Is there a Role for Inhaled Nitric Oxide Therapy in Premature Infants?

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Early reports of inhaled nitric oxide (iNO) therapy in near-term and term newborns with acute hypoxemic respiratory failure and pulmonary hypertension described marked improvements in gas exchange, and subsequent multicenter, randomized trials have demonstrated that iNO decreases the need for extracorporeal life support in this population. INO is uniquely suited for the treatment of persistent pulmonary hypertension of the newborn (PPHN) due to its ability to selectively dilate of the pulmonary circulation and the absence of apparent short term toxicities when used at low doses.

Laboratory and clinical studies have also shown that in addition to its effects on reducing pulmonary artery pressure, other beneficial effects of iNO may include improvements in ventilation/perfusion matching, decreasing lung inflammation and oxidant stress, and favorably modulating angiogenesis and growth in the immature lung. As a result, in addition to considerable interest in the potential role of iNO in premature newborns to acutely improve cardiopulmonary function, iNO may also serve to modulating the severity of lung injury and reduce long-term respiratory morbidities. However, persistent concerns about potential toxicity have limited the use of iNO in premature newborns to controlled, clinical trials.

The results of recent clinical trials have helped to more clearly define the potential role of iNO in the premature newborn with respiratory failure, particularly as it relates to the prevention of bronchopulmonary dysplasia (BPD) and its effects on brain injury. The effects of iNO in the premature newborn may be dependent on the timing, dose, and duration of therapy, and the nature of the underlying disease. The available evidence from clinical trials suggests that low-dose iNO may be safe and effective in reducing the risk of death/BPD for a subset of premature newborns, in particular infants with birth weights > 1000 g. A neuroprotective effect of iNO has been demonstrated in large multicenter, randomized controlled trials, but the relationship of disease severity and intracranial hemorrhage or PVL risk is uncertain. Treatment of premature newborns with respiratory failure between 7-14 days after birth appears to be safe and effective in reducing the incidence of BPD. Currently, an industry (INO Therapeutics) sponsored trial of low dose iNO in premature newborns is underway in Europe (N=428). The results of this trial will provide more information about the safety and efficacy of iNO in this population. Indeed, if neuroprotection and/or BPD reduction with early iNO treatment are confirmed in this study, and long term follow-up studies describe lasting neurodevelopmental benefit, then routine use of iNO in premature newborns should gain regulatory approval. Meta-analysis of these clinical trials will follow, but should be limited to studies that were properly masked and designed to effectively measure relevant outcomes. Finally, early concerns about the potential adverse effects of iNO on

surfactant function and PDA risk have been effectively eliminated with the cumulative results of clinical trials, however, routine use of iNO in premature newborns should await the results of follow-up studies from the largest clinical trials, and the results of the ongoing European trial.

References

- Kinsella JP, Abman SH. Inhaled NO in the premature newborn. J Pediatr. 151:10-15, 2007.