Operating Instructions for Inhaled Nitric Oxide Therapy

Purpose

To provide guidelines for the initiation of inhaled nitric oxide therapy via the INOvent delivery system by completing the pre-use system purge and performance test.

Audience

Physicians, Nursing staff, and Licensed Respiratory Care Practitioners.

Scope

Inhaled Nitric Oxide is a selective pulmonary vasodilator. It is supplied as a gaseous blend of 0.8% NO and 99.2% nitrogen (N_2).

Physician's Order

Physician orders must include the following:

- Mechanical ventilation parameters
- Nitric Oxide concentration in ppm
- Methemoglobin levels prior to the initiation of therapy, every hour times 4 hours after initiation of therapy, and at least every morning throughout the duration of treatment.

Indications

Inhaled nitric oxide therapy is indicated in term and near-term (>34 weeks) neonates with hypoxic respiratory failure that is associated with:

- Meconium aspiration syndrome (MAS)
- Pneumonia/ Sepsis
- Persistent Pulmonary Hypertension of the Newborn (PPHN)
- Congenital Diaphragmatic Hernia (CDH)
- Respiratory Distress Syndrome (RDS)

The use of inhalational nitric oxide for conditions associated with pulmonary artery hypertension in the adult and pediatric patient has not been approved by the FDA and is considered to be “off-label” use of the drug.

Goals

The goals of delivering inhaled nitric oxide are to:

- Improve and maintain oxygenation
- Reduce the need for extracorporeal membrane oxygenation (ECMO)

Relieve primary pulmonary artery hypertension

Adverse Effects

The adverse effects associated with inhaled nitric oxide therapy include:

- Rebound (abrupt discontinuation of INO may lead to worsening oxygenation and increasing pulmonary artery pressure)
- Methemoglobinemia (increases with dose of INO)
- Increased levels of NO_2
- Inhaled nitric oxide therapy should not be used in patients that are dependent on right-to-left shunting of blood

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Equipment

- **1 -** INOmax delivery system
- **2 -** Full NO cylinders
- **Select Patient Application Device:**
  - Avea ventilator
  - Infant SiPAP/ CPAP device
  - High Flow Nasal Cannula Set-up
  - High Frequency Oscillatory Ventilator
  - Adult, pediatric, or infant nasal cannula
  - Adult, pediatric, infant, or neonatal manual resuscitation bag

Procedure

Pre-Use System Purge and Performance Test

Step	Action
1	Check the INOmax gas cylinders for the correct product identity labels, cylinder concentration, and expiration date. Ensure that at least one INOmax gas cylinder with more than 200psig is available.
2	Connect one of the high pressure regulators to an INOmax cylinder and tighten the fitting to the INOmax cylinder.
3	Connect the INOmax DS regulator hose to one of the INOmax inlets.
4	If using the INOblender with the INOmax DS, connect the INOblender hose to the INOmax DS outlet and slide the Quick-Connect cover into place.
5	Ensure water trap bottle and water separator cartridge are in place.
6	Connect the Infrared cable from the INOmax cart to the back of the INOmax DS system.
7	Turn the INOmax DS ON.
8	Open and then close the cylinder valve.
9	Check for adequate cylinder pressure (if there is any decrease, make sure the backup NO delivery and the INOblender are off.
10	Perform low range calibration.
11	Perform system Purge and Alarm Verification: • Ensure the INOmax cylinder is closed

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	• Set the O2 flowmeter to 10L/min • Set the INOmax dose to 40ppm • "Cylinder Valve Closed" alarm will occur • Cylinder gauge pressure should drop to 0psig • Measured NO2 will increase and then decrease as NO2 is purged from the system. • "Low NO/N2 Pressure" alarm will occur. • Open the INOmax cylinder valve • Turn the INOmax dose to zero (the "Set Dose is Zero, Close Cylinder Valve" indicator will appear).
12	Backup INOmax Delivery test: • Turn the back INOmax delivery ON (250mL/min) • "Backup ON" alarm will occur • Allow 2-3 minutes for the monitored values to stabilize and make sure the NO and NO2 readings are within the following ranges: **NO = 14-26 ppm NO2 = <1.0 ppm** • Turn the backup INOmax delivery OFF
13	Performance Test: • Ensure that the O2 flowmeter is set to 10L/min • Set the INOmax dose to 40ppm • Compare the INOmax DS monitor values to the values below: **NO = 35-45 ppm NO2= <1.5 ppm FiO2 = ≥92%** • Turn INOmax dose to zero.
14	INOblender Test: • Remove the Pre-Use set-up oxygen tubing from the oxygen flowmeter and connect it to the front of the INOblender. • Remove the Injector Module from the Pre-Use set-up and reconnect the adapters. • On the INOblender, set the INOmax dose to 40 ppm and the O2 flow to 10L/min. • Verify that the monitored value for NO is within the following range: **NO= 32-48 ppm** • Turn the dose and flow to zero and remove the Pre-Use set-up from the INOblender.
15	Purge the Regulator Supply Line: • If not immediately connecting to a patient, turn the INOmax cylinder OFF.

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	• Purge the pressure from the regulator using the purge port on the back of the INOmax DS unit. • Reconnect the regulator line to the INOmax DS inlet. • If the INOmax DS unit is depressurized and not used within 12 hours, repeat the pre-use procedure.

Initiation of Therapy with Conventional Mechanical Ventilation, Infant Nasal CPAP, and High Flow Nasal Cannula Systems

Step	Action
1	Obtain arterial blood gas analysis of methemoglobin level prior to the initiation of therapy.
2	Insert the Injector Module on the dry side of the breathing circuit prior to the humidifier (following the directional arrow located on the Injector Module) using a 15mm and 22mm adapter.
3	Insert 6” extension tubing with sample tee adapter at the patient wye on the inspiratory side of the breathing circuit distal to the temperature probe adapter. This extension tubing minimizes sampling of mixed inspiratory/ expiratory gases.
4	Set the INOmax dose to be delivered to the patient.
5	After the monitored values have stabilized, set or change the user-adjustable alarms to the appropriate ranges. **NO_2 high alarm should be set at 3.0 ppm** **NO alarms should be set $\pm$ 5 ppm of desired level**
6	Attach an appropriate sized resuscitation bag to the INOblender for the manual delivery of NO.
7	Methemoglobin levels should be drawn one hour after the initiation of therapy and checked q1° times four hours to monitor for increases in methemoglobin.
8	A low range calibration of sensors needs to be completed daily throughout the duration of therapy.

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Initiation of Therapy with High Frequency Oscillatory Ventilation (HFOV)

Step	Action
1	Perform pre-use system purge and performance test as outlined above
2	Obtain arterial blood gas analysis of methemoglobin level prior to the initiation of therapy.
3	Assemble Injector Module for patient delivery of NO as outlined in the Operation Manual (page 46-47). **Note: Omission of the one-way valve may result in high NO delivery.**
4	Insert patient gas sample line connection as outlined in the Operation Manual using a 90° luer elbow adapter.
5	After connecting the INOmax delivery system to the patient HFOV Circuit, set the nitric oxide dose to be delivered.
6	After the monitored values have stabilized, set or change the user-adjustable alarms to the appropriate ranges. **NO_2 high alarm should be set at 3.0 ppm** **NO alarms should be set ± 5 ppm of desired level**
7	Attach an appropriate sized resuscitation bag to the INOblender for the manual delivery of NO.
8	Methemoglobin levels should be drawn one hour after the initiation of therapy and checked q1° times four hours to monitor for increases in methemoglobin.
9	A low range calibration of sensors needs to be completed daily throughout the duration of therapy.

Procedure Continued

Initiation of Therapy Through a Low Flow Nasal Cannula

Step	Action
1	Perform pre-use system purge and performance test as outlined above
2	Obtain arterial blood gas analysis of methemoglobin level

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	prior to the initiation of therapy.
3	Assemble Injector Module for patient delivery of NO as outlined in the Operation Manual (page 62).
4	Insert patient gas sample line connection as outlined in the Operation Manual using an O2 Tubing Sample Tee.
5	Set oxygen concentration in L/min at the wall flow meter.
6	After connecting the INOmax delivery system to the patient nasal cannula, set the nitric oxide dose to be delivered.
7	After the monitored values have stabilized, set or change the user-adjustable alarms to the appropriate ranges. **NO_2 high alarm should be set at 3.0 ppm** **NO alarms should be set ± 5 ppm of desired level**
8	Attach an appropriate sized resuscitation bag to the INOblender for the manual delivery of NO.
9	Methemoglobin levels should be drawn one hour after the initiation of therapy and checked q1° times four hours to monitor for increases in methemoglobin.
10	A low range calibration of sensors needs to be completed daily throughout the duration of therapy.

Assessment of Outcome

- Arterial, venous and capillary blood gas values
- Pulse oximetry
- Pulmonary artery pressures

Infection Control

Follow procedures as outlined Healthcare Epidemiology Policies and Procedures: #2.24 Respiratory Care Services.
http://www.utmb.edu/policy/hcepidem/search/02-24.pdf

Safety Precautions

Oxygen safety techniques as outlined in the INOmax Manual will be followed.

All alarms on ventilators will be activated at all times.

All alarms on INOvent delivery system will be activated at all times.

References

Sensormedics High Frequency Oscillatory Ventilator Operating Manual.

Whitaker, K., Comprehensive Perinatal and Pediatric Respiratory Care, Delmar, Albany, New York, 2001.

Cornfield DN, Abman SH. Inhalational nitric oxide in pulmonary

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parenchymal and vascular disease. Journal of Laboratory Clinical Medicine 1996 Jun; 127(6): 530-539.

Miller CL. Nitric oxide therapy for the persistent pulmonary hypertension of the newborn. Neonatal Network 1995 Dec; 14(8): 9-15.

Angelucci P. A new weapon against ARDS…adult respiratory distress syndrome. RN 1996 Nov; 59(11): 22-25.

Addendum:

Use of Inhaled Nitric Oxide (iNO) in the ISCU

Clinical Practice Guideline

Indication iNO therapy is FDA-approved for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (iNO package insert, 2004). The rationale for use of iNO in other clinical situations should be documented carefully in the medical record.

Definitions (Jumar 2007, Carriedo 2003)

Responder: A patient is classified as a responder to iNO therapy if the post-ductal PaO_2 increases 20mmHg within 30 minutes of starting iNO without any change in the inspired oxygen concentration. If there is no increase with the initial dose (5-15 ppm), iNO should be increased to 20 ppm.

Non-Responder: If, after 30 minutes at 20 ppm, the post-ductal PaO_2 does not increase >20mmHg, the patient is classified as a non-responder and therapy should be discontinued, as follows:

Recommended Weaning Strategy for Discontinuation of iNO – Non-Responders	
Time (min)	iNO Concentration (ppm)
0	20
30	10
60	5
90	2
120	0

- The patient should be classified as a responder or a non-responder after <1 hour of iNO. Non-responders should start the weaning process, as above.
- An increase in O_2 saturation >10% will be considered equivalent to an increase in PaO_2 >20 mmHg.

Monitoring during iNO

The risk of methemoglobinemia increases with the dose of nitric oxide. In clinical trials, the maximum methemoglobin levels were typically reached 8 hours after the initiation of therapy, though peak levels were seen as late as 40 hours after the start of therapy (iNO package insert, 2004).

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- Methemoglobin levels will be checked at 1 and 8 hours after starting therapy and then daily (i.e. with morning labs) until the discontinuation of therapy.

Methemoglobin Range	Action
>10%	Discontinue iNO, repeat metHb every 2 hours until <5%; if needed, restart therapy at 50% of the iNO at discontinuation
5-10%	Wean iNO by 50% and repeat metHb in 2 hours; repeat sequence until metHb is <5%
<5%	No Action Needed

Weaning from iNO (Davidson, 1999)
Responders may be weaned from iNO when any of the following conditions are met:

- PaO_2 >60 on FiO_2 <.60
- MAP on mechanical ventilation <10 cmH2O
- Oxygenation Index (OI) <10

- If PaO_2 falls to <45 mmHg after any weaning step, the dose of iNO may be increased back to the previous dose, with appropriate increases in FiO_2
- If PaO_2 falls after weaning, but remains >45 mmHg, only FiO_2 should be increased.

Recommended Weaning Strategy for Discontinuation from iNO therapy – Responders*				
Time (hours)	**iNO Concentration (ppm)**			
0 (Start of Wean)	5	10	15	20
1	4	5	10	15
2	3	4	5	10
3	2	3	4	5
4	1	2	3	4
5	0	1	2	3
6	-	0	1	2
7	-	-	0	1
8	-	-	-	0
Total	5	6	7	8

**Deviations from this strategy may be indicated if the patient is particularly sensitive to changes.*

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References

Barringtion K, Finer N. Inhaled Nitric Oxide for Preterm Infants: A Systematic Review. Pediatrics. 2007; 120; 1088-1099.

Carriedo H, Rhine W. Withdrawal of Inhaled Nitric Oxide from Non-Responders After Short Exposure. Journal of Perinatology. 2003; 23:556-558

Davidson D, Barefield E, Kattwinkel J, et al. Safety of Withdrawing Inhaled Nitric Oxide Therapy in Persistent Pulmonary Hypertension of the Newborn. Pediatrics. 1999; 104; 231-236

INOmax® [Package Insert]. Clinton, NJ: INO Therapeutics, Inc; 1999. Revised April 2004.

Kumar VH, Hutchison AA, et al. Characteristics of Pulmonary Hypertension in Preterm Infants. Journal of Perinatology. 2007, 1-6.

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