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CONSENSUS CONFERENCE

Inhaled nitric oxide therapy in neonates and children: reaching a European consensus

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Abstract Inhaled nitric oxide (iNO) was first used in neonatal practice in 1992 and has subsequently been used extensively in the management of neonates and children with cardiorespiratory failure. This paper assesses evidence for the use of iNO in this population as presented to a consensus meeting jointly organised by the European Society of Paediatric and Neonatal Intensive Care, the European Society of Paediatric Research and the European Society of Neonatology. Consensus Guidelines on the Use of iNO in Neonates and Children were produced following discussion of the evidence at the consensus meeting.

Keywords Inhaled nitric oxide · Pulmonary hypertension · Persistent pulmonary hypertension of the newborn · Extracorporeal membrane oxygenation · Vasodilator · Pulmonary

Introduction

Inhaled nitric oxide (iNO) has been used in Europe to treat a variety of conditions in neonates and children since 1992, foremost in persistent pulmonary hypertension of the newborn (PPHN), which has remained a major therapeutic challenge in the NICU [1, 2]. Introduction of iNO into clinical use was virtually unregulated in Europe, where supplies of industrially produced gas were freely available. Subsequently clinical trials have established roles for iNO therapy in the treatment of term neonates with severe respiratory failure and a pharmaceutical quality product has recently become available in Europe and the United States. The high cost of the licensed product, compared to previous industrial supplies, and the narrow scope of the drug's licensed indications suggested to our group that a consensus should be established on the use of iNO therapy in neonates and children covering both its approved and potential indications.

Methods

An Advisory Board was established under the auspices of the European Society of Neonatal and Paediatric Intensive Care to co-ordinate the scientific programme of the meeting. The board consisted of experts with proven scientific or clinical expertise relevant to the clinical use of iNO. The board identified a further panel of experts who were invited to act as section leaders whose role was to review the literature in their designated subject area. Section leaders were asked to produce written summaries of their subject area, which were then circulated to delegates prior to the meeting and which formed the basis of the evidence presented to delegates at the consensus meeting itself.

A further panel of opinion leaders were invited to attend the meeting on the basis of their known interest in the use of iNO or their status as opinion leaders in the field of neonatal and paediatric intensive care. The European Society of Paediatric Research and the European Society of Neonatology were officially represented at the meeting. At the consensus meeting each subject area was presented in summary by the section leader(s), following which open discussion led to the composition of draft consensus statements. These were then edited and re-presented to delegates with further discussion leading to final agreement on the individual consensus statements.

Results

Inhaled nitric oxide in term and near-term neonates

Neonatal hypoxaemia may result from *intra-pulmonary shunting*, from *extra-pulmonary shunting* (so-called PPHN) or from cyanotic congenital heart disease. The presence of interstitial pulmonary infiltrates or a low volume lung (<6–7 ribs) on chest X-ray strongly suggests parenchymal lung disease. Alveolar recruitment has been shown to render babies with severe hypoxaemic respiratory failure responsive to iNO, when they were previously unresponsive [2]. Exogenous surfactant and ventilatory manoeuvres [3] should therefore be deployed to optimise lung volume before iNO is introduced. If cyanosis persists after any necessary lung recruitment manoeuvres have been applied, an echocardiogram should be obtained to confirm or exclude the presence of congenital heart disease or pulmonary hypertension as causes of cyanosis. Inhaled NO is most likely to benefit babies with PPHN with recruited lung volume and is unlikely to benefit babies with cyanotic heart disease.

The recent Cochrane Review was used as a framework in this discussion [4]. The review, last updated in December 2000, included 12 relevant trials in its analysis, all of which used random allocation [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. One further on-going study received limited analysis since, at the time of review, it was on-going and published only as an abstract [16]. A literature search up to October 2003 failed to reveal any new randomised, controlled trials not already included in the Cochrane review.

The limitations of the studies presented within the Cochrane review were highlighted. Of major importance, the entry criteria differed markedly between trials as did dosage and ventilatory strategies, there being a suggestion that high frequency oscillatory ventilation (HFOV) appears beneficial in achieving a response to iNO [10]. Eight of the 12 clinical trials studied the effect of iNO on the overall clinical course of the babies included and, in particular, whether the need for extracorporeal membrane oxygenation (ECMO) was reduced. Only six trials did not allow crossover [6, 7, 8, 11, 12, 13]. Of the six studies which did not allow crossover, three [6, 11, 12] found a statistically significant reduction in the combined outcome of death or requirement for ECMO in the NO group. A meta-analysis of all six studies found that iNO treatment resulted in a reduction in the incidence of death or requirement for ECMO (relative risk 0.65) [4].

Inhaled nitric oxide therefore appears to improve outcome in hypoxaemic term and near-term infants. The improvement is due mainly to a reduction in the need for ECMO, since mortality was not reduced. The two largest studies [6, 11] included infants with congenital diaphragmatic hernia as sub-groups. A separate analysis has been presented from one of these studies [17]. There was no evidence that outcome was improved in these babies through the use of iNO, even if short-term improvements in oxygenation did occur. It is important to note that whilst iNO reduced the need for ECMO, the majority of mature babies in these studies went on to ECMO.

Only one study has considered long-term follow-up as a primary or secondary hypothesis. In this study, the incidence of disability, the incidence of deafness and infant development scores were all similar between tested survivors who received NO and those who did not [18].

The major randomised, controlled trials of iNO in term or near-term babies have used echocardiography to

exclude congenital heart disease as a cause of hypoxaemia prior to exposure to iNO. Babies with such lesions are at best unlikely to benefit from iNO, as cyanosis is due to extra-pulmonary shunting. Inhaled NO exposure may even be harmful in some babies with congenital heart disease, such as those with obstructed total anomalous pulmonary venous drainage or severe left ventricular dysfunction with right-to-left ductal shunting [19], in whom pulmonary arteriolar vasoconstriction may be clinically beneficial by reducing left heart filling.

Dosage and response to inhaled nitric oxide treatment in term and near-term neonates

Decisions regarding continued use of iNO therapy cannot be based on the primary end points used in the pivotal studies, such as reduced mortality or 'avoidance' of ECMO. Instead clinicians must use surrogate physiological end points in order to establish whether an initial test exposure to iNO is effective. Improvement in oxygenation of approximately 20% over baseline values at 30–60 min has been used in many studies as an indicator of early response to iNO including six of the studies in the Cochrane review [5, 6, 7, 9, 11, 12].

Four published studies have reported dose-response data for this group of babies [7, 20, 21, 22]. All four studies suggest that a maximal beneficial effect of iNO is already seen at concentrations of less than 30 ppm. Further increases of iNO (to 80–100 ppm) do not appear to result in further improvement of oxygenation above that achieved at 20–30 ppm. The large NINOS study [11] used initial doses of 20 ppm iNO, but exposed 'partial responders' to 80 ppm. Only 6% of these partial responders were converted to full response by 80 ppm iNO.

In the small study published by Tworetzky et al. a maximum reduction of pulmonary artery pressure was observed at 20 ppm NO, whereas maximal improvement in oxygenation occurred at 5 ppm [23]. Response to the introduction of iNO usually occurs rapidly in 'responders'. Some investigators attribute clinical improvements seen several hours later to iNO administration [24]. However it was the expert group's view that there is a serious danger that babies with very severe hypoxaemia could be harmed if ECMO referral were to be delayed whilst waiting for a 'late' response.

If no substantial effect has been achieved during a trial of iNO, treatment with iNO should be rapidly discontinued or the baby transferred on iNO to a level 3 or tertiary neonatal unit. This should occur as soon as the clinician is convinced that iNO is not inducing a beneficial effect judged by improving oxygenation. The trial to improve oxygenation with NO should not last longer than 4 h. The reason not to prolong NO therapy unnecessarily is that NO synthase is down-regulated, with suppression of endogenous NO production. Down-regulation of endogenous NO synthase by the use of iNO has been suggested [25, 26, 27].

We were unable to identify studies establishing the optimal regime for maintenance of iNO therapy once an initial response has been established. It is, however, logical in clinical practice to seek to minimise iNO exposure by lowering the iNO dose, provided the beneficial effects on oxygenation and general clinical stability are maintained. This approach was described by Kinsella et al. [28] in the early stages of the clinical exploration of iNO therapy and further validated by Clark et al. [6].

Discontinuation and weaning

Some information is available on strategies for weaning patients from iNO as clinical improvement occurs. In a prospective study, Demirakca et al. evaluated the clinical response to iNO in neonates and children with acute respiratory distress syndrome (ARDS) [21]. Attempts to discontinue iNO were made as soon as a stable respiratory status (PEEP<6 cmH_2O, inspiration/expiration ratio of 1:2, FiO_2 <0.8 and an iNO concentration of 5 ppm) had been achieved. Oxygenation index (OI) values of less than 5 predicted successful withdrawal with a sensitivity of 75%, a specificity of 89%, a positive predicted value of 69% and a negative predictive value of 91% [21].

Aly et al. [29] adopted a weaning strategy for babies with PPHN which included step-wise 5 ppm decrements of iNO doses. Discontinuation of iNO was performed as soon as the patient was stable with an FiO_2 less than 0.5. Weaning was successful at the first attempt in 9 out of 16 patients. In the remaining seven neonates, major signs of deterioration (oxygen saturation drop >10% or below 85%) prompted a reinstitution of iNO treatment for 30 min. Subsequently, FiO_2 was raised by 0.4 and a successful withdrawal of iNO was then obtained. Interestingly, FiO_2 could be returned to the pre-weaning value in a few hours. Sokol et al. [30] noted that significant deterioration of PaO_2 occurred in some babies even when weaned from 1 to 0 ppm, suggesting that iNO is physiologically active even at very low concentrations. There may be a role for other vasodilators such as epoprostenol, iloprost, endothelin antagonists or selective phosphodiesterase inhibitors [31] when weaning babies from iNO after treatment courses of sufficient duration to down-regulate NO synthase.

Toxicity

Nitric oxide reacts with oxygen to form nitrogen dioxide (NO_2) where the reaction rate is proportional to the square of the NO concentration and directly proportional to the

oxygen concentration. Whilst NO itself is a relatively reactive molecule, NO_2 is demonstrably more reactive and toxic and is a radical (it has an unpaired electron). Due to the fact that NO is usually administered in combination with high inhaled oxygen concentrations and that NO_2 in animal experiments is damaging to the lungs already at low concentrations when administered with other oxidants, the main toxicological concern should be focused on NO_2 exposure and this should be kept to a minimum. In long-term exposure lung damage may occur at 0.5 ppm NO_2 and acute lethal effects are seen from 100 ppm. Human subjects inhaling 2–3 ppm NO_2 for 5 h demonstrated reductions in antioxidant defences and an increase in alveolar permeability [32]. Reactive species such as peroxynitrite formed from NO_2, as well as being implicated in short-term toxicity, have the potential to cause damage to DNA, raising the possibility of mutagenic or carcinogenic effects. However, the concentrations of iNO and NO_2 to which patients are exposed clinically are largely within the permitted limits for occupational exposure [33]. There is as yet no evidence that inhalation of NO has any lasting adverse effects. Long-term follow-up of children exposed to iNO therapy will be required to establish any late adverse effect.

When NO reacts with haemoglobin, methaemoglobin (metHb) is formed. MetHb is not directly toxic, but is unable to carry oxygen. If metHb is allowed to accumulate it can significantly reduce the oxygen-carrying capacity of blood. The monitoring and management of metHb during clinical iNO therapy is discussed below.

Inhalation of NO has been shown by some investigators [34], but not by others [35], to inhibit platelet function. The randomised controlled neonatal trials have, however, not shown any difference in bleeding complications between groups administered iNO or control gas [4].

Delivery and monitoring

Nitric oxide administration systems should deliver constant concentrations of iNO within the respiratory gas mixture independent of ventilator mode or settings, ensure a rapid mixing and minimise contact time between NO and oxygen, thereby reducing the possibility of generating high NO_2 levels [36, 37, 38]. The delivery system should display the pressure within the NO cylinder to permit timely cylinder changes to be undertaken without loss of gas supply. The system should ideally encompass a backup power supply for use in the event of mains failure or during intra-hospital transport. A manual backup or 'hand bagging' facility must be provided for use in the event of ventilator failure or other indications for hand ventilation, as sudden discontinuation of iNO therapy can be life-threatening [36, 37, 39].

The safest approach to iNO delivery is probably to use only pharmaceutical grade NO stored in cylinders and at concentrations and conditions approved by drug regulatory bodies and delivered by devices tested and approved according to the appropriate medical device legislation.

In the clinical setting, measurement of iNO and NO_2 concentrations can be undertaken using chemiluminescence or electrochemical devices. There are a number of practical disadvantages of chemiluminescence analysers in the clinical setting, including their high cost, their need for relatively high sample volumes, noise, their need for regular calibration and their relative inaccuracy in measuring NO_2 due to the "quenching" effect [37]. Electrochemical analysers use two separate fuel cell sensors for NO and for NO_2, placed either in the gas mainstream or side stream of the ventilatory circuit. Electrochemical devices do not underestimate NO_2 levels, are inexpensive, silent, easy to calibrate and require very low gas sample volumes. Most devices are portable. Electrochemical analysers are, however, relatively insensitive (resolution 0.5 ppm) and their measurements may be affected by temperature, pressure, humidity and the presence of other gases in the environment [37]. Although many early studies of iNO delivery systems were constructed by investigators for their own studies, a number of delivery and monitoring systems have been developed for clinical use and are commercially available [39, 40].

Inhaled NO_2 concentrations should be kept to a minimum. Clinical and experimental evidence show that it is possible to administer 20 ppm iNO whilst generating NO_2 concentrations of less than 0.2 ppm [38]. Direct comparisons with tolerable environmental NO_2 concentrations should take into account that the awake person inhaling NO_2 is exposed to at least 50% lower NO_2 concentrations in their trachea due to efficient scavenging of NO_2 in the upper airways.

Nitric oxide has been supplied for clinical use by a number of suppliers as a compressed gas diluted in a balance of nitrogen with final NO concentrations of between 100 and 1000 ppm. The gas is supplied in aluminium cylinders filled to pressures of 150–200 bar. Very concentrated preparations may be difficult to deliver accurately whilst mixtures with low NO concentrations can reduce FiO_2 excessively [41]. The final choice of cylinder NO concentration will, therefore, depend on the characteristics of the delivery system in use and the required FiO_2 and FiNO. The future availability of iNO as a pharmaceutical within Europe may encourage standardisation.

Environmental safety

The US National Institute for Occupational Safety and Health (NIOH) suggest a "Permitted Exposure Limit" for

NO_2 of 5 ppm and NO 25 ppm over an 8-h period for these potentially toxic substances [33]. Several European countries have regulated maximal occupational exposure to 2 ppm NO_2. Extrapolating this to the ICU in which iNO would be administered for a 24-h period, it would be prudent to aim for environmental levels of NO_2 in the ICU below 1.5 ppm. Environmental NO contamination can occur from two sources during iNO administration: dumped waste ventilator gas and accidental leakage of concentrated gas from a delivery system or cylinder. The US Food and Drug Administration state, in their specification for medical delivery of NO, that such delivery "does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required" [42]. A similar ruling is applied by the UK National Health Service, which states that scavenging of waste NO is unnecessary provided that ventilation in the ICU meets required standards [43]. Several studies confirm that this advice is sound [44, 45]. There must, however, be a small risk of high environmental levels occurring from uncontrolled release of a large volume of concentrated gas from a cylinder in the event of a serious error or accident. For this reason, the consensus group suggest that it is reasonable to measure environmental levels of NO_2 continuously.

Transport

In 30–50% of babies given a trial of iNO the therapy does not result in a sustained positive oxygenation response [4]. Most babies who fail to respond to iNO are potential ECMO candidates. Since acute withdrawal of iNO may be associated with severe rebound hypoxaemia, even in babies who apparently respond poorly [46, 47], arrangements must be in place for these babies to be transferred to an ECMO centre without interruption of iNO delivery. Occasionally non-neonates may require transport within or between hospital whilst receiving iNO.

Apart from the ability to deliver iNO safely to the baby during transport, consideration must also be given to safety of the staff and crew within the transport vehicle, and compliance with any regulations governing such use. Kinsella et al. recently reported concentrations of NO and NO_2 in the cabin environment of various transport vehicles during iNO use and confirmed them to be negligible. Furthermore, they calculated the effects of uncontrolled release of a full US D-type NO cylinder containing 350 l NO gas. In this " worst case scenario" environmental NO levels were unlikely to reach dangerous levels (maximum 40 ppm fixed wing aircraft, 34 ppm ground ambulance, 94 ppm small helicopter) [48].

The expert group recommend that equipment for delivery and monitoring of iNO during transport should comply with standards for medical devices and the safety and test requirements of the specific aircraft or other transport vehicle used. Several delivery systems have been used during transport and at least two portable systems are commercially available, one of which is specifically designed as a transport system [48].

Staff training

Clinical use of iNO involves potential hazards for both staff and patients, mainly from the risk of exposure to toxic levels of NO and NO_2, but also issues such as safe handling of gas cylinders. The safe and appropriate use of medical equipment requires adequate preparation and training. Regulatory authorities frequently recommend standards for training in the use of medical equipment, typically stating that training should include both theoretical and practical instruction [49]. US guidelines for neonatal use recommend physician training [50] and some nursing authors have discussed the need for training [51]. It has also been recommended that protocols or guidelines should be compiled by hospitals using iNO, covering all aspects of its use including responsibility for off-label prescription. Such protocols should aim to help staff deliver iNO therapy that is both safe and effective [52].

Use of inhaled nitric oxide in preterm neonates

For the purposes of this paper, 'preterm' neonates are defined as those babies too premature to be considered for ECMO should their condition require it, i.e. babies less than 34 weeks completed gestation [53].

Inhaled NO may improve oxygenation in preterm neonates with hypoxaemic respiratory failure in one of two ways: (1) it may reverse extra-pulmonary shunting by selectively decreasing pulmonary vascular resistance (PVR) and (2) it may reduce intra-pulmonary shunting (and/or V/Q mismatch) by redistributing pulmonary blood flow. The former mechanism is likely to be the most important in infants with primary or secondary PPHN, whereas the latter will be more important in the majority of preterm infants who have parenchymal lung disease as the primary cause of their hypoxaemic respiratory failure.

There are three published, randomised, controlled trials (RCTs) of iNO therapy in preterm infants [14, 54, 55], overviews of which have been reported in the form of two systematic reviews [53, 56]. A total of 207 infants have been studied in these RCTs. Other RCTs (such as the UK INNOVO trial, NICHD Preemie iNO trial and other US trials) are either on-going or have only just completed recruiting and results are not yet available. One small RCT has reported the long-term neurodevelopmental outcome following iNO therapy [57].

A Cochrane Review has summarised the results of the three RCTs in preterm infants [53]. The study of Kinsella

et al. [55] is the single most useful trial in that it recruited neonates with hypoxaemic respiratory failure early in the course of their respiratory disease, the intervention was masked, an important primary outcome (mortality) was chosen, there was no crossover treatment with iNO and infants were carefully evaluated for intraventricular haemorrhage (IVH). There is no evidence of an effect of iNO on mortality or chronic lung disease (CLD) at 36 weeks, or on survival without CLD in preterm infants with hypoxaemic respiratory failure. Doses of between 5–20 ppm iNO appear to be effective in improving arterial oxygenation within the first 2 h of treatment. One study showed a reduction in days of ventilation with 5 ppm iNO in survivors [55] whilst another study reported no difference [14].

Sufficient data are lacking for evaluation of the possible effects of iNO on periventricular haemorrhage or on long-term neurodevelopmental outcome. Thus, with the data currently available, the consensus group do not recommend the routine use of iNO in the preterm infant and strongly recommend its use in this indication only within controlled clinical trials. The use of iNO could, however, be justified as rescue therapy in life-threatening hypoxaemia after lung recruitment has been optimised.

Use of inhaled nitric oxide in paediatric acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) may result from many systemic disease processes, and affects people of all ages. No drug therapy has been found to impact substantially on survival in ALI cases. Inhaled NO has been used in this setting principally because of its effect in improving oxygenation as therapy commences, due to improved ventilation-perfusion matching.

The comments in this section are aimed at guiding the clinical use of iNO in paediatric practice. Recommendations on ALI and ARDS had to be formed on a very limited base of information as, apart from case series and anecdotes about children, almost all data on such clinical use of iNO were only available for adult patient populations. Five randomised controlled trials were evaluated (Dellinger [58], Dobyns [59], Lundin [60], Troncy [61], Michael [62]) in a recent Cochrane review [63] assessing 535 patients, with only one trial focused on children [59]. Inhaled NO had no impact on mortality in trials without crossover (relative risk 0.98, 95% confidence intervals 0.66, 1.44) or with crossover of treatment failures to open-label iNO (RR 1.22, 95% CI 0.65, 2.29). Evidence published in one study demonstrated that iNO resulted in a transient improvement in oxygenation in the first 24 h of treatment: the oxygenation index (OI) showed a mean difference of −3 (95% CI −5.354, −0.646), and PaO_2/FiO_2 ratio and a mean difference of 35 (95% CI 20.236–49.764) [58]. Other clinical indicators of effectiveness, such as duration of hospital and intensive care stay, were inconsistently reported. There were no complications reported to be directly attributable to this treatment.

Based on these data, it appears that iNO has no effect on mortality and only transiently improves oxygenation in ALI/ARDS. There is insufficient data to assess other end points. The authors of the Cochrane review suggest that any further trials of iNO in this indication must stratify for underlying disease, since outcome is thought to be more related to this than to respiratory failure alone.

Use of inhaled nitric oxide in children with cardiac disease

Pulmonary hypertension is an important problem in many children with acquired or congenital heart disease. As a selective pulmonary vasodilator, as in neonatal PPHN, iNO has the potential to improve the management of these patients. Numerous reports of iNO usage in such patients have been published including its use in the assessment of the reversibility of pulmonary hypertension as a diagnostic procedure [64, 65] and in the perioperative management of pulmonary hypertension or RV afterload reduction [66, 67, 68]. Inhaled NO has also been shown to complement standard methods of differentiating reactive from fixed pulmonary vascular disease [64, 65].

Inhaled NO has been shown to be effective in the management of some patients with severe reactive pulmonary hypertensive episodes following cardiac surgery [69, 70]. In these patients, iNO is believed to replace endogenous NO production, which is temporarily impaired due to the effects of cardiopulmonary bypass on the pulmonary endothelium. One randomised, controlled trial [71] reported that the prophylactic administration of 10 ppm iNO was associated with a significant reduction in pulmonary hypertensive events and a reduction in time to meeting extubation criteria. Mortality and length of ICU stay were, however, unaffected. Another similar, but smaller, study failed to demonstrate any benefit from prophylactic iNO [72]. The view of the consensus meeting experts was that data from other clinical trials was required before the routine prophylactic use of iNO could be recommended in children at risk of pulmonary hypertensive events after repair of congenital heart surgery. Inhaled NO has also been shown to improve the haemodynamic status in patients with elevated PVR after the Fontan operation [73] and in those with failing right ventricles [74]. There are no RCT's in this group of patients.

In summary, there are few RCTs on the use of iNO in children with cardiac disease from which to draw evidence-based conclusions. There is insufficient evidence to recommend the routine use of prophylactic

postoperative iNO in congenital heart patients at risk of pulmonary hypertension. The expert group felt that there is, however, sufficient evidence (from large case series) to support a trial of 20 ppm iNO for 10 min, increasing to 40 ppm if no response to the lower dose, in patients with clinically significant pulmonary hypertension complicating their perioperative course. In this setting it is recommended that iNO should only be continued if there is documented evidence of important haemodynamic improvement. After a 30-min trial of iNO at 20 ppm, increasing to 40 ppm, consideration should be given to discontinuing the drug if no clinically significant response has occurred.

Conclusion

These guidelines, "Use of iNO in neonates and children: consensus guidelines from the European Society of Paediatric and Neonatal Intensive Care, the European Society of Paediatric Research and the European Society of Neonatology", (please see ESM), were compiled by a group of practitioners with knowledge of iNO therapy drawn from the majority of European states. The guidelines are designed to allow the safe use of this therapy, within both its permitted and its potential uses. It is hoped that these guidelines will encourage evidence-based practice and further clinical trials on the use of iNO therapy.

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