Operating Instructions for Inhaled Nitric Oxide Therapy

Purpose
To provide guidelines for the initiation of inhaled nitric oxide therapy via the iNOmax 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. Nitric Oxide, the active substance in iNOmax is a gaseous blend of 0.08% NO and 99.2% Nitrogen respectively for 800 ppm concentration.

Physician's Order
Physician orders must include the following:
- Mechanical ventilation parameters
- Nitric Oxide concentration in ppm
- Methemoglobin levels are recommended at 1 hour and 8 hours after initiation of therapy and at physician discretion.

Indications
Inhaled nitric oxide therapy is indicated in term and near-term (>34 weeks) neonates with hypoxic respiratory failure that is associated with: (INO package insert 2014)
- Meconium aspiration syndrome (MAS)
- Pneumonia/ Sepsis
- Persistent Pulmonary Hypertension of the Newborn (PPHN)
- Congenital Diaphragmatic Hernia (CDH)
- Respiratory Distress Syndrome (RDS)
- Off label use for post-op Cardiac Patients such as LVAD
- Respiratory Failure (ARDS)

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

Equipment

- INOmax delivery system
- Full NO cylinders

Procedure

Pre-Use System Purge and Performance Test

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Turn ON iNOmax DSIR. Low calibration automatically starts following the iNOmax DSIR self-test. Check the iNOmax DSIR gas cylinders for the correct product identity labels, cylinder concentration, and expiration date. Ensure that at least one iNOmax DSIR gas cylinder with more than 50 psig is available.</td>
</tr>
<tr>
<td>2</td>
<td>Connect one of the high pressure regulators to an iNOmax DSIR cylinder and tighten the fitting to the iNOmax cylinder</td>
</tr>
<tr>
<td>3</td>
<td>Connect the iNOmax DSIR regulator hose to one of the iNOmax inlets</td>
</tr>
<tr>
<td>4</td>
<td>If using the iNOblender with the iNOmax DSIR, connect the iNOblender hose to the iNOmax DS outlet and slide the Quick-Connect cover into place</td>
</tr>
<tr>
<td>5</td>
<td>Ensure water trap bottle and water separator cartridge are in place.</td>
</tr>
<tr>
<td>Step</td>
<td>Instruction</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>6</td>
<td>Connect the Infrared cable from the iNOmax DSIR cart to the back of the iNOmax DSIR system</td>
</tr>
<tr>
<td>7</td>
<td>Open and then close the cylinder valve.</td>
</tr>
<tr>
<td>8</td>
<td>Check for adequate cylinder pressure, if no pressure decrease is observed in 30 sec., high pressure leak test is complete.</td>
</tr>
<tr>
<td>9</td>
<td>Confirm injector module is out of patient breathing circuit or pre use circuit. Press NEXT button to start the purge process. Low cylinder pressure alarm may activate. Open cylinder valve when purge is complete.</td>
</tr>
</tbody>
</table>
| 10   | 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 |
| 11   | Performance Test  
Assemble the pre-use set up connectors and tubing (press show diagram button if needed). Set the Oxygen flowmeter to 10 L/min. Press NEXT button to automatically set the INOMAX dose to 40ppm. Allow values to stabilize  
Compare the iNOmax DSIR monitor values to the values below:  
- NO = 35-45 ppm  
- NO2= <1.5 ppm  
- FiO2 = ≥92  
**Performance Test is complete.**  
The iNOmax is automatically set to zero.
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**12**  
**iNOblender Test:** If using the iNOblender with the INOmax DS:

- Remove the Pre-Use flow to zero and remove the Pre-Use set-up from the oxygen flowmeter.
- 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.

- 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:
  
  \[ \text{NO} = 32-48 \text{ ppm} \]

- Turn the dose and flow to zero and remove the Pre-Use set-up from the iNOblender.

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**13**  
**Purge the Regulator Supply Line:**

- If not immediately connecting to a patient, turn the INOmax cylinder OFF.
- 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.

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**Initiation of Therapy with Conventional Mechanical Ventilation, Infant Nasal CPAP (NCPAP), and High Flow Nasal Cannula Systems (HFNC)**

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Perform pre-use system purge and performance test as outlined above</td>
</tr>
<tr>
<td>2</td>
<td>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.</td>
</tr>
</tbody>
</table>
3 Neonatal Application
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 (6” extension tubing NOT NEEDED for NCPAP or HFNC)

Adult Application: Insert a Sample Tee Adapter on the inspiratory side of the breathing circuit, and connect the sample tee adapter to the gas sample line.

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.

   NO₂ high alarm should be set at 3.0 ppm
   NO alarms should be set ± 5 ppm of desired level

6 Attach an appropriate sized resuscitation bag to the iNOblender for the manual delivery of NO.

Initiation of Therapy with High Frequency Oscillatory Ventilation (HFOV)

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Perform pre-use system purge and performance test as outlined above</td>
</tr>
</tbody>
</table>
| 2    | Assemble Injector Module for patient delivery of NO as outlined in the Delivery System pocket guide (page 37-38). Ensure the injector module is on the dry side of the heater.  
   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. |
After the monitored values have stabilized, set or change the user-adjustable
alarms to the appropriate ranges.

**NO₂ high alarm should be set at 3.0 ppm**
**NO alarms should be set ± 5 ppm of desired level**

Attach an appropriate sized resuscitation bag to the iNOblender for the manual
delivery of NO.

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**Assessment of Outcome**

1. Arterial, venous and capillary blood gas values
2. Pulse oximetry
3. Pulmonary artery pressures

**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,
2014).

<table>
<thead>
<tr>
<th>Methemoglobin Range</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>Discontinue iNO, repeat metHb every 2 hours until &lt;5%; if needed, restart therapy at 50% of the iNO at discontinuation</td>
</tr>
<tr>
<td>5-10%</td>
<td>Wean iNO by 50% and repeat metHb in 2 hours; repeat sequence until metHb is &lt;5%</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>No Action Needed</td>
</tr>
</tbody>
</table>

**Infection**

Follow procedures as outlined Healthcare Epidemiology Policies and Control Procedures: #2.24 Respiratory Care Services.

Use of Inhaled Nitric Oxide (iNO) Clinical Practice Guideline

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>iNO Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
</tr>
</tbody>
</table>

- 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.

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
- Oxygenation Index (OI) <10

• If PaO_2 or SpO2 falls >10% mmHg after any weaning step, the dose of iNO may be increased back to the previous dose, with appropriate increases in FiO_2

Recommended Weaning Strategy for Discontinuation from iNO therapy – Responders*

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<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>iNO Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Start of Wean)</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5</td>
</tr>
</tbody>
</table>
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Implementation of iNO

Order For iNO

Baseline
SpO2
PaO2
PAP

Wait 1 Hour
Start iNO at 20ppm

≥ 10% change in any
SpO2_____ (increase)
PaO2_____ (increase)
PAP_____ (decrease)

Yes
Wait 1 Hour
Wean iNO to 10ppm
No

Discontinue iNO following the Non-responder wean

Return here after 12 Hours

≥ 10% change in any
SpO2_____ (decrease)
PaO2_____ (decrease)
PAP_____ (decrease)

Yes
Return to 20 ppm for 12 hours. Refer to iNO weaning protocol
No

Wait 1 Hour
Wean iNO to 5ppm and wait 1 hour

Return here after 12 Hours

≥ 10% change in any
SpO2_____ (decrease)
PaO2_____ (decrease)
PAP_____ (decrease)

Yes
Return to 10 ppm for 12 hours. Refer to iNO weaning protocol
No

Wait 1 Hour
Wean iNO by 1 ppm every 30 minutes

Wean iNO off

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

**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.


**References**

*Respiratory Care. May 2015 Vol.60 No.5*


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

