failure, cor pulmonale, and death.(21) While we still need to learn more about the epidemiology and outcomes, several case series suggest that the mortality in infants with BPD-associated PH approaches 50% by 2 years of life, and there is tremendous concern about the ability of surviving infants to reach adulthood and whether this neonatal illness will create lasting residual deficits.(15, 22)

While there continues to be a major focus on prevention, we also need safe and effective therapies to treat infants who have already developed BPD and BPD-associated PH. Over the years, many therapies including diuretics, inhaled bronchodilators, and steroids have been attempted to improve the pulmonary function in infants with significant BPD. However, no clearly effective therapy has emerged that improves pulmonary mechanics

without important side effects.(4, 23) Even less is known about appropriate therapy for BPD-associated PH.

There is considerable evidence that NO-cGMP signaling is disrupted by preterm birth, lung injury, and neonatal pulmonary hypertension, which has generated interest in therapies targeted toward this pathway.(24, 25) For instance, inhaled nitric oxide acutely improved PA pressures during cardiac catheterization of infants with BPD-associated PH, but its long-term efficacy remains uncertain, and logistical challenges limit its use in the outpatient setting.(26) Sildenafil is a selective cGMP-specific phosphodiesterase inhibitor that was recently approved for treatment of adult pulmonary arterial hypertension.(27) Interestingly, pulmonary hypertension and therapies such as oxygen may increase expression and activity of cGMP-specific phosphodiesterases, which would be expected to lower cGMP concentrations and exaggerate pulmonary hypertension.(28) Sildenafil was recently investigated in term infants as a potential therapy for persistent pulmonary hypertension of the newborn (PPHN). Oral sildenafil improved survival in small cohort of term infants with PPHN vs. placebo (85% vs. 17%), (29) and a recent pilot trial of intravenous sildenafil showed acute improvements in oxygenation in infants treated with or without iNO.(30) Because oxygenation index was used as the endpoint, it was unclear whether the improvement seen with sildenafil was due purely to its vascular effects or whether there might have been some improvement in lung function as well.

The availability of sildenafil as an enteral preparation makes it feasible for long-term therapy for infants with BPD. In rodent models of BPD, sildenafil improved alveolarization and decreased BPD-associated remodeling of the pulmonary vasculature and right ventricular hypertrophy. (31, 32) More recently, Mourani et al described that long-term treatment with chronic oral sildenafil was well tolerated in infants with chronic lung disease and PH, and improved echocardiographic findings of pulmonary hypertension, including decreased systolic pulmonary artery pressure and reduced septal flattening.(22)

In this issue of *Journal of Perinatology*, Nyp et al extend these studies by providing an additional large case series of 21 infants that explores whether oral sildenafil produces short-term improvements in pulmonary hemodynamics and gas exchange in infants with moderate to severe BPD-associated PH. As noted in other case series, the authors found a high number of SGA infants in their population.(14) Patients were more than 5 months old at the time of sildenafil initiation, and at a median of 49 weeks corrected gestational age. Sildenafil was well tolerated, with transient hypotension observed in only one infant. While sildenafil acutely decreased PA pressures, unlike PPHN, there was no improvement in pulmonary gas exchange. Concurrent use of iNO did not appear to affect the response to sildenafil.

Nyp's findings highlight the challenging, multifactorial nature of the clinical problem. PPHN in term infants is most commonly a delayed vascular transition from intrauterine to extrauterine life. Even infants with vascular remodeling or hypoplasia often experience short-term improvements in oxygenation. In contrast, the infant with BPD-associated PH has both vascular hypoplasia and vascular remodeling in conjunction with alveolar simplification and parenchymal lung disease. While Nyp's study provides additional evidence that sildenafil improves the hemodynamic findings of pulmonary hypertension, a fixed component of vascular or parenchymal dysfunction appears to remain. Furthermore, long-term outcome data are still needed to determine whether benefits are sustained and whether reductions in PA pressure will improve long-term outcomes. We agree with the authors that chronic sildenafil therapy for BPD-associated PH should be approached cautiously at present, and hope that despite the considerable challenges, appropriate clinical studies will answer these important questions.

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