Treatment of newborn infants with inhaled nitric oxide

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Considerable interest has focused on the use of inhaled nitric oxide (NO) as a specific treatment for refractory hypoxia caused by pulmonary vasoconstriction. The pharmacology and toxicology of NO have been reviewed in the previous article, and this one examines the potential therapeutic applications of inhaled NO in the treatment of sick newborn infants.

Rationale for inhalational NO treatment

The therapeutic options for severe hypoxaemia associated with pulmonary hypertension currently include mechanical ventilation and the intravenous administration of pharmacological agents to reduce pulmonary vascular resistance.¹ However, the effect of intravenous vasodilator drugs is often limited by lack of responsiveness, inability to sustain vasodilation, or harmful side effects.² Efforts to dilate the pulmonary vasculature often result in systemic vasodilation and hypotension, which may worsen coexisting right-to-left shunting.³ Within the lung intravenous vasodilators may dilate vessels in non-ventilated lung regions and increase intrapulmonary shunting, further impairing gas exchange. Inhalation of NO aims to introduce a vasodilator stimulus directly to those areas of lung which are ventilated, and avoid exacerbating ventilation:perfusion mismatch, while rapid inactivation of NO by haemoglobin in the blood will protect the systemic vascular bed from vasodilation and unwanted systemic hypotension.^{4 5}

Indications for NO treatment

A considerable body of experimental evidence suggests that inhaled NO may be beneficial in disease states characterised by pulmonary vasoconstriction and ventilation:perfusion mismatch.⁶ However, few largescale therapeutic trials have been completed and there is as yet insufficient evidence to conclude that NO is a lifesaving treatment.⁷ Currently the best indication for NO administration is as part of a clinical trial during intensive treatment for life threatening hypoxaemia associated with one of the many causes of pulmonary vasoconstriction.

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Infants with idiopathic persistent pulmonary hypertension of the newborn (PPHN) have an

anatomically normal heart. They present soon after birth with cyanosis due to right-to-left shunting through the ductus arteriosus and foramen ovale.^{8 9} PPHN can be secondary to perinatal hypoxia, sepsis, meconium aspiration, diaphragmatic hernia, congenital heart disease, severe respiratory distress syndrome or polycythaemia.¹

Specific treatments include intravenous vasodilators, hyperventilation, high frequency oscillatory ventilation and extracorporeal membrane oxygenation.¹ Intravenous vasodilators such as tolazoline,¹⁰ prostacyclin,¹¹ and magnesium sulphate,¹² can produce unpredictable responses and may lead to systemic hypotension or increased intrapulmonary shunting.¹⁰ The value of hyperventilation has been questioned because of the respiratory morbidity^{13 14} and potential neurological sequelae.¹⁵ It has recently been suggested that high frequency oscillatory ventilation may be effective.¹⁶ These treatments have not yet been subjected to critical analyses in controlled trials.

Although the causal mechanism of PPHN is not known, several recent reports have provided additional information on the pathophysiology of the disorder. Enhanced activity of endogenous NO has been shown to contribute to the normal decline in pulmonary vascular resistance at birth.¹⁷ A decreased production of endogenous NO may contribute to the failure of postnatal pulmonary vascular adaptation seen in PPHN: hypoxia¹⁸ and hypertension,¹⁹ which characterise PPHN, are known to inhibit the release of endogenous NO, and a lower synthetic rate of NO has been reported during the acute phase of PPHN.²⁰ Furthermore, L-arginine, a substrate for NO synthesis, may be deficient in some infants with PPHN.²¹ Thus inhaled NO treatment may circumvent a deficiency in the two substrates for NO synthesis, oxygen and L-arginine, and supply the vasodilator directly to the pulmonary vasculature.

Two preliminary studies have shown that inhaled NO is effective in reversing the hypoxaemia due to PPHN. Inhaled NO at a dose of 80 ppm with an inspired oxygen fraction of 0.9 raised the mean postductal oxygen tension from 5.4 kPa to 15.4 kPa within 10 minutes.²² Thirteen of 15 infants with severe PPHN were successfully treated with 6 ppm NO.²³ In one patient 30 minutes of treatment produced a permanent improvement in gas exchange and resolution of PPHN, and another received prolonged NO treatment for 23 days (median concentration 20 ppm) which permitted a sustained improvement in oxygenation.²² In an

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open multicentre trial involving over 100 term and preterm infants a French group reported similar success in treating PPHN with 10–80 ppm NO.²⁴

CONGENITAL HEART DISEASE

Pulmonary vascular disease is a serious complication of congenital heart disease. In infants with this condition pulmonary endothelial cells are morphologically abnormal, and endothelial dysfunction is evident even before any morphological changes become apparent.²⁵ Furthermore, congenital heart disease is often complicated by hypertensive crises, especially following open heart surgery, when pulmonary arterial pressure can rise swiftly to exceed the systemic arterial pressure, so that left atrial return falls and cardiac output rapidly declines²⁶; transient endothelial dysfunction due to endothelial damage is thought to contribute to these crises.²⁷ The condition is difficult to reverse, and a substantial part of postoperative morbidity and mortality is related to these crises.²⁸

Pulmonary hypertensive crises characteristically occur in infants who had a high pulmonary blood flow preoperatively. Miller *et al* have demonstrated that chronic increases in blood flow augment endothelium derived relaxing factor (EDRF) activity,²⁹ and it is tempting to speculate that these infants may have raised basal endogenous NO release to counteract the raised pulmonary vascular tone. Endothelial damage and dysfunction during surgery (with a concomitant reduction in endogenous NO release) would render these patients more susceptible to a pulmonary hypertensive crisis.³⁰

Management has largely consisted of hyperoxic hyperventilation and administration of intravenous vasodilators.³¹ NO inhalation seems to be an effective alternative treatment: NO at doses as little as 1 ppm has been successful in treating pulmonary hypertensive crises.^{27 32 33} In infants with congenital heart disease complicated by pulmonary hypertension inhaled NO at 20–80 ppm effectively reduced the pulmonary arterial pressure.³⁴

RESPIRATORY DISTRESS SYNDROME

Echocardiographic studies have demonstrated increased pulmonary vascular resistance in preterm neonates with respiratory distress syndrome (RDS) which correlated with disease severity and mortality.^{35–37} Severe RDS was associated with a delayed fall in pulmonary artery pressure in the immediate postnatal period, suggesting that high pulmonary vascular resistance may contribute to the mortality of RDS in premature infants.³⁷ The extent to which decreased pulmonary production of NO is a mechanism of this pulmonary vasoconstriction is unclear, but endothelial dysfunction is likely to exacerbate any tendency to high pulmonary vascular resistance.

In premature infants with RDS who required an inspired oxygen fraction (FIO₂) greater than 0.6, brief exposure to NO at 5–40

ppm produced significant improvements in oxygenation.³⁸ Although these data are preliminary, it is possible that early treatment with inhaled NO in severe RDS may allow reductions in ventilation pressures and FIO₂, potentially reducing the injury caused by barotrauma and oxygen toxicity in the susceptible premature lung.

BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia (BPD) is characterised by hypoxia and hypercapnia with pronounced maldistribution of ventilation to perfusion.³⁹ Pulmonary hypertension is a frequent and serious complication.⁴⁰ Inhaled NO at a dose of 3–10 ppm was used successfully in treating acute hypoxaemic respiratory failure in six infants with BPD complicated by pneumonia.⁴¹ All six patients survived and were successfully weaned off NO after periods of up to 20 days of continuous NO inhalation. In another study of six infants with BPD brief inhalation NO treatment at doses of 5–40 ppm significantly improved oxygenation, and prolonged NO inhalation with ≤10 ppm NO for up to 52 days did not produce tachyphylaxis.⁴² These observations suggest that inhaled NO improved the ventilation:perfusion relation and reduced intrapulmonary shunting. Inhaled NO may thus potentially represent an alternative approach to treating infants with severe BPD and pulmonary hypertension. However, we have treated four other infants with severe BPD using prolonged inhalational NO treatment, and found that they could not be weaned off NO. Suppression of endogenous nitric oxide synthesis in these infants may have accounted for our observations and this remains a potential risk in conditions requiring prolonged inhalational NO treatment.

OTHER DISORDERS

Current treatments for acute hypoxaemic respiratory failure are often unsuccessful, with mortality remaining at about 60%.^{43 44} Acute hypoxaemic respiratory failure is characterised by severe ventilation:perfusion mismatch with pulmonary hypertension.^{45 46} Approaches that improve oxygenation despite lower ventilatory pressures and inspired oxygen concentrations may potentially improve outcome, in part by decreasing secondary lung injury.^{47 48} Rossaint *et al* reported a survival rate of 80% when inhaled NO was used to treat adults with adult RDS.⁵ Inhaled NO reduced intrapulmonary shunting and ventilation:perfusion imbalance, improving oxygenation. One study has reported some success in treating 10 paediatric patients with severe adult type RDS using prolonged inhalational NO treatment (up to 24 days) at a concentration of 3–10 ppm.⁴¹ Another study reported acute improvements in oxygenation and a reduction in pulmonary vascular resistance with brief inhalations of 10–60 ppm NO.⁴⁹ Further work is required to define the potential role of inhaled NO in other pulmonary disorders associated with acute lung injury.⁵⁰

Administration of nitric oxide

Administration should embrace a system that: (a) permits continuous accurate measurements of NO and NO₂ concentration in inspired gas; (b) minimises the time of contact between oxygen and NO; and (c) removes NO and NO₂ from exhaled gas. NO should probably only be used when full monitoring facilities (including blood methaemoglobin concentrations) are available, and long term follow up of treatment is carried out.

NO is usually supplied in nitrogen at a variety of concentrations. Stainless steel pressure regulators and flow meters are required along with Teflon tubing for administering the gas into the ventilator circuit, as NO and NO₂ are corrosive. The NO may ideally be fed into the inspiratory limb of the ventilator circuit between the patient manifold and the humidifier. The resulting gas mixture should be sampled downstream of the input port just proximal to the patient manifold.

Monitoring of inhaled NO concentrations should be routine, and several methods are available. A commercial electrochemical system which relies on the oxidation of NO+H₂O to HNO₃+3e+3H⁺ has been used by several groups.⁵¹ Measurement of NO concentration by chemiluminescence depends on oxidising NO with ozone to give NO₂ in an electronically excited state which emits light on returning to the ground state.⁵² Chemiluminescence is highly sensitive and, although costly and more difficult to use, has been effective in many clinical studies.

It is recommended that the exhaust gases be scavenged to avoid any buildup of toxic byproducts which could potentially corrode the ventilator expiratory valve. Exhaust gases may alternatively be passed through carbon and purafil filters, soda lime, or activated charcoal. The exhaust gases may also first be passed through a tube with potassium permanganate coated aluminar beads to convert NO into NO₂ which may then be passed through the filters.

Dose considerations

Measurement of exhaled gas from normal lungs suggests that endogenous NO concentration in lung approximates to 8 parts per billion (ppb)⁵³ and free NO has been found in human plasma at about 3 nM concentrations.⁵⁴ The optimal therapeutic doses of inhaled NO for different disease states are unknown and are likely to vary depending on the pathology.

It is important to optimise ventilator settings before starting treatment with NO. Administration usually begins at 10–20 ppm NO, and this can frequently be reduced to below 10 ppm for maintenance of therapeutic effects. Higher concentrations are effective, and some studies have used 80 ppm, although with little added benefit. As most patients will be receiving high fractions of inspired oxygen, NO concentrations in excess of 80 ppm are not currently recommended.⁵⁵ The response is usually immediate but may take up to 15 minutes and infrequently longer. Sudden withdrawal of NO treatment can lead to life

threatening hypoxia, and the dose should probably be reduced slowly.

Infants with PPHN have been successfully treated with doses of 6–80 ppm^{22 23} and one study found no difference in response to doses between 5–80 ppm.⁵⁶ Effects have been reported with concentrations as low as 10 ppb in adults with adult RDS.⁵⁷ The lowest effective dose observed in our studies of RDS and BPD was 40 ppb (Mupanemunda *et al*, unpublished data).

Conclusion

NO is a promising new treatment. However, largescale trials have yet to define its true value, and until such data are available, administration should properly be restricted to infants enrolled in formally conducted trials. The successful introduction of surfactant treatment offers a challenge to the paediatric community to manage the advent of NO with similar rigour.

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