Subject: Inhaled Nitric Oxide in Newborns

Overview: Inhaled nitric oxide (iNO) is used to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) in term and late preterm infants with severe persistent pulmonary hypertension of the newborn (PPHN).

Policy and Coverage Criteria:

Harvard Pilgrim considers inhaled nitric oxide medically necessary for term or near-term neonates (≥ 34 weeks gestational age) with all of the following:
- Confirmed hypoxic respiratory failure with evidence of pulmonary hypertension; AND
- No congenital diaphragmatic hernia

Harvard Pilgrim considers inhaled nitric oxide investigational/experimental for all indications not outlined above.

Exclusions: N/A

Supporting Information:

1. Technology Assessment
Nitric Oxide inhalation (iNO) therapy is a noninvasive treatment for PPHN that involves inhalation of gaseous nitric oxide in conjunction with ventilator support. The potential of exogenous NO as a therapeutic agent is based on its potent vasodilator properties and its ability to be delivered as a gas to the lung. Exogenous NO increases the partial pressure of arterial oxygen by dilating pulmonary vessels in better ventilated areas of the lung. NO inhalation therapy, in conjunction with ventilatory support, has been investigated for the treatment of term and near-term newborns, ≥ 34 weeks gestational age, with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

2. Literature Review
Ryan and Tobias (2007) retrospectively reviewed their experience with iNO in a pediatric ICU. In 19 patients who presented with respiratory failure, 15 of 19 showed an increase in oxygenation with iNO treatment. The 15 patients who responded to iNO treatment survived, while the other 4 patients who did not respond died. In 19 patients with pulmonary hypertension following cardiopulmonary bypass and surgery for CHD, iNO was used to treat the pulmonary hypertension. A high pulmonary artery pressure was documented in 13 of these 19 patients and iNO resulted in a decrease in the PA pressure in 9 of these patients.
Finer and Barrington (2006) conducted a review to determine whether treatment of hypoxic term and near-term newborn infants with iNO improves oxygenation and reduces the rates of death, the requirement for ECMO, or affects long term neurodevelopmental outcomes. Fourteen RCTs were included in the review. Seven of these trials compared iNO to control in infants with moderate or severe illness. Four of these trials compared iNO to control, but allowed iNO backup treatment for some infants over time. Two trials enrolled infants with moderate severity of illness and randomized to immediate iNO treatment or iNO treatment only if they deteriorated to more severe criteria. One trial studied only infants with congenital diaphragmatic hernia, and one trial enrolled both preterm and term infants, but reported the majority of the results separately for the two groups. Inhaled nitric oxide appears to improve outcome in hypoxemic term and near term infants by reducing the incidence of the combined endpoint of death or need for ECMO. The reduction seems to be entirely a reduction in need for ECMO; mortality is not reduced. Oxygenation improves in approximately 50% of infants receiving nitric oxide.
infants have clear echocardiographic evidence of PPHN or not does not appear to affect outcome. The outcome of infants with diaphragmatic hernia was not improved and there is a suggestion that outcome was slightly worsened. The authors concluded that the use of NO is reasonable for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.

Sadiq et al (2003) conducted a randomized, prospective multicenter study to assess whether NO in patients with moderate PPHN would improve PaO2, prevent progression to severe PPHN, and improve outcomes. A total of 80 patients were randomized to receive either standard medical therapy or standard medical therapy plus NO. In the NO group, NO concentration was increased in steps of 10-20 ppm every 30 minutes until there was no further improvement in PaO2. 58% of control patients compared to 15% of NO patients failed assigned therapy and developed severe PPHN. PaO2 improved from 112 +/- 48 to 133 +/- 100 in the control group compared to an improvement of 101 +/- 29 to 208 +/- 118 in the NO group. For the first 36 hours after the study, entry AaDO2 levels and ventilator support were significantly lower in the NO group compared to control. The authors concluded that treatment with NO improves PaO2, reduces the amount of ventilator support needed, and prevents progression to severe PPHN in patients with moderate PPHN.

Clark et al (2000) conducted a clinical trial to determine whether low-dose NO would reduce the use of ECMO in neonates with PPHN who were born after 34 weeks’ gestation, were 4 days or older, required assisted ventilation, and had hypoxic respiratory failure as defined by an oxygenation of 25 or higher. A total of 248 neonates were included and 126 were randomly assigned to the NO group and 122 to the control group. ECMO was used in 64% of the control group and 38% of the NO group. There was a similar 30-day mortality rate in the two groups. Neonates in the NO group developed less chronic lung disease than in the control group. The authors concluded that NO reduces the extent to which ECMO is needed in neonates with hypoxic respiratory failure and pulmonary hypertension.

Davidson et al (1998) assessed the dose-related effects of iNO as a specified adjunct to early conventional therapy for 155 term infants with PPHN, with regard to neonatal outcome, oxygenation, and safety. Infants were randomized to receive either a control or NO and treatment was administered until success or failure criteria were met. The authors found that for term infants with PPHN, early NO as the sole adjunct to conventional management produced an acute and sustained improvement in oxygenation for 24 hours without short-term side effects, and suggests ECMO use may be reduced.

A study conducted by the Neonatal Inhaled Nitric Oxide Study Group (1997) sought to determine whether inhaled NO would reduce mortality or the initiation of extracorporeal membrane oxygenation in infants with hypoxic respiratory failure. Infants who were included in the study consisted of 235 infants born after gestation of >/= 34 weeks who were 14 days old or less, had no structural heart disease, and required assisted ventilation and whose oxygenation index was 25 or higher on two measurements. Infants were randomly assigned to receive NO at 20 ppm (n=114) or control of oxygen only (n=121). 64% of the control group and 46% of the NO group died within 120 days or were treated with ECMO. Significantly fewer infants in the NO group received ECMO. The NO group had significantly greater improvement in PaO2 and in the oxygenation index. The authors concluded that NO therapy reduced the use of ECMO, but had no apparent effect on mortality in critically ill infants with hypoxic respiratory failure.

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Kinsella et al (1997) conducted a randomized, multicenter clinical trial to determine the relative roles of NO and high-frequency oscillatory ventilation (HFOV) in the treatment of severe PPHN in 205 neonates. Infants were stratified by disease then randomly assigned to either HFOV (n=98) or NO (n=107). 26% of infants recovered with the initially assigned therapy without crossover. Of infants whose initial treatment failed, crossover treatment with the alternative therapy was successful in 21% for NO and 14% for HFOV. Both treatment strategies failed in 125 infants and 32% of these infants responded to combination therapy with NO plus HFOV. Overall, 60% responded to either treatment alone or combination therapy. The authors concluded that the treatment with HFOV plus NO is often more successful than treatment with HFOV or NO alone in severe PPHN.

Wessel et al (1997) conducted a prospective, randomized trial to determine the effect of NO on clinical outcome in 49 mechanically ventilated newborns with PPHN. Infants were randomized to receive treatment with iNO or
without iNO. Mortality (8%), use of ECMO (33%), median days on mechanical ventilation (9 days), and duration of supplemental oxygen (13 days) were not different between treatment groups. PaO2, oxygen saturation, and OI improved in the NO group compared with baseline and to control patients at 15 minutes. The median percent change in OI (-31%) in the NO group was significantly different from baseline and from the control group. Before cannulation for ECMO, oxygenation was better in the NO group compared with control patients. There was a tendency to observe fewer adverse neurologic events (seizure and intracranial hemorrhage) in the NO group (4/26 vs 8/23). The authors concluded that sustained improvement in oxygenation with NO and better oxygenation at initiation of ECMO may have important clinical benefits.

3. Professional/Governmental Organizations

FDA:
INOmax is a vasodilator, which, in conjunction with ventilator support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020845s014lbl.pdf

CMS: No LCD/NCD

ACCF/AHA 2009 Consensus Statement:
Persistent PH [pulmonary hypertension] of the newborn is a syndrome characterized by increased pulmonary vascular resistance, right to left shunting, and severe hypoxemia. Treatment options include inhaled nitric oxide (INO) and extracorporeal membrane oxygenation. Pediatric IPAH [idiopathic pulmonary arterial hypertension] is treated similar to that in adults. A higher percentage of children are acute responders and candidates for calcium channel blockers.

AAP:
Recommendations:
• iNO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label (http://www.fda.gov). An echocardiogram to rule out congenital heart disease is recommended. Center-specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.
• Administration of iNO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remains experimental. As such, iNO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed parental consent.

Codes:

CPT:
93463 - Pharmacologic agent administration (eg, inhaled nitric oxide, intravenous infusion of nitroprusside, dobutamine, milrinone, or other agent) including assessing hemodynamic measurements before, during, after and repeat pharmacologic agent administration, when performed

References:


Summary of Changes

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<th>Date</th>
<th>Change</th>
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<tr>
<td>4/17</td>
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