Inhaled Nitric Oxide (iNO)

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of October 7, 2020
Molecule with multiple biological functions

Regulator of several processes in CNS, immune and CV systems

Potent vasodilator

Multiple drugs act as NO precursors, or act on NO pathway

Abnormal NO concentrations associated with multiple disease states

In vitro data suggest NO inhibits SARS-CoV-1 replication

iNO utilized for treatment of multiple pulmonary disorders

Mechanism of Action

- Rapidly defuses across alveolar-capillary membrane to pulmonary smooth muscles
- Activates guanylate cyclase
- ↑ Intracellular cyclic GMP (cGMP)
- Pulmonary smooth muscle relaxation
- ↑ PaO₂, ↓ PVR, ↔ SVR

Legend: PaO₂: Partial pressure of oxygen
PVR- Pulmonary vascular resistance;
SVR- Systemic vascular resistance
**Other iNO Applications**

### ARDS
- Pulmonary vasodilation
- Transient ↑ Oxygenation, ↑ PaO2: FiO2 ratio
- No impact on overall survival, ventilator-free days, quality of life, ICU/hospital LOS

### Pulmonary Hypertension (PH)-Adults
- Pulmonary vasoreactivity testing
- Perioperative PH
- Cardiac transplantation
- LVAD insertion

### Pulmonary Hypertension (PH)-Neonates
- Idiopathic PH
- Premature closure of the ductus arteriosus
- Meconium aspiration
- Prematurity
- Lung hypoplasia

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**Legend:** PaO2: Partial pressure of oxygen  
FiO2: Fraction of inspired oxygen  
LOS: Length of stay

Adverse Drug Reactions

• Methemoglobinemia
• Need for continued mechanical ventilation
• Pulmonary edema
• Rebound pulmonary hypertension
• Acute renal failure
• Increased bleeding risk

Potential mechanisms for iNO in COVID-19

- Pulmonary vasodilatory effects
- Bronchodilator effects
- Anti-inflammatory effects
- Anti-viral properties

Available Data: iNO in SARS

- **Two Chinese Hospitals**
- **Non-randomized, non-blinded**
- **SARS diagnosis**
  - ≥ 18 years age
  - >1 week duration of SARS symptoms
  - PaO$_2$ : FiO$_2$ ratio <300 OR an oxygen saturation of ≤ 93% OR an FIO2 of 0.5

- **iNO regimen**
  - Day 1: 30 ppm
  - Day 2: 20 ppm
  - Day 3: 10 ppm
  - Day 4: 0 ppm

- **Concomitant therapy**
  - Ribavirin IV 0.5-1g/day
  - MTP IV 40-160 mg/day

- **N= 14**
  - iNO: 6/14
  - Control: 8/14

- **Symptom duration**
  - iNO: 32 days
  - Control: 25 days

- **Ventilatory support**
  - iNO: 5/6
  - Control: 6/8

- **Improved oxygenation**
- **Reduced FiO2 requirements**
- **Persisted after iNO treatment**
- **Decreased infiltrates on chest radiography**
- **No difference in in-hospital mortality**

**Legend:** MTP: Methylprednisolone; IV: Intravenous
Single-center (U.S.)
Non-randomized, non-blinded, case series

Pregnant
Respiratory distress due to COVID-19
iNO regimen used varied based on oxygen requirements

iNO regimen
- O2 < 3L/min: 200 ppm for 30 min BID
- O2 > 3L/min: 5-20 ppm continuous + 200 ppm for 20 mins BID
- iNO started within 48 hours of hospital admission

N= 6
- Age: 24-33 years
- Symptom duration: 3-14 days
- Disease severity*
  - Severe: 2/6
  - Critical: 4/6
- Remedesivir use: 2/6 (DOT: 3-7 days)

Improved oxygenation in patients with lowest SpO2
Subjective relief of shortness of breath
Transient decrease in RR
Negative SARS-CoV-2 RT-PCR by day 28
Sustained ↓ CRP until hospital discharge
Baseline and peak methemoglobin similar (baseline 0.9%, IQR 0.5–1.3%; peak: 2.5%, IQR 2-3%)

Legend: *Severe: RR >30 and lung infiltrates > 50%; Critical: Presence of severe respiratory distress, shock, or multiple organ dysfunction

Zamanian, et al. 2020

- Case report of 34-year-old patient with COVID-19 and PAH exacerbation
- Lived 350 miles away from PAH care center
- Ambulatory iNO delivery system delivered to residence
- Remote monitoring and home assessment of 6MWD
- Initial regimen: 20 ppm + 2L/min supplementary oxygen via nasal cannula for 12-14 hrs/day
  - Gradually weaned to 0 ppm each night, and restarted in the AM
  - Titrated down at iNO day 7, iNO day 9
- Normal methemoglobin levels throughout iNO treatment
- 11 days of iNO therapy
  - Symptomatic improvement, near return to baseline 6MWD, gradual improvement in EmPHasis-10 score
  - No urgent care, ED, or hospital visit required

Legend: 6MWD; 6-minute walk distance; E10- EmPHasis-10; PAH- Pulmonary arterial hypertension

## iNO: Making Sense of The Noise

**What we (think) we know**
- iNO transiently improves oxygenation
- Relatively safe
- Expensive ($100+/hr)

**What we don’t know**
- Improvement in clinical outcomes? (ARDS data would say no)
- Specific subsets of patients who may benefit from iNO (if any)?
- Cost-benefit ratio?
- Antiviral/anti-inflammatory properties of iNO?
- NO analogues?
Ongoing Clinical Trials: COVID-19

- 7 Trials in the US assessing iNO in COVID-19, 11 worldwide
- US: 1 active, 6 recruiting (All adults)
- Wide variety of dosing ranges and delivery methods

<table>
<thead>
<tr>
<th>NCT number</th>
<th>Study Phase</th>
<th>iNO Dose</th>
<th>Comparator</th>
<th>Estimated enrollment</th>
<th>Estimated study completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04421508</td>
<td>3</td>
<td>20 ppm continuous pulse dose</td>
<td>Placebo (inhaled N₂)</td>
<td>500</td>
<td>June 2021</td>
</tr>
<tr>
<td>NCT04388683</td>
<td>2</td>
<td>80 ppm continuous</td>
<td>SOC</td>
<td>200</td>
<td>March 2022</td>
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<tr>
<td>NCT04338828</td>
<td>2</td>
<td>140-300 ppm for 30 minutes daily</td>
<td>Placebo (inhaled O₂)</td>
<td>260</td>
<td>April 2022</td>
</tr>
<tr>
<td>NCT04305457</td>
<td>2</td>
<td>140-180 ppm for 30 minutes BID</td>
<td>SOC</td>
<td>67</td>
<td>April 2022</td>
</tr>
<tr>
<td>NCT04312243</td>
<td>2</td>
<td>160 ppm for 15 mins BID (HCW prevention)</td>
<td>SOC</td>
<td>470</td>
<td>April 2022</td>
</tr>
<tr>
<td>NCT04306393</td>
<td>2</td>
<td>20 ppm continuous</td>
<td>SOC</td>
<td>42</td>
<td>July 2021</td>
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<tr>
<td>NCT04397692</td>
<td>N/A</td>
<td>80 ppm for 40 mins QID</td>
<td>SOC</td>
<td>20</td>
<td>September 2020</td>
</tr>
</tbody>
</table>

Legend: HCW- Healthcare worker; ppm- parts per million; SOC- Standard of care
<table>
<thead>
<tr>
<th>NIH</th>
<th>Surviving Sepsis</th>
<th>IDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The Panel recommends <strong>against</strong> the routine use of inhaled nitric oxide (aI)</td>
<td>• In mechanically ventilated adults with COVID-19 ARDS, we recommend <strong>against the routine use of inhaled nitric oxide</strong>. (strong recommendation, low-quality evidence)</td>
<td>• Not addressed</td>
</tr>
<tr>
<td></td>
<td>• In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, we <strong>suggest</strong> a trial of inhaled pulmonary vasodilator as a rescue therapy (Weak recommendation, low-quality evidence)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Pearls

• iNO can be safely inhaled when delivered by face mask, by nasal cannula, or via an endotracheal tube.
• An ideal inhaled NO delivery device requires delivery synchronized with respiration and minimal production of NO₂.
• Ideally, delivery should be simple to use with full monitoring capacity
  • High and low alarms and precise monitoring of NO, NO₂, and O₂.
• Many institutions have guidelines for use to ensure safe care
  • Indication, restricted prescribers, monitoring parameters, indication, team roles and responsibilities, weaning parameters to prevent rebound pulmonary vasoconstriction, etc.
Summary

- iNO is a promising agent in the management of COVID-19
- Several plausible reasons for iNO use in COVID-19 are reported, although none have been fully substantiated
- Current understanding of its role in COVID-19 is limited by lack of robust evidence supporting or refuting its use
- At this time, iNO cannot be recommended for routine use in COVID-19 patients, however several clinical trials are underway
- If considering iNO as salvage therapy, should be performed at centers with experience using therapy
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