Use of Inhaled Nitric Oxide in Infants Treated in Neonatal Units in England

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NO News Is Good News

A startlingly simple molecule unites neuroscience, physiology, and immunology and redefines scientists' understanding of how cells communicate and defend themselves.

A decade ago, nitric oxide (NO) was just another toxic molecule, one of a lengthy list of environmental pollutants found in unsavory haunts such as cigarette smoke and some natural processes of ozone, suspected carcinogen, and contributor to acid rain, trash.

But over the past 5 years, diverse lines of evidence have converged to show that this sometime poison is a fundamental player in many physiological and pathological processes, and recently researchers realized they were studying the same molecule. Like a squirt of powerful perfume, a puff of nitric oxide spurs different cells into an array of different activities, from communication to defense to regulation.

Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn

Jesse D. Roberts, David M. Polaner, Peter Lang, Warren M. Zapol

Nitric oxide (NO) has vasodilatory effects on the pulmonary vasculature in adults and animals. We examined the effects of systemic oxygenation and blood pressure of inhaling up to 80 parts per million by volume of NO at FIO2 0.9 for up to 30 minutes by 6 infants with persistent pulmonary hypertension of the newborn (PPHN). In all infants this treatment rapidly and significantly increased predural oxygen saturation (SpO2); in 5 infants postdural SpO2 and oxygen tensions also increased. Inhalation of NO did not cause systemic hypotension or increase methaemoglobin. These data suggest that low levels of inhaled NO have an important role in the reversal of hypoxaemia due to PPHN.


In persistent pulmonary hypertension of the newborn (PPHN)—a syndrome that can be idiopathic or associated with various neonatal cardiorespiratory diseases, including meconium aspiration and group B streptococcal sepsis—increased pulmonary vascular resistance results in right-to-left shunting of blood across the patent ductus arteriosus and...
Inhaled Nitric Oxide: Product Licence

[EMEA 2001]

Licensed for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.
Using data submitted from Badgernet platform into the NNRD database:

1. To investigate trends in iNO usage in neonates in a geographically defined population

2. To define the extent of unlicensed (off-label) use of iNO in neonates.

3. To describe variation in iNO use between neonatal units
• Retrospective cohort study of iNO use in neonates

• Badgernet – NNRD data download (2010-2015)

• English neonatal units (n~165)

• 6-year period, 3 epochs (2010-11, 2012-13, 2014-15)

• 3 gestation bands, <29w, 29-33w, >=34w

• Baby-level and unit-level analyses
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<tr>
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<th>2010-2011</th>
<th>2012-2013</th>
<th>2014-2015</th>
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<tbody>
<tr>
<td>Neonatal admissions [babies receiving ≥ 1 day of IC]</td>
<td>37,885</td>
<td>43,160</td>
<td>48,838</td>
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<tr>
<td>Infants treated with iNO</td>
<td>1,296 (3.4%)</td>
<td>1,941 (4.5%)</td>
<td>3,112 (6.4%)*</td>
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* p < 0.001 [2010-2011 compared with 2014-2015]
iNO use by Gestation

% of babies receiving > 1 day IC

\[ p < 0.001 \]
iNO use by Gestation

% of babies receiving > 1 day IC

p = <0.001

< 29w

29-33 w

2010-11

2012-13

2014-15
iNO use by Gestation

% of babies receiving > 1 day IC

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<td>Preterm infants &lt; 34 weeks’ gestation treated with iNO</td>
<td>772 (48%)</td>
<td>926 (48%)</td>
<td>1712 (55%)**</td>
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** p < 0.0001 [2010-2011 compared with 2014-2015]
iNO use by Unit

% of babies receiving > 1 day IC treated with iNO

[Excludes units treating fewer than 5 babies]
Summary

1. The use of iNO increased significantly in English neonatal units between 2010 and 2015 with ~900 more babies treated/year.

2. 55% of all infants treated with iNO are preterm < 34 weeks’ gestation in whom iNO is used outside its licensed indication.

3. The largest proportional increase was in preterm infants (3-4 fold increase).

4. There is wide variation in iNO usage between English neonatal units, especially in extreme preterm infants.
Why has the use of iNO increased?

• Increased familiarity with the drug, no reports of significant adverse safety signals in term infants

• Absence of other proven treatments in preterm hypoxaemic respiratory failure +/- PPHN physiology

• Emerging evidence of promise in specific disease conditions – expert consensus statements (eg. in PPHN/PPROM)

• No national guidelines/no financial restrictions on off-label use of iNO in preterm infants