Inhaled Nitric Oxide (iNO)

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

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Data as of October 7, 2020

Background

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

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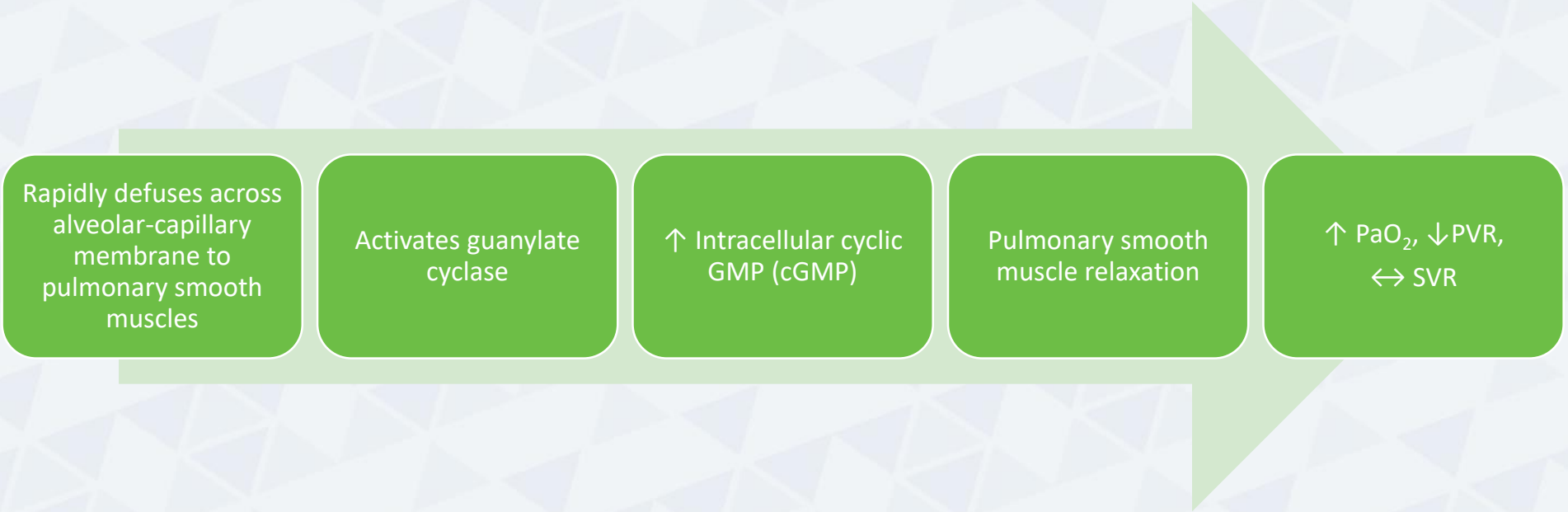
Akerstrom S, et al. J Virol. 2005;79:1966-1969. https://10.1128/JVI.79.3.1966-1969.2005.

Mechanism of Action



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Legend: PaO2: Partial pressure of oxygen
PVR- Pulmonary vascular resistance;
SVR- Systemic vascular resistance

Ichinose F, et al. Circulation. 2004;109:3106-311. https://doi.org/10.1161/01.CIR.0000134595.80170.62.

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

1. Ichinose F, et al. Circulation. 2004;109:3106-3111. https://doi.org/10.1161/01.CIR.0000134595.80170.62.
2. Karam O, et al. Anaesthesia. 2017; 72: 106–117 . https://doi.org/10.1111/anae.13628.
3. Gebistorf F, et al. Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD002787. https://doi.org/10.1002/14651858.CD002787.pub3.

Adverse Drug Reactions

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

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Potential mechanisms for iNO in COVID-19

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

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Ichinose F, et al. Circulation. 2004;109:3106-311. https://doi.org/10.1161/01.CIR.0000134595.80170.62.

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

iNO treatment was resumed if arterial oxygenation deteriorated during weaning.

- 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

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Legend: MTP: Methylprednisolone; IV: Intravenous

Chen L, et al. Clin Infect Dis. 2004;39:1531-35. https://doi.org/10.1086/425357

Relevant iNO Experience: COVID-19

- 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)

- Median iNO dose: 160 ppm (range: 160- 200)
- Median # of iNO sessions: 4.5 (range: 2-18)

- 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%)

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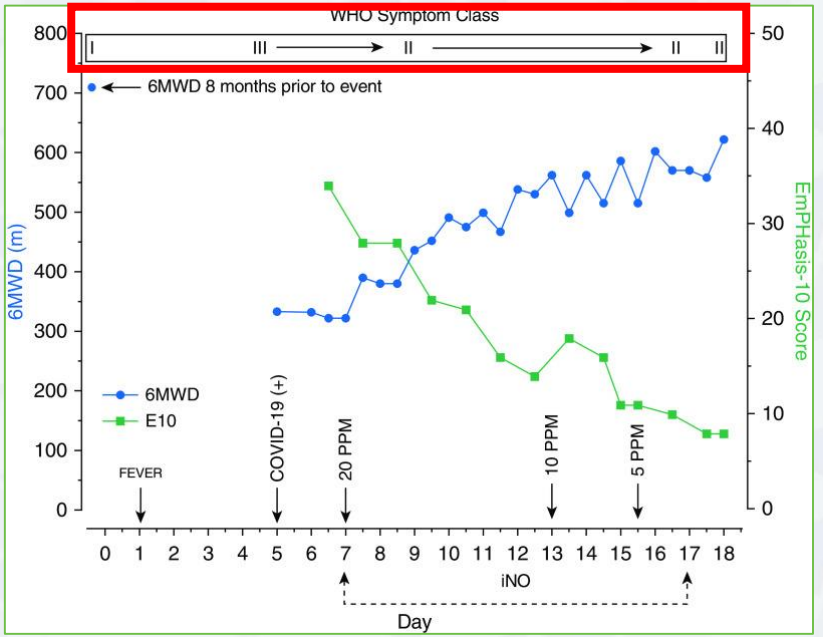
Legend: *-Severe: RR >30 and lung infiltrates > 50%; Critical: Presence of severe respiratory distress, shock, or multiple organ dysfunction

Farkh BS et al. Obstet Gynecol. 2204;39:1531-35. https://doi.org/10.1097/AOG.0000000000004128.

Outpatient iNO: COVID-19

- 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



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

Zamanian RT, et al. Am J Respir Crit Care Med. 2020;202:130-32. https://doi.org/10.1164/rccm.202004-0937LE.

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?

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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

NCT number	Study Phase	iNO Dose	Comparator	Estimated enrollment	Estimated study completion
NCT04421508	3	20 ppm continuous pulse dose	Placebo (inhaled N_2)	500	June 2021
NCT04388683	2	80 ppm continuous	SOC	200	March 2022
NCT04338828	2	140-300 ppm for 30 minutes daily	Placebo (inhaled O_2)	260	April 2022
NCT04305457	2	140-180 ppm for 30 minutes BID	SOC	67	April 2022
NCT04312243	2	160 ppm for 15 mins BID (HCW prevention)	SOC	470	April 2022
NCT04306393	2	20 ppm continuous	SOC	42	July 2021
NCT04397692	N/A	80 ppm for 40 mins QID	SOC	20	September 2020

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Legend: HCW- Healthcare worker; ppm- parts per million; SOC- Standard of care

Clinicaltrials.gov. Accessed Oct 1, 2020

Clinical Practice Guidelines: iNO and COVID-19

NIH

- The Panel recommends **against** the routine use of inhaled nitric oxide (AI)

Surviving Sepsis

- In mechanically ventilated adults with COVID-19 ARDS, we recommend **against the routine use of inhaled nitric oxide**. (strong recommendation, low-quality evidence)
- In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, we **suggest** a trial of inhaled pulmonary vasodilator as a rescue therapy (Weak recommendation, low-quality evidence)

IDSA

- Not addressed

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1. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed Oct 7, 2020
2. Waleed A, et al. Intensive Care Med. 2020;46:854-887. https://doi.org/10.1007/s00134-020-06022-5.
3. Bhimraj A, et al. Infectious Diseases Society of America. Available at: http://www.idsociety.org/COVID19guidelines. Accessed Oct 7, 2020.

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 NO_2
- Ideally, delivery should be simple to use with full monitoring capacity
  - High and low alarms and precise monitoring of NO, NO_2, and O_2
- 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.

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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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