Guideline for the nursing management of inhaled nitric oxide therapy (iNO)

Using the INOmaxDSIR

1. Introduction

Nitric oxide (NO) is a naturally produced compound within the vascular endothelium of the body. It acts by increasing cyclic guanosine monophosphate which in turn relaxes vascular smooth muscle (Fioretto 2003:S178, Soll 2009:S63).

iNO produces pulmonary vasodilation when inhaled (Soll 2009:S63). As nitric oxide is inhaled, it travels across the alveolar capillary membrane to the pulmonary circulation. The effects of which are reduction in pulmonary artery pressure and pulmonary vascular resistance. This vasodilation of pulmonary vasculature results in improved gas exchange (Ichinose et al 2004:3106, Wendel and Nathan 2006:100, Soll 2009:S63).

2. Guideline Statement

This guideline is intended for use by the registered nurse undertaking care of neonates requiring iNO therapy.

3. Principles / Guidelines

3.1 Indications for use

Treatment of hypoxic respiratory failure associated with pulmonary hypertension in the term or near term (>34 weeks) neonate. (Finer and Barrington 2009:2, TGA 2010).

Please refer to RPA Newborn Care guidelines on iNO and persistent pulmonary hypertension of the newborn for more detailed information.

3.2 Absolute contraindications

iNO should be ceased if a significant cyanotic cardiac anomaly is diagnosed using echocardiography (Steinhorn and Farrow 2007:e19, Kinsella 2008:711). As a precaution echocardiography is routinely performed prior to commencement of iNO in RPA Newborn Care.

A hypothetical risk is the infant with methaemoglobin reductase deficiency as this would not normally be recognised before the use of nitric oxide. Methaemoglobin reductase is an enzyme that is present in the blood. It modifies methaemoglobin back to haemoglobin. If there is an

3.3 Relative contraindications

Coagulopathies, intracranial haemorrhage- iNO is thought to inhibit platelet function and prolong bleeding time (Fioretto 2003:S184, Wendel and Nathan 2006:101).

3.4 Pharmacokinetics

3.4.1 Absorption and distribution;

iNO is rapidly inactivated once it crosses into the pulmonary capillary bed and combines with oxyhaemoglobin. Products of this union are methaemoglobin and nitrate. This ensures that the vasodilatory effect of iNO is limited to the pulmonary vessels. It has not been shown to affect systemic circulation. (Finer and Barrington 2009:3, Fioretto 2003:S178).

3.4.2 Excretion

The main nitric oxide metabolite nitrate is excreted in the urine and completely eliminated by around 48 hours. (Ichinose 2004:3107)

3.4.3 Half life

Short half life 3-6 seconds (time required for half the drug to lose its pharmacological activity). Onset of action 1-3 minutes (Nieves and Kohr 2010:S77, Cuthbertson et al 1997a:1214). iNO has a fast onset of action. Despite this, it should be remembered that it may take up to four hours for maximal effect (Cuthbertson 1997a:1214).

3.5 Prior to commencing iNO therapy

Effects of iNO are limited to areas of well ventilated lung. Therefore oxygenation must be maximised through optimum use of ventilation and surfactant prior to commencement of iNO therapy (Macrae et al 2004:373).
3.6 Delivery methods in RPA Newborn Care

Ikaria currently has an international patent on the therapeutic use of iNO. The current mode of nitric oxide delivery is the INOmaxDSIR (Ikaria).

Due to the nature and severity of illness, neonates requiring iNO most often require intubation and mechanical ventilation.

iNO therapy can also be delivered via a CPAP circuit. The INOmaxDSIR (Ikaria) has no recommendations for this route at present. Due to the limited literature documenting safety and efficacy this method must undergo careful consideration before use as the pop off system must be removed to facilitate delivery of the iNO.

iNO must be diluted with oxygen/air. It must not be given undiluted.

Set up procedures for the iNOvent can be accessed through the main computer at the nursing station. Alternatively refer to iNOvent setup package kept with the iNOvent in the store room.

During set up:

- Ensure all connections are secure- unsecure connections can result in reduced flow to the infant resulting in a rise in iNO which can be dangerous.
- Ensure system is purged prior to use- this prevents any nitric oxide and nitrogen dioxide which has settled in the system being bolused to the infant.
- Ensure a Neopuff® or bag and mask circuit is setup using a flow of air/oxygen and iNO.

3.7 Prescription and dosing

iNO is a registered S4 drug with the Australian therapeutic goods agency. iNO must be prescribed by a registered medical officer and signed for on the medication administration chart (MR70).

Usual prescribed doses are between 5-20/parts per million (ppm). Doses up to 40ppm have been used in RPA Newborn Care under medical guidance. Doses of up to 80ppm are documented within the literature but are associated with much higher levels of methaemoglobin and nitrogen dioxide which may be toxic (Finer and Barrington 2009:11).

The maintenance dose used should be the lowest dose which has the required effect.
3.8 Weaning

It has been suggested that the use of exogenous nitric oxide results in the down regulation of nitric oxide synthase therefore impacting on endogenous nitric oxide production (Macrae et al 2004:374, Kinsella 2008:713, Weinberger et al 2001:6). Weaning should be performed gradually to avoid a rebound occurrence of pulmonary hypertension (Cornick and Kent 2006:184, Dewhurst et al 2007:74).

3.9 Drug Interactions

Care should be taken when administering concurrent nitrate drugs or phosphodiesterase inhibitors such as sildenafil, sodium nitroprusside and nitroglycerin. This may lead to additive effects and cumulative side effects.

4. Nursing care and considerations

4.1 Calibration/Safety checks

Each day the nurse must ensure a low range calibration is done on the INOmaxDSIR along with safety checks of the circuit, gas cylinder type, Neopuff®, ventilator, suction and all other bedside equipment. The Neopuff® must be setup via the INOmaxDSIR blender.  

(See INOmaxDSIR setup procedures).

The INOmaxDSIR and ventilator must be plugged into the blue electrical sockets to ensure that in the event of a power failure, ventilation and iNO therapy will continue uninterrupted. The INOmaxDSIR has up to 6 hours back up battery if fully charged.

4.2 Monitoring

Infants must have cardio-respiratory monitoring, oxygen saturation monitoring (pre-ductal if possible) and an indwelling arterial catheter. It is advisable to have central venous access. The rainbow masimo monitor is also to be utilised which measures continuous methaemoglobin via infrared sensor. For infants >28weeks transcutaneous monitoring of PaO₂ and PaCO₂ may also be used.

Arterial blood gases should be monitored for improvements or deterioration in clinical status.
4.3 Alarms

Ensure all alarms are appropriately set (as per RPA Newborn care alarms policy).

On the INOmaxDSIR:

- Nitrogen dioxide (NO₂) alarm must be set at 0.5 ppm. Medical staff are to be informed if levels rise greater than this. There may be a requirement to reduce or stop the nitric oxide therapy.
- iNO alarms are to be set 5ppm above and below the set prescribed dose.

4.4 Observations/Documentation

The registered nurse will record on the intensive care observation chart (MR581) hourly heart rate, blood pressure, respiratory rate, oxygen saturation, FiO2 (fraction of inspired oxygen), iNO dose in parts per million (ppm), nitrogen dioxide level, methaemoglobin percent as measured via the rainbow masimo. Documentation of iNO cylinder pressure should also be recorded.

Also note that readings of FiO2 from the INOmaxDSIR will be 3-5% lower than set FiO2. This is because the iNO is displacing some of the oxygen.

The nurse will also document response and tolerance to interventions in the progress notes (MR45).

4.5 Patient Assessment

A full patient assessment should be done at the beginning of each shift and documented in the progress notes (MR45).

4.6 Suctioning

Use an inline suction system (to prevent loss of iNO therapy- half life of nitric oxide is only a few seconds) and also to prevent disconnection from the ventilator and loss of positive end expiratory pressure (PEEP) (See RPA newborn care suction protocol).
4.7 Using Neopuff (manual ventilation)

Ensure a Neopuff® or bag and mask circuit is connected to the iNO blender and the iNO dose is set at the same level the infant is receiving via the ventilator. Ensure that when connected to the INOmaxDSIR, pressures on the Neopuff® are checked and the flow is set at 8 L/min. The INOmax blender will always deliver 100% oxygen, regardless of the oxygen concentration delivered by the INOmaxDSIR.

When an infant requires bagging or use of Neopuff® in an emergency such as ventilator failure, ensure that when the flow meter is turned on, 3 quick ventilations are made prior to connecting to the infant. This is to ensure that any NO₂ within the tubing is purged out.

4.8 Scavenging and environmental monitoring

With modern air filtration systems within well ventilated intensive care units that have 10-12 air changes per hour, it is suggested that environmental monitoring of iNO is no longer necessary (Cuthbertson et al 1997b:698). If gases are scavenged set suction outlet at -5mmHg.

4.9 Disconnecting from ventilator

If the infant is disconnected from the ventilator, the ventilator should not be stopped and then restarted without purging the INOmaxDSIR first as iNO and NO₂ levels will rise within the tubing. If possible connect to a test lung and leave the ventilator on.

4.10 Methaemoglobin monitoring

iNO has a high affinity for haemoglobin. Once bound it forms methaemoglobin. Methaemoglobin cannot bind with oxygen and transport it to the tissues. The haemoglobin which is unaffected has an increased affinity for oxygen causing a left shift in the oxygen dissociation curve (Pabalan et al 2009:698). The result of which is reduced unloading of oxygen to the tissues (Zaky et al 2009:3, Stephens and Fawcett 2007:73).

Neonates have reduced amounts of the enzyme methaemoglobin reductase which aids conversion of methaemoglobin back to haemoglobin (Weinberger 2001:11, Camp 2007:174). Methaemoglobinemia can occur when there is insufficient supply of this enzyme.

Elevated levels of methaemoglobin are dependent upon dose and duration of therapy (Dewhurst et al 2007:74).
**Doses up to 20ppm**- For the first 24 hours methaemoglobin blood levels should be checked every 12 hours. This may be reduced to 24 hourly once the infant is stable.

**Doses > 20ppm**- risks of methaemoglobinaemia and elevated nitrogen dioxide levels are increased (Dewhurst et al 2007:74). Monitoring should be done at 6 and 12 hours initially and then every 12 hours.

PaO₂ measures from arterial blood samples measure dissolved oxygen in the blood, not from the red blood cell; therefore this is an inadequate assessment of methaemoglobin formation (Sachdeva et al 2003:309).

A methaemoglobin level needs to be ordered by medical staff. Take 0.3ml of blood from an arterial line using a blood gas syringe and place in a bag of ice and send to the labs for immediate analysis. An arterial blood gas analysis can also be requested on this sample.

Continuous monitoring of methaemoglobin should also be insitu for all infants via the rainbow masimo. The methaemoglobin from the rainbow masimo should correlate with blood methaemoglobin levels. The nurse should record the methaemoglobin level on the masimo monitor at the time of taking a blood gas.

Normal physiological levels of methaemoglobin are 0-2% but levels less than 5% may be acceptable upon discussion with the medical team. If methaemoglobin levels rise above 5% iNO should be reduced or stopped. The half life of methaemoglobin is 55 minutes (Coleman and Coleman 1996:396, Sachdeva et al 2003:308).

Methaemoglobinemia has been shown to directly inhibit surfactant activity (Weinberger et al 2000:10). Infants with severe methaemoglobinaemia will exhibit signs such as cyanosis, respiratory distress/increasing ventilator requirements and lethargy.

Of note is the fact that methaemoglobin can hinder oxygen saturation readings via a pulse oximeter which only reads functional haemoglobin (oxygenated and deoxygenated haemoglobin). Methaemoglobin has a brown colour which can be read by the oximeter as desaturated haemoglobin (Stephens and Fawcett 2007:74).
4.11 Nitrogen dioxide- NO₂ monitoring

Nitrogen dioxide (NO₂) can form rapidly in mixtures containing nitric oxide and oxygen (Sokol 1999:382). Elevated levels of nitrogen dioxide may cause airway inflammation and injury. High levels of inspired oxygen have the potential to increase concentrations of nitrogen dioxide (Finer and Barrington 2009:12, Weinberger et al 2001:6, Riddle et al 2002:443).

The INOmaxDSIR continuously monitors levels of NO₂ and should not exceed 0.5ppm. These levels should be documented hourly.

4.12 Platelet function


4.13 Changing cylinders

Due to the fact that 2 cylinders of iNO are connected to the INOmaxDSIR at any one time, cylinder change may occur when the pressure reaches 200psi (See RPA Newborn Care INOmaxDSIR setup procedures).

5. Definitions

iNO – inhaled nitric oxide

NO₂- nitrogen dioxide

PaO₂- partial pressure of arterial oxygen

PaCO₂- partial pressure of arterial carbon dioxide

G6PD- glucose 6 phosphate dehydrogenase
6. References and links


