

Annotation

Inhaled nitric oxide in neonates

Scientific foundation

Nitric oxide (NO) is a major regulator of vascular smooth muscle tone. Generated enzymatically by one of several NO synthases from L-arginine,¹ NO activates guanylyl cyclase by binding to its haem component,² leading to the production of cyclic GMP.³⁻⁴ This then relaxes vascular and bronchial smooth muscle by a mechanism which probably involves inhibition of an activation induced increase in cytosolic calcium concentration.⁵ NO has a high affinity for the iron of haem proteins, including reduced haemoglobin, forming nitrosyl haemoglobin (NOHb), which is then oxidised to methaemoglobin with the production of nitrate.⁶⁻⁷ As a result, when given as an inhalation, NO relaxes pulmonary vascular smooth muscle and is inactivated without altering the systemic vascular bed. NO mediates the reduction in pulmonary vascular resistance associated with birth.⁸⁻¹⁰ Inhalation of NO, in a variety of animal models, is an effective, selective pulmonary vasodilator which improves ventilation perfusion matching.¹¹⁻¹² In adults with severe respiratory distress syndrome treatment with inhaled nitric oxide (INO) reduced pulmonary arterial pressure and increased oxygenation secondary to a decrease in intrapulmonary shunting,¹³ with an improvement in oxygenation and a reduction in pulmonary vascular resistance (PVR) noted at INO doses as low as 1 ppm.¹⁴⁻¹⁵ The clinical use of INO in neonates has mushroomed since the original reports by Roberts¹⁶ and Kinsella¹⁷ which demonstrated sustained improvements in oxygenation in hypoxic near term infants with persistent pulmonary hypertension (PPHN), using 80 ppm and 20 ppm of INO, respectively. A subsequent preliminary dosing study did not demonstrate a significant dose effect in hypoxic neonates.¹⁸

Prospective controlled trials in neonates

As a result of these observations, a multicentre, multinational, prospective placebo controlled randomised trial was conducted to evaluate whether INO would reduce the incidence of death or the need for ECMO in neonates of 34 weeks gestation or greater with hypoxic respiratory failure (NINOS Study).¹⁹ Eligible infants required assisted ventilation with two oxygenation indexes ($OI = (MAP \times FIO_2 \times 100) / PaO_2$) equal to or greater than 25. While echocardiograms were performed before randomisation, the diagnosis of PPHN was not a required inclusion criteria. This trial encouraged maximal conventional treatment before randomisation. Thus rescue surfactant treatment was given to over 70% of the enrolled infants; about 55% of infants were treated with high frequency ventilation; and over 90% of infants received blood volume support, vasopressors, sedation and/or analgesia, and muscle paralysis. Alkalosis was induced in over 75% of enrolled infants before randomisation with no differences observed in the use of such treatments between INO and placebo (oxygen) treated infants. The trial was terminated on 2 May, 1996 following the second planned review by the Data Safety Monitoring Committee at which time 235 of the planned 250 infants

had been enrolled. Treatment with INO resulted in a significant reduction in the primary outcome (combined incidence of death <120 days or the need for ECMO) from 64% in control infants to 46% in INO treated infants; $P=0.005$, $RR=0.71$, 95% $CI\ 0.56, 0.90$. There was no difference in the occurrence of death (17% of controls *vs* 14% of INO infants), and there was a significant reduction in the need for ECMO from 55% in control infants to 39% in INO treated infants ($P=0.014$).¹⁹ INO treatment resulted in a significant improvement in PaO_2 ($\Delta PaO_2 +59.6 \pm 85.6$ *vs* 9 ± 51.8 , $P<0.001$) and a significant fall in the OI (-14.1 ± 21.0 *vs* 1 ± 21.2 , $P<0.001$).

Other prospective controlled studies of near term infants with hypoxic respiratory failure and PPHN have been completed and the preliminary findings reported. Kinsella *et al*²⁰ enrolled 205 ECMO candidates in a prospective randomised multicentre crossover clinical trial of HFOV (high frequency oxygen ventilation) and INO. This study found no difference in the need for ECMO or death in the INO group compared with the HFO group, and the authors suggested that combined treatment with INO and HFO may improve outcome. Wessel *et al*²¹ studied 49 neonates with PPHN of 34 weeks gestation or greater and reported that oxygenation was better in the NO group than in controls ($P<0.02$). Roberts *et al*²² treated 50 term infants with PPHN and found that treatment with INO was more successful than conventional treatment in reducing the OI to less than 40.

Published trials to date include that of Day *et al*,²³ who studied 22 infants with PPHN and OIs between 25 and 40 in a prospective randomised trial of INO, and also treated all infants who had, or developed, an OI of greater than 40 with INO. They found that INO was associated with improved oxygenation, especially in patients with minimal or focal lung disease, whereas infants with lung hypoplasia and severe diffuse lung disease on chest radiograph were less likely to show a favourable response. Goldman *et al*²⁴ described four patterns of response to INO, and similar to Day *et al*,²³ noted that infants who had a sustained fall in OI to less than 40 did well, whereas those infants whose OIs increased above 40 either died or, with one exception, required ECMO. They also noted a group of infants who responded but became dependent on higher doses of INO and died of pulmonary hypoplasia and dysplasia. We have seen a small number of infants who have failed to respond to lower doses of NO and who respond exclusively to high dose—60 to 80 ppm of INO—similar to those described by Goldman *et al*.²⁴ In our experience a significant portion of such infants have fatal congenital abnormalities of their pulmonary vasculature, so called misalignment of the pulmonary veins or alveolar capillary block.²⁵⁻²⁶ In contrast to the previous studies, no reduction in the need for ECMO was found in one other prospective randomised crossover trial of 17 neonates.²⁷

Congenital diaphragmatic hernia

The NINOS pilot trial of term and near term infants with congenital diaphragmatic hernia (CDH) enrolled 53

infants and found that there was no significant difference in the occurrence of the primary outcome, death, and/or the need for ECMO between the INO and control groups, although INO infants required ECMO more frequently than control infants (80% *vs* 53.6%, $P=0.043$).²⁸

Other published case series have also noted a general lack of a sustained improvement in oxygenation in response to INO in the early management of CDH, with occasional exceptions.²⁹⁻³³ Some infants seem to develop improved oxygenation in association with INO treatment used later in their disease course.³⁰

Premature infants

Pulmonary hypertension is not unique to the full term infant, and Stahlman *et al* described raised pulmonary artery pressures in premature infants with significant respiratory distress over 20 years ago,³⁴ a finding which has recently been reconfirmed by echocardiography.^{35 36} We and others have reported a small number of premature infants who were treated with INO with significant improvements in oxygenation.^{37 38} The preliminary results of a prospective study of INO on premature infants of less than 32 weeks gestation requiring mechanical ventilation reported that infants who received INO had a sustained fall in OI and a reduction in pulmonary artery pressure (PAP) (Subhedar *et al*, abstract presented at the British Neonatal Society, November 1996). In the study by Day *et al*³³ 16 infants of less than 36 weeks gestation responded similarly to the more mature infants treated in this study. Skimming *et al* administered either 5 ppm or 20 ppm INO to 20 premature infants of 28 weeks gestation with respiratory distress syndrome and reported significant increases in PaO₂ at both doses.³⁹ No prospective trials evaluating clinically important outcomes with adequate numbers of premature infants have been reported to date.

Infants with congenital heart disease

Infants with congenital heart disease and preoperative or postoperative pulmonary hypertension have been treated with INO using very low doses of INO to lower their pulmonary vascular resistance,^{40 41} and to compensate for reduced pulmonary endothelial NO production following cardiopulmonary bypass.^{42 43} No prospective placebo controlled trials have yet been reported in infants with congenital heart disease.

Other clinical considerations

Clinicians who have treated significant numbers of neonates with INO will have observed the dramatic decrease in oxygenation seen in some infants when INO is discontinued, even if such infants have not had a dramatic initial improvement in their arterial oxygen concentrations. This response has been described in children⁴⁴ and older patients⁴⁵ and may reflect down-regulation of endogenous NO synthase activity secondary to the administration of exogenous NO. An alternate explanation may be that during exogenous NO treatment, cGMP specific phosphodiesterase may be increased. Following discontinuation of INO, therefore, the increased phosphodiesterase activity may continue to degrade endogenous NO resulting in vasoconstriction. Whatever the cause, INO should be cautiously weaned, with a reduction to very low doses (1 to 2 ppm) before stopping the inhalation. A similar rebound effect in pulmonary artery pressure has been described in infants and children receiving NO for pulmonary hypertension following cardiac surgery.⁴⁶ Such infants should continue to be carefully monitored for the next 1 to 2 hours and the clinician should be prepared to reinstate treatment if clinical deterioration occurs.

If the response of an infant has been equivocal, especially if transportation is required for other treatments such as ECMO, a trial of withdrawal of INO before transport is indicated. If the infant deteriorates INO should be continued until other rescue treatments are directly available. INO can be safely administered during transport.^{47 48}

Under rare circumstances INO may result in an acute clinical deterioration, such as in infants with ductal dependent systemic blood flow, or as the result of an unexplained paradoxical response.⁴⁹ However, most infants not showing a significant improvement in oxygenation following treatment with INO do not show any deterioration associated with this treatment and, in fact, may have less physiological variability and clinical instability, possibly resulting from decreased pulmonary artery reactivity.

The monitoring of INO can be done using other chemiluminescence or electrochemical sensors, the latter tending to be somewhat smaller and more portable, and current iterations of either device provide for continuous and reasonably accurate monitoring of both NO and NO₂. Continuous monitoring is required to avoid inadvertent increases in NO or sudden discontinuation of NO as a result of gas lines becoming disconnected or a loss of NO gas supply.

Toxicity

Nitric oxide reacts with oxygen to form nitrogen dioxide, NO₂.^{50 51} Both NO and NO₂ are toxic, causing death in dogs at concentrations between 0.1 and 2%, due to methaemoglobinaemia, hypoxaemia, and pulmonary oedema; much lower concentrations of NO₂ (17 ppm) produce changes in rat lungs.⁵²⁻⁵⁴ In humans exposure to 2.3 ppm NO₂ for five hours produced a 14% decrease in serum glutathione peroxidase activity and a 22% decrease in alveolar permeability 11 hours after the start of exposure, suggesting that even very low concentrations of NO₂ may produce a delayed response.⁵⁵ Occupational health guidelines set 25 ppm as the limit for 8 hours/day NO exposure in the workplace and 3 ppm (measured as the time weighted average) as the limit for NO₂.^{56 57} Bouchet *et al*⁵⁸ have shown that using 80 ppm INO in a neonatal ventilator with an FIO₂ of 0.9 could produce 5 ppm NO₂ in less than 20 seconds.

Methaemoglobin concentrations must also be carefully monitored, and it is encouraging that, to date, there have been no reports of serious methaemoglobinaemia in spite of prolonged inhalation (up to 23 days for a neonate,¹⁶ 53 days for an adult¹³).

When NO reacts with superoxide, peroxynitrite is rapidly formed and this can result in membrane lipid peroxidation. There is no human information to date with respect to the actual formation of such peroxynitrites in patients receiving INO, but the potential remains for resultant tissue injury, especially in the lung,⁵⁹ with damage to surfactant and its related proteins.^{60 61}

NO inhibits platelet aggregation and adhesion and as such has an important role in vascular homeostasis.⁶² It is believed that INO does not exert systemic effects because of the previously mentioned interaction with haemoglobin, Hogman *et al* have reported increased bleeding times in rabbits and humans exposed to 30 ppm of INO.^{63 64} This is of concern especially if INO is proposed as treatment for critically ill, hypoxic premature infants at risk of intracranial bleeding who may have been already treated with indomethacin (to produce ductal closure), an agent that also inhibits platelet function.

Related issues

By decreasing PVR, INO has also been found to decrease transvascular albumin flux in the lung, which may be an additional benefit in treating adult RDS-like pulmonary

disorders.⁶⁵ NO may have a significant role in preventing reperfusion induced endothelial dysfunction and the associated increases in microvascular permeability by inhibiting neutrophil-endothelial cell activation and adhesion.⁶⁶ Barbotin-Larrieu *et al* reported that INO during reperfusion of isolated ischaemic piglet lungs prevented increases in PVR and transvascular permeability and prevented the decrease seen in circulating neutrophils.⁶⁷ Inhaled nitric oxide for more than 24 hours in human neonates resulted in a reduced superoxide anion production by N-formyl-methionyl-leucylphenylalanine or *E coli* stimulated neutrophils,⁶⁸ similar to results seen by Guidot *et al*⁶⁹ in isolated rat lungs.

Interestingly, the nasal mucosa produces NO, which is normally inhaled, and the normal newborn infant has concentrations of NO in the upper airway comparable with those of an adult.⁷⁰ Endotracheal intubation bypasses the nasal airway and leads to decreased tracheal concentrations,⁷¹ which suggests that auto-inhalation of endogenous NO produced from the upper airway may be important in regulation of pulmonary blood flow and gas exchange.

As noted above, INO exerts its vasorelaxant properties by the production of cGMP. Inhibition of the specific phosphodiesterase which metabolises cGMP can enhance the vasorelaxation of INO.⁷² While the use of such treatment has already been reported,⁷³ caution is required as phosphodiesterase inhibition is not selective and has the potential to alter systemic haemodynamics.

Future questions

Many questions are still to be answered. What is the lowest effective dose? We are, no doubt, currently well above the response threshold with current management, and the use of lower doses will reduce the likelihood of accumulations of methaemoglobin and NO₂. Will the earlier use of INO result in better outcomes? Does pretreatment with surfactant improve the response to INO in humans as it seems to in some animal models? Is INO more effective during high frequency ventilation? Will improved or earlier treatments with more conventional modalities, including surfactant and high frequency ventilatory techniques, be as effective as INO? What is the appropriate role of INO in the premature infant? Does the loss of endogenously produced NO in intubated patients result in significant clinical morbidity and require replacement therapy? Should INO be used as a treatment even if it is only able to improve oxygenation or reduce PVR without improving clinical important outcomes? What is the role of INO in infants and children with cardiac disease and pulmonary hypertension, and what studies are required in this group to establish efficacy? Most importantly, what are the long term effects, if any, of INO on the developing lung and on the infant's neurodevelopment? Will NO prove to be safer and more effective than other inhaled pulmonary vasodilators?^{74 75} It may well be that we know more about INO treatment in neonates than many other current treatments, but that only serves to remind us that we repeatedly expose our most vulnerable patients to our most unproved treatments.

Conclusions

Inhaled nitric oxide is, at present, the only effective, selective, pulmonary vasodilator which has been established by prospective, randomised trials to reduce the need for ECMO in the near term infant with hypoxic respiratory failure. The lack of effect on systemic haemodynamics, coupled with the relative safety of administration, when appropriately monitored, would support the use of INO in preference to other systemically administered vasodilators,

including prostacyclin and tolazoline. Similar prospective, multicentre, randomised trials are required to evaluate the benefit of INO in premature infants with hypoxic respiratory failure and should include a careful evaluation of the occurrence of intracranial haemorrhage in this population. One would hope that the introduction of INO for the premature infant in the United Kingdom would parallel the introduction of ECMO for the near term neonate and that, at present, such treatment should be given only within the context of an appropriately designed randomised control trial, such as the INNOVO study.

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