Paediatric Intensive Care Unit

Indications and Use of Inhaled Nitric Oxide (iNO)

Staff relevant to:	Medical and Nursing staff caring for children in the PICU
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Related Guidelines and Policies:	
C162/2008	Persistent Pulmonary Hypertension of the Newborn UHL

1. Introduction

Nitric oxide (iNO) is a colourless, odourless toxic and non-inflammable gas that can be administered via the ventilator circuit as an additional therapy in PICU/CICU. iNO is an established and widely used pulmonary vasodilator used to treat children with severe hypoxaemia.

This Guideline applies to Medical staff prescribing iNO and to Band 5 and above nursing staff who are involved in the administration of iNO. It is for the safe administration of Nitric Oxide via the INOmax & INO blender system to a ventilated child within the Paediatric Intensive Care Unit.

Contents

Flow chart for use of iNO on PICU/CICU

Evidence hypoxic respiratory failure/Right heart failure

1. Pre Ductal SaO2<90%, FiO2>0.75 (neonates)

2. Hypoxic Respiratory Failure SaO2<90%, FiO2 >0.75 and/or one of the following:
   PaO2<8kpa
   PF ratio <300
   PIP>30

3. Right heart failure; evidence of Pulmonary Hypertension/RV dysfunction on ECHO

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Start iNO at 2ppm/titrate up to 20ppm
Continue for 15-20 minutes

Optimize ventilation/ Lung recruitment
Correct acidosis
Ensure adequate sedation, analgesia. Muscle relaxation where indicated
Optimize glucose, calcium and magnesium

Observe for positive response

Positive response: (any of below)
- 20% increase in PaO2 from baseline
- Reduction in FiO2 by 0.1
- Normalisation pre/post ductal saturation difference (to less than 20%)
- Improvement in haemodynamic status

Positive response

- ✓ Continue iNO at appropriate dose (2-20ppm)
- ✓ Measure NO2 continually and MetHb 4 hourly on Blood Gases
- ✓ Reduce dose if NO2>5ppm or MetHb>2%
- ✓ Check daily for iNO response by reducing iNO by 5ppm for 15-20 minutes (or if below 10ppm to off) and monitoring SaO2 and PaO2
- ✓ Once FiO2<60% or cardiovascular stability wean iNO at 0.1-5ppm/hr. Caution below 2ppm (see above text)
- ✓ If refractory symptoms on repeated weaning attempts, consider oral Sildenalfil or non-invasive iNO if extubation considered possible

Negative response

- ➢ Stop iNO (turn to 0ppm)
- ➢ If parameters remain stable, turn off iNO cylinder
- ➢ If deterioration in oxygen, or cardiovascular status restart iNO @ 10ppm and continue as for positive response

Monitoring
- **Continual in-line Monitoring of NO and NO2 levels.**
- **NO2 levels should not exceed 5ppm (usually around 1ppm)**
- **4-6hrly MetHb levels on ABG, 12hrly in steady state.**
- **Keep Met Hb<2%**

2. Clinical Pharmacology

Nitric Oxide (NO) a vasodilator operates by promoting selective smooth muscle relaxation. It is produced naturally by endothelial cells of blood vessels and causes relaxation of vascular smooth muscle cells by activation of cyclic guanosine monophosphate (cGMP).
In therapeutic terms, use of inhaled nitric oxide leads to selective reduction in pulmonary vascular tone without having significant effects on systemic vascular tone. This results in a reduction in pulmonary arterial pressures, as well as a reduction in the ratio of pulmonary to systemic arterial pressures. The increase in blood flow promotes an improvement in the ventilation perfusion ratio (V/Q) matching. This improvement in gas exchange is due to vascular relaxation resulting primarily from the administration of NO and secondarily from improved absorption of oxygen, also a powerful pulmonary vasodilator, reducing intrapulmonary shunting.

NO is also a neurotransmitter essential to the inflammatory response and host immunity. It is also the signalling molecule involved in the second messenger system responsible for the regulation of smooth muscle tone.

The NO molecule is highly reactive and extremely short-lived. The bulk of circulating NO is deactivated by readily binding to haemoglobin to form nitrosylmethaemoglobin. Phosphodiesterases (PDEs), predominantly PDE5, regulate the magnitude and duration of vascular smooth muscle relaxation by catalysing the breakdown of cGMP. The endogenous half-life of NO is 0.1 to 5 secs, but when administered via mechanical ventilation (in a dose range of 5 to 80 ppm), the half-life increases to 15 to 30 secs. Inhalation of NO selectively reaches the pulmonary vasculature; its rapid metabolism typically precludes any undesirable systemic effects, such as systemic hypotension.

2.1 Indications

Neonatal Hypoxic Respiratory Failure
Inhaled nitric oxide (iNO) therapy is a well-established treatment for newborns with hypoxemic respiratory failure (PPHN and pathologic states associated with PPHN, e.g. Meconium aspiration, Sepsis, Pneumonia, RDS, CDH). Hypoxaemia can be defined as Pre Ductal SaO2 <90%, or Pre Ductal/Post ductal difference >20% with FiO2> 0.75.

Right sided heart failure
iNO is used in the treatment of right-sided heart failure. It is used to increase right-sided ejection and left-sided preload by reducing pulmonary arterial pressure (PAP) and pulmonary vascular resistance.

Pulmonary hypertensive crises

Innovative antimicrobial therapy for lung infections/ SARS –COVID 19
Increasing evidence suggest that when delivered at high doses iNO has been described as having antimicrobial properties. (20)

Hypoxaemic respiratory failure due to ARDS/ALI
iNO has been used as a salvage therapy in cases of severe refractory hypoxemia unresponsive to conventional ventilatory modalities. Thus, inhaled NO has been used in the treatment of acute lung injury and acute respiratory distress syndrome, albeit with dubious results. Although a temporary improvement in PaO2/FIO2 ratio has been noted, days of support by mechanical ventilation and mortality remained unchanged. Nevertheless, iNO continues to be used as a salvage therapy in this context. Consider introduction of iNO therapy in the following circumstances: Pao2 <8Kpa with FiO2 >0.75, in context of Lactate > 2mmol/l, PF ratio <300, PIP >30cmH20.

2.2 Inhaled Nitric Oxide Administration in PICU/CICU

Therapeutically, NO can be delivered during mechanical ventilation via a specialized delivery system in tandem with a conventional ventilator.(see separate policy of administration of iNO) iNO is very expensive, it is charged at a fix price up until 96hrs of use then hourly thereafter.
It should be a Consultant decision to commence iNO based on one of the indications above (hypoxemic respiratory failure, right heart failure, pulmonary hypertension). iNO should be prescribed on the drug chart

Treatment typically starts with an iNO concentration of 2ppm and titrated up to 20ppm to effect. Doses above 20ppm are not indicated as generally a response is obtained prior to this, and may be associated with an increased risk of toxicity, in particular NO2 and methaemoglobin formation.

The patient should be observed for a positive response. In hypoxaemia this is defined as 20% increase in Pao2 or Sao2, which should occur within 15 or 20 min of iNO administration, and/or as a reduction in FiO2 of 0.1, and/or normalisation of the pre/post ductal saturation difference in neonates.
In right heart failure there should be an observed improvement in haemodynamic status (difficult to define; potentially reduction in inotropes, or assessment of function on ECHO).

The response to iNO should be documented in the notes and if no positive response treatment should be discontinued. If on discontinuing iNO, despite lack of positive response as above, there is deterioration in oxygenations or patient condition, consider continuing iNO therapy.

NO concentrations should be titrated down slowly as the pulmonary pressures and oxygenation issues resolve. Weaning should be done cautiously due to rebound pulmonary hypertension. This is due to down regulation of endogenous nitric oxide production that occurs during the administration of exogenous nitric oxide, resulting in a rebound vasospasm when the exogenous nitric oxide is withdrawn.

Typically, iNO will be weaned when the Fio2 on the ventilator is ≤60%.
Wean at 0.1-5ppm per hour carefully monitoring oxygenation (pO2 > 8kPa and/or sats > 92%. It is common to see no effect of weaning until iNO dose gets below 2ppm. Slower weaning may be required to get from 2ppm to off.
If used for cardiac support, the weaning parameters may not involve measures of mechanical ventilatory support.

The course of treatment usually lasts between 3 days and as long as a few weeks. If refractory symptoms occur on weaning iNO consider the introduction of oral Sildenafil for 24-48hrs to facilitate weaning (start at 0.3mg/kg/dose qds and increase to max 4mg/kg/dose qds).

2.3 Cautions/Possible Adverse Effects

Tissue damage by toxic free radical formation and Nitrogen dioxide production.
iNO can rapidly react with oxygen in the lung to form NO2, which is a potent pulmonary irritant that may alter the surfactant and capable of causing acute lung injury. It can theoretically damage the lung through lipid peroxidation. In the presence of water, NO can form nitric acid, another potent irritant, while NO can also react with superoxide anion to form peroxynitrite, a cytotoxic free radical that disrupts surfactant activity and interferes with mitochondrial respiration. Normal Nitrogen Dioxide levels in current iNO systems should be no more than 5ppm. At higher inhaled NO2 doses, pulmonary oedema is the major toxicological effect.

Methaemoglobinaemia
At high levels (> 80 ppm) and for prolonged periods, iNO converts oxygen- carrying haemoglobin into methaemoglobin, potentially leading to impaired tissue delivery of oxygen. Normal methaemoglobin levels <2%.
Methemoglobinemia is fatal if not detected early as hypoxia due to it is refractory to oxygen therapy. In critically ill, ventilated patient receiving INO, even lower dose may produce severe tissue hypoxia

as the patient may be in hypoperfused state. Alteration in dosing should be considered if methaemoglobin level more than 5%. High level with clinical findings of severe lactic acidosis and tissue hypoxia warrants treatment with intravenous methylene blue 1–2 mg/kg, which will rapidly convert ferric iron back to ferrous form with resultant unloading of oxygen to tissues.(21)

Immunosupression
There is the potential for NO to act as an immunosuppressant and thus, theoretically, increase the risk of infection, which is likely to be nosocomial given the therapeutic context of iNO use.

Platelet dysfunction
NO has been shown to inhibit platelet agglutination and adhesion.

Abnormal lung growth
Potential for mutagenic DNA alterations adversely affecting normal lung development in newborns (through increasing levels cGMP).

Pulmonary Oedema
Use of iNO in certain conditions (e.g. pulmonary venous obstruction, obstruction at LA, MV level or LVOTO) may lead to pulmonary oedema

Rebound and/or persistent Pulmonary Hypertension
Abrupt reduction of NO concentrations or interruption of iNO therapy have been shown to cause a rapid reversal of any therapeutic gains, resulting in increased V/Q mismatching and increased pulmonary hypertension, leading to hemodynamic collapse. This is caused by the rapid influx of ionic calcium and a decrease in NOS leading to a dramatic increase in smooth muscle tone.
In some patients underlying disease process results in persistent pulmonary hypertension which precludes patient coming off invasive ventilation due to dependence on iNO (e.g. undiagnosed VSD, Chronic lung disease, Post CDH repair)

In the patient tolerating oral medications there is evidence the addition of oral phosphodiesterase inhibitors such as Sildenafil reduces the incidence of rebound pulmonary hypertension and facilitates the weaning of iNO. As with all vasodilators there is a risk of causing systemic hypotension with Sildenafil so should be started cautiously at low dose and increased as tolerated (**Sildenafil**: dose 250-500mcg/kg po every 4-8hrs, adjusted according to response. Max 30mg daily).

There is also emerging evidence that **Non-invasive inhaled NO** treatment may reduce the duration of mechanical ventilation while safely treating late/persistent pulmonary hypertension, by facilitating the transition from mechanical ventilation to spontaneous breathing. Data shows the delivery of non-invasive iNO to be safe, deliver effective iNO doses and has a measurable effect on systolic arterial pressure, pulmonary vascular resistance and transpulmonary gradient. The measured nasopharyngeal concentration of INO is approximately half of that measured proximally in the delivery device. The Vapotherm Precision Flow system® used on PICU to deliver non-invasive high flow oxygen was cleared by the FDA for the administration of nitric oxide via high flow nasal cannula in 2011.

Long term sequelae
Long-term follow-up data are only now beginning to become available. Increased incidences of moderate cerebral palsy and sensorineural hearing loss have been reported following neonatal iNO usage. No data yet exists for long-term effects such as bronchoreactivity, hematologic changes, or impact on immune function.

2.4 Personnel

Registered Nurses with at least 1 years' experience within the Children's Intensive Care Unit will be deemed competent to safely administer Nitric Oxide to a ventilated child. As there are no adequate data and the potential risk is unknown, passive exposure to nitric oxide during pregnancy and lactation should be avoided.

2.4.1 Structure/Resources

 INOmax & INO blender Delivery System
 INOmax cylinders
 Blood Gas Analyser
 Paediatrician Specialist Registrar and a competent Registered Nurse with 1 year experience within Paediatric Intensive Care Unit
 Medical Physics Technician (Mon-Fri 9-5)

2.4.2. Process & Rationale

All Actions are in chronological order of the process needed to safely administer Nitric Oxide to a ventilated child via INOmax & INO blender.

ACTION	RATIONALE
Obtain an arterial blood gas and methaemoglobin prior to commencing nitric oxide.	To obtain a baseline observation.
Perform pre-use check of INOmax & INOblender, using the check list procedure from the IKARIA Reference folder. (inomax.com Operational manual of INOMAX https://www.inomax.com/)	To ensure the INOmax & INOblender are safe to use.
Check nitric oxide cylinder.	To ensure the certificate verifies nitric oxide is contained within the cylinder.
Perform a system purge and performance test according to IKARIA protocol (inomax.com Operational manual of INOMAX)	To flush away any residual gas left in the system, failure to do so will potentially result in excessive levels of nitrogen dioxide being delivered to the patient.
Assist medical staff to connect the child to the ventilator.	To ensure safe connection.
Commence nitric oxide therapy as prescribed by Paediatric Intensive Care Consultant.	Ensures safety requirements are adhered to.
Note the time treatment commenced and recorded clearly on allocating.	To enable medical/nursing staff to evaluate treatment.
Fully complete INOmax Return-user log & treatment record for evidence of usage time.	All INOmax cylinders are fitted with an INOtherapeutics timing device, which shows how many hours of use we will be charged for.
Record nitric oxide and nitrogen dioxide readings from the INOmax on to the observation chart. **Nitrogen dioxide <2 parts per million.**	Correct treatment of nitric oxide is being delivered by the ventilator to the patient. In the presence of oxygen, nitric oxide is converted into nitrogen dioxide. Nitrogen dioxide is toxic to the lungs when it mixes with water as it forms nitric and nitrous acids which can cause pulmonary oedema, pneumonitis and death. It is Important that nitrogen dioxide is kept <2ppm.
Repeat arterial blood gas 20 minutes following the commencement of treatment.	To re-evaluate efficiency of treatment after the start.
Methaemoglobin to be less than 2 If MetHb is rising, alert medical staff immediately: 5-10% reduce iNO dose by 50%. >10 % stop iNO >20% Methylene blue 1-2 mg/kg IV.	Nitric Oxide when bound to haemoglobin forms methaemoglobin which is not toxic to the body. However it is an unstable form of haemoglobin which hinders the binding of oxygen to the cell, therefore causing further hypoxaemia.

Continue with hourly observations recording **Nitric oxide and Nitrogen dioxide**	To ensure correct documentation is recorded
Blood Gases to be performed 2 hourly after each change in Nitric oxide concentration or 4 hourly once Nitric Oxide stabilised.	To check changes in treatment and monitor effectiveness of therapy.
Check nitric oxide cylinder at start of shift. Record time and date. If cylinder needs changing, complete following IKARIA reference folder. Ensure adequate gas supply available. Contact technician if surplus nitric oxide supply is low, return any used gas cylinders to a technician who will order replacement.	Sudden discontinuation of treatment may cause severe patient decompensation.
Ensure Appropriate sized anaesthetic bagging circuit is connected to INOblender at all times, for manual inflation.	In order to be able to continue treatment if child requires manual ventilation or hyperinflation.
In line closed suction unit to be used.	To prevent disconnection of treatment whilst child is being suctioned via endotracheal tube.
Elephant tubing to be attached to the expiration valve on ventilator and pointing in direction of floor.	To reduce the circulation of any toxic gas exhausted by ventilator.
Use of non-sterile gloves and aprons when emptying water traps and when discarding ventilator tubing.	Water traps and ventilator tubing can potentially contain nitrous acid which is corrosive.

Emergency iNO cylinder (800ppm) use:

O2 flow bagging circuit L/min x iNO ppm /800ppm = iNO flowmeter

10L/min x 20ppm/800 = 0.25 L/min

3. Education and Training

A minimum of 1 year clinical experience within the Paediatric Intensive Care Unit is required and completion of clinical competencies desired.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Daily iNO response checks in patients on INO	Audit	PICU/CICU Consultants	As required	Clinical Practice Meeting
NO2 and MetHb levels in patients on iNO	Audit	PICU/CICU Consultants	As required	Clinical Practice Meeting

5. Supporting Reference

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6. Key Words

Hypoxic Respiratory Failure, Inhaled nitric oxide, INOmax, INOblender, Nitric Oxide, Pulmonary vasodilation, Right sided heart failure, Ventilated Child

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Claire Westrope – Consultant PICU/ECMO Updated by A Iqbal – Higher Specialty Doctor	**Executive Lead** **Chief Nurse**
Details of Changes made during review: October 2022 Added optimisation of patient to flow chart Added a short statement regarding innovative antimicrobial therapy Risk of toxicity if dose >20ppm statement added. Weaning advice updated Updated 2.3 cautions/possible adverse effects, including additional info re- Methaemoglobinaemia	