

Does Nitric Oxide Inhalation Need to be Reassessed?

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Background: Inhaled nitric oxide is a drug which has been given FDA approval in 1999 but was not found prior to approval to be safe for use in premature neonates. **Aim:** To review and assess the studies which was done prior to its approval in order to find out what evidences the approval by the FDA was based on. **Methods:** A thorough search of the electronic data-base, Medline, Embase, Cinahl, Google. **Conclusion:** The use of this drug in treatment of the Pulmonary hypertension in premature babies is still contraversial and hold a serious untoward effects on the health, it should only used as the last ditch.

Key words: inhaled nitric oxide, pulmonary hypertension, premature neonates.

The Neonatal Inhaled Nitric Oxide study group (1997) declared that inhaled nitric oxide (iNO) is efficient and safe in treating persistent pulmonary hypertension in full-term and nearly full-term infants with hypoxic respiratory failure (Ninos 1997A). However, concerns remain that iNO is involved a wide variety of biological activities and possibly potential toxicity (Bernasconi and Beghetti 2002), the efficacy of the drug is not well established for the treatment of infants with hypoxic respiratory failure (Barrington and Finner 2001), nor has any statistically significant effect on reducing mortality been demonstrated (Sokol et al 2005). Prior to approval of nitric oxide (NO) for medicinal use in 1999, 3500 trials and studies were carried out on this drug between 1985 -1998 (Niall et al 2000). spite of this quantity of research, nitric oxide is still viewed as a drug under investigation (Brough et al 2004).

Hascoet et al., (2005) and Hamon et al., (2005), however, found that NO is an effective drug when used for premature babies with primary pulmonary hypertension (PPHN) in the first 28 days of life. Even so, up to 40% of infants failed to respond to it. Therefore, it should be administered only in centres where ECMO is available (Mupanemunda and Watkinson (2005).

This Review aims to:

- Describe the disadvantages and advantages of NO use.
- Critically assess the evidence for supporting or discouraging the use of iNO in neonatal and pediatrics wards.

Definition: NO is a highly diffusible, colourless gas with a sweet sharp odour (Yeo H 2000).

It is produced from L-arginine by an enzyme called NO synthase (Levin and Morriss 1997). This free radical is rapidly converted into other active substances such as nitrogen dioxide, Peroxynitrates and nitrotyrosine (Pryor 1995). It has been found that in primary pulmonary hypertension of newborn there is decreased ability to produce this substance (Mitchell 1996). So administration of this substance directly to the lung of those newborn may lead to reduction of the pulmonary hypertension and improvement of oxygenation (Michele et al 2000).

Disadvantages of Nitric Oxide: Inhaled NO has an injurious effect on lung tissues of rats (Kao et al., 2003). This occurs through different mechanisms (McAndrew 1997) and is mostly due to diffuse inflammation of lungs tissues (Muller et al., 1994). This is caused by the release of active substances, such as nitrogen dioxide, peroxy nitrates and nitrotyrosine, in the presence of superoxide (Pryor 1995). Inhaled NO may cause acute lung injury in humans (Palmer et al., 1987) Or impair surfactant function (Haddad 1993). Fortunately, these toxic substances are maintained at low levels and their toxic effects can be moderated by dietary and endogenous antioxidants as well as signal transduction and repair pathways (Ames et al., 1993). In contrast, Gaston et al 1994 found no side effects with doses up to 40-80 ppm. Studies on rats have shown that no side effects are seen after exposure to up to 1500 ppm for 15 minutes. However, if extreme doses are used it seems to lead rapidly to methaemoglobinemia and a toxic pulmonary oedema, which may be more, related to the transformation of NO to NO₂ than to a direct effect of NO (Stavert et al., 1990).

The possibility of pulmonary hypertension rebound after withdrawal of inhaled nitric oxide (Carvalho et al., 2000), is due to cyclooxygenase (Chen et al., 2003). Different mechanisms can explain this phenomenon, i.e.: a possible down reduction in endogenous production of NO by the administration of exogenous iNO, slow recovery from cell dysfunction taking several days or a combination of both (Bernasconi and Beghetti 2001). Recently, an increase in endogenous endothelin has also been suggested as a potential mechanism (McMullan et al 2001). The rebound effect has been overcome by the use of cyclooxygenase inhibitor (Chen et al., 2003). Care also needs to be taken not to stop the therapy suddenly (Morton et al). Non steroidal anti-inflammatory drugs such as Ibuprofen also have cyclooxygenase inhibiting properties (Wallace and Del Soldato 2003) and transient increase in the fraction of inspired oxygen (Aly et al., 1997). The use of dipyridamole allows high levels of cGMP in the smooth muscle cells to be maintained, thus prolonging the effect of inhaled NO (Ivy et al., 1998 and Alaiyan 1996). The use of

sildenafil has also been reported to be beneficial (Atz and Wessel 1999).

Inhaled nitric oxide inhibits platelets aggregation and has an antileukocytic effect (Gries et al., 2003). Causing hemorrhagic complications (Miller 1995). This effect is due to the activation of platelet quanyl cyclase and the formation of cGMP (Levin and Morriss 1997).

NO has been demonstrated to be mutagenic to mammalian cells (Tamir et al., 1996). Recent data suggest that lower doses (e.g., 1 ppm) may be safer and more effective than the higher doses used previously (Dellinger et al., 1998).

The cost of NO therapy has forced many clinicians in the USA to reconsider their indications for this treatment and think of an alternative (Stuart and Lawson 2002) fortunately, NO cost still less than using ECMO which is not only more expensive but also more invasive than NO (Angus C 2003), but may carry potential toxicity to attendant medical and nursing staff more than ECMO (Mupanemunda and Watkinson 2005).

Side Effects of NO₂: iNO is clearly a cytotoxic product, leading to pulmonary epithelial cell damage, interstitial atrophy and fibrosis (Gaston et al., 1994), NO₂ toxicity is 5-25 times as high as NO as estimated by centres for disease control (1988), even in small doses over 5ppm (Foubert et al. 1992), it's toxicity can be controlled by instituting the following guidelines when using nitric oxide: administer the lowest effective dose of iNO with a maximal dose of 40 to 80 ppm, administer the lowest possible concentration of O₂, monitor O₂, NO and NO₂ concentrations; minimise the transit time in the ventilator by using high gas flow rates to flush out alveolar gases; minimise the exposure time of NO to oxygen before it reaches the patient (Bernasconi and Beghetti 2002).

Toxicity of Methemoglobin The formation of methemoglobin and resultant methemoglobinemia leads to decreased haemoglobin oxygen binding capacity, causing seizures, coma, cardiac dysarrhythmias and death (Morton et al., 2005). Populations with low methemoglobin reductase activity, apt to develop high methemoglobin concentrations during administration of NO, are neonates and Native Americans (Rogers and Helfaer 1999). Fortunately, high levels of methemoglobin are a rare incident (Roberts et al., 1997). To counteract this side effect, methemoglobin levels should be monitored daily in infants receiving iNO (Cloherty et al., 2004).

Advantages of NO Inhalation: The main advantage of iNO is it selectively acts on the lungs and is quickly inactivated by haemoglobin leaving no systemic effects (Studel et al., 1999 and Rogers and Helfaer 1999), iNO mainly causes pulmonary vasodilatation in lung units which are already open for ventilation and thus would not have the adverse effect of increased intrapulmonary shunt noted with systemically administered vasodilators (Levin D and Morriss F 1997). Conditions in which inhaled NO is associated with a survival benefit are those in which there

is acutely raised pulmonary vascular resistance which is not secondary to severe lung disease (Vickers et al., 1999). There is growing evidence that iNO has extrapulmonary effects due to a growing body of data suggesting that inhaled nitric oxide can cause measurable vasodilatation in extrapulmonary circulation (Quezado et al., 1998) which may be observed by the binding of nitric oxide to circulating albumin or haemoglobin.

iNO may be useful as a rescue treatment for a short period of time; 24 - 96 hours (Sokol et al., 2005) in a variety of conditions such as acute vasoocclusive crisis (Weiner et al., 2003), and infants who have respiratory failure and sepsis (Aikio et al., 2003). It decreases RV afterload and can produce an immediate improvement in hemodynamic status permitting a decrease in catecholamines administration from day 2-8 (Meaudre et al., 2005). It has also been used with conventional or high frequency ventilation to improve oxygenation in patients with meconium aspiration syndrome (Mupanamunda and Watkinson 2005), leading to a reduction in the use of extra corporeal membrane oxygenation (Clarke et al., 2000).

After a lung transplant, the graft rejection was decreased by NO use (Cornfield et al., 2003), in addition, it prevented progression to severe PPHN and reduced the need for ventilatory support (Sadiq et al., 2003). NO also helped patients with VSD and severe pulmonary hypertension to be weaned from cardiopulmonary bypass (Honda et al., 2003), as well as in patients of atrial septal defects with pulmonary hypertension (Kim et al., 2002). There is no contraindication to performing chest physiotherapy in-patients receiving NO but monitoring for elevation in pulmonary artery pressure, desaturation, or variances in pulmonary artery pressure (Levin and Morriss 1997). Clinical trials indicate the need for extracorporeal membrane oxygenation (ECMO) is diminished by iNO (Kinsella and Abman 2000), fortunately, clinical and subclinical effects related to NO and NO₂ exposure, such as methemoglobinemia and respiratory irritation, are not expected during the use of the iNOvent delivery system (Margaret et al., 1999).

iNO may have a bronchodilatation effect (Rogers and Helfaer 1999) therefore, shows promise in the treatment of severe bronchial asthma (Lewin and Morriss 1997), in addition, inhaled nitric oxide can improve exercise capacity in patients with pulmonary artery hypertension (Hasuda 2000), however, this treatment requires a continuous inhalation device and is impractical (Liu and Cheng 2005).

Evidence against the use of iNO in preterm infants before FDA approval:

In a report produced by (Nicholl R 2002) involving 349 preterm neonates who were exposed to inhaled NO for PPHN treatment, It was concluded that none of the studies were able to answer the original question. The largest studies were under powered and failed to show important benefits for iNO in preterm babies. The smaller studies

showed short-term physiological changes e.g. Subhedar: transient fall in OI with 5ppm iNO; Skimming: equal increases in oxygen tension after 15min of either 5 or 20ppm iNO. The possible longer-term side effects of iNO are not known. In spite of this, iNO is being routinely used in many UK neonatal units, without the safeguards implicit in participation in a clinical trial. Therefore, Preterm infants should not be treated with inhaled nitric oxide outside of prospective, randomised-controlled trials. Long-term follow up is needed (Nicholl 2002).

In the Franco Belgium Collaborative NO trial group (1999) randomly assigned 204 preterm (<33 weeks) and near term neonates (33 weeks) with oxygenation indices

from 12.5 to 50 and 15 to 40, respectively, were randomly assigned to 10 ppm iNO (n=105) or control ventilation therapy without iNO (n=99). Neonates with a gestational age 33 weeks had a significant reduction in OI, duration of mechanical ventilation and duration of NICU stay. But in the group < 33 weeks there was no significant reduction. This study was underpowered.

A French study conducted by Dupont et al (1999) concluded that efficacy of inhaled NO in improving oxygenation is moderate and difficult to predict, response to first NO inhalation was not associated with prognosis, and treatment of the most severe ARDS patients with inhaled NO did not influenced their intensive care unit survival.

Report of the trials supporting the use of iNO in premature infants (Adapted from Nicholl 2002).

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Subhedar NV et al, 1997, UK	42 preterm babies (<32wk) randomised to iNO alone; dexamethasone alone; both; neither	Open RCT (1b)	Death before discharge and/or CLD	RR 1.05, 95% CI 0.84-1.25 for iNO v controls	Neither treatment prevented CLD or death
Skimming JW et al, 1997, USA	23 preterms randomised to either 5 or 20ppm iNO	Open RCT (1b)	Arterial blood oxygen tension, 15mins after intervention	Equal increases in primary outcome, both groups	Short term physiological study No control group
The Franco-Belgium Collaborative NO trial Group, 1999, France/Belgium	204 preterm babies, randomised to 10ppm iNO or control	Open, multi centre, RCT	OI at 2h	Median 8.4 (iNO) v 12.4 (control); p= 0.005. Greatest in near-term infants	Study underpowered Baseline OI higher in the experimental group
Kinsella JP et al, 1999, USA	80 preterm babies, <34wk, randomised to 5ppm iNO or control.	Double blind RCT, single centre (1b)	Survival to discharge	RR 1.11, 95% CI 0.70-1.8	Exp. Group had improved PaO2 at 60min Study underpowered

The current published evidence from randomised trials does not support the use of nitric oxide in preterm infants with hypoxic respiratory failure (Barrington and Finner (2001). Nor demonstrated any statistically significant effect on mortality (Sokol et al 2003).

Subhedar et al (1997), included 42 preterm neonates < 32 weeks, who were recruited at 4 days of age if they were at high risk of developing bronchopulmonary dysplasia. Neonates were randomised to receive either iNO or dexamethasone, or both or none of the treatments. There was no difference in survival, chronic lung disease, or intracranial haemorrhage between iNO treated infants and control group. One of the major restrictions of this study is the small number of neonates randomised.

On the other hand, Kinsella et al (1999) assessed the effects of low dose iNO (5ppm) in 80 premature neonates with severe hypoxaemic respiratory failure and found that iNO induced a significant improvement in oxygenation after 60minutes. There was, however, no difference in survival. The low dose of iNO did not increase the risk of

bleeding complications. They further concluded that low dose iNO may be effective as a lung anti-inflammatory therapy because this treatment may affect neutrophil adhesion in the microcirculation. Their study was randomised and all participants were analysed but has relatively low number of patients recruited which makes it difficult to be generalised, In the mean time ignored the weights and the gestational ages of the premature infants who were recruited in the study.

In a systematic review done by Sokol et al (2003), five randomised-controlled trials were evaluated, assessing 535 patients with acute hypoxemic respiratory failure (age range not provided). Lack of data prevented assessment of all outcomes, there was no significant difference of nitric oxide on mortality in trials without crossover (RR 0.98, 95%CI 0.66,1.44). Published evidence from one study demonstrated nitric oxide to transiently improve oxygenation in the first 72 hours of treatment. Limited data demonstrated no significant difference in ventilator-free days between treatment and placebo groups, and no

specific dose of nitric oxide was significantly advantageous over another. Other clinical indicators of effectiveness, such as duration of hospital and intensive care stay, were inconsistently reported.

Evidence supporting the efficacy of NO in premature neonates

Three major studies have provided evidence that iNO substantially improves oxygenation when administered in severe hypoxic respiratory failure (Ninos 1997) or in persistent pulmonary hypertension of the newborns, (Roberts et al 1997) and (Davidson 1998). The trials of ninos, Roberts, and Davidson can be compared on several important points. The studies were limited to term infants (39 to 40 weeks-mean gestation) with birth weights of 3.2 to 3.5 kg, with enrolment occurring at an average of 1 to 11/2 days of life. The proportion of infants with meconium aspiration syndrome, and with idiopathic pulmonary vascular disease, appeared to be similar in each study. All three studies used placebo treatment and prohibited crossover or rescue. Two of the studies, Roberts and Ninos (A) were blind. All provided for ECMO for treatment failures. All the enrolled infants demonstrated at least moderate to severe respiratory failure, as defined by oxygenation index. Cumulatively, the three studies enrolled infants from 26 treatment centres in the United States and Canada. The studies were conducted essentially concomitantly. One limitation in comparing these studies is that the dosage of nitric oxide varied slightly among studies and the characteristics of peak dosage and weaning were unique to each study. Also the need for ECMO was significantly reduced (Ninos 1997).

Peliowski et al., (1995) reported their experience with iNO therapy in 8 premature neonates between 24 and 31 weeks of gestation. Significant reduction of oxygen index and mean airway pressures were described during iNO inhalation.

However, generalised conclusions cannot be drawn from this study due to the small number of premature infants studied.

Conclusion:

In December 1999, the Food and Drug Administration (FDA) granted approval to market nitric oxide for inhalation. In spite of the fact, that nitric oxide is a new drug with promising scope, caution must be the rule with this molecule due to its wide variety of biological activity and potential toxicity (Bernasconi and Beghetti 2002). It's true efficacy and effects on morbidity and mortality remain to be determined especially in premature neonates (Levin D and Morris F 1997). Michele et al., (2000) recommended that care should be taken while using this medication due to side effects which have mainly occurred when it is administered by inexperienced people. All side effects of this drug can be dealt with and counteracted.

iNO is superior to other pulmonary vasodilators due to its higher selectivity and the relative absence of systemic side effects during its use.

Currently it is used as a last ditch measure to improve oxygenation in acute severe respiratory distress syndrome, nevertheless, it seems that many more trials should be carried out before this drug becomes available universally. Further research on its long-term side effects is needed.

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