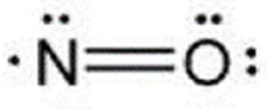
INOmax 800 ppm mol/mol medicinal gas, compressed (Nitric oxide)
Guide for healthcare professionals

- Introduction

INOmax 800 ppm mol/mol medicinal gas, compressed (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (155 bar).

The structural formula of nitric oxide (NO) is shown below:



INOMAX (nitric oxide) Structural Formula Illustration

The clinical effects of inhaled NO (INOmax), being rapid and selective for the pulmonary circulation, lend themselves to many different clinical situations.

Its application has grown over the past decade too, from being used to improve oxygenation in newborn infants and preventing hypoxic respiratory failure, to also being used in both adult and child heart surgery patients.

Today INOMAX application as part of ventilation therapy is an effective non-systemic option to improve oxygenation in patients with pulmonary hypertension often before extracorporeal membrane oxygenation (ECMO) is necessary.

Today it is well established that NO is an important signaling molecule throughout the body:

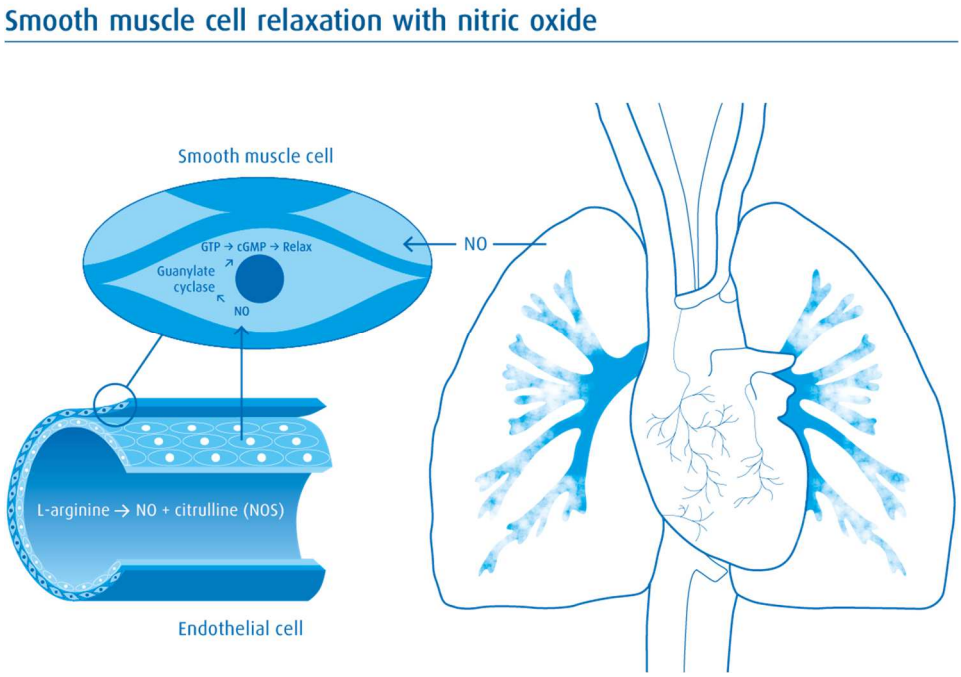
- Acts as local vasodilator restricted to pulmonary circulation[1]
- Significantly improves oxygenation as measured by partial pressure of arterial oxygen (PaO2) and oxygenation index (OI)[2]
- Decreases pulmonary vascular pressure, reducing right heart cardiac afterload[3]
- Alleviates ventilation/perfusion mismatch associated with hypoxaemia[4]

The ability to dilate blood vessels without any subsequent effect on systemic circulation has been key to the development of INOmax as a valuable therapy in neonatal intensive care and cardiac surgery.

Conventional treatment such as nitrates, calcium antagonists or prostaglandins, supplemented with pulmonary vasodilators or inotropic vasodilators can cause systemic vasodilation and severe systemic arterial hypotension.[7,8]

In contrast, INOmax has shown to be a selective pulmonary vasodilator limited to pulmonary vasodilation effects without systemic vasodilatory effects.
INO works rapidly to significantly reduce increased pulmonary artery pressure (PAP) while significantly reducing pulmonary vascular resistance (PVR).[7,9–13]

INOmax acts through the same physiological pathway as endogenous NO:



It promotes calcium-dependent smooth muscle cell relaxation by entering vascular smooth muscle cells.

By activating guanylate cyclase, INOMAX increases intracellular levels of cyclic guanosine mono-phosphate (cGMP), which then leads to vasodilation.

- The risk of rebound effect and the precautions to take when discontinuing the treatment

Abrupt discontinuation of the administration of inhaled nitric oxide may cause rebound reaction; decrease in oxygenation and increase in central pressure and subsequent decrease in systemic blood pressure. Rebound reaction is the most commonly adverse reaction in association with the clinical use of INOmax. The rebound may be seen early as well as late during therapy.

Clinically significant increases in pulmonary vascular resistance have been noted on acute withdrawal of inhaled nitric oxide (NO).

In order to avoid the risk of rebound effect attempts to wean INOmax should be commenced as soon as the haemodynamics have stabilised in conjunction to weaning from ventilator and inotropic support. The withdrawal of inhaled nitric oxide therapy should be performed in a stepwise manner. The dose should be incrementally reduced to 1 ppm for 30 minutes with close observation of systemic and central pressure, and then turned off.

The INOmax dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO2). Deterioration in oxygenation and elevation in PAP may also occur in neonates with no apparent response to INOmax. Weaning from inhaled nitric oxide should be performed with caution. For patients transported to other facilities for additional treatment, who need to continue with inhaled nitric oxide, arrangements should be made to ensure the continuous supply of inhaled nitric oxide during transportation. The physician should have access at the bedside to a reserve nitric oxide delivery system.

Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of INOmax. Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in pulmonary artery pressure with subsequent circulatory instability.

- The risk of abrupt discontinuation of Inomax therapy in the event of critical failure of the delivery system and how to prevent it

Nitric oxide is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved (CE-marked) nitric oxide delivery system.

Before initiation of therapy, during set-up, secure that the device setting is in agreement with the cylinder gas concentration.

The delivery system must provide a constant inhaled INOmax concentration irrespective of the ventilator. With a continuous flow ventilator, this may be achieved by infusing a low flow of INOmax into the inspiratory limb of the ventilator circuit. Intermittent flow ventilation may be associated with spikes in nitric oxide concentration. The nitric oxide delivery system for intermittent flow ventilation should be adequate to avoid spikes in nitric oxide concentration.

The inspired INOmax concentration must be measured continuously in the inspiratory limb of the circuit near the patient. The nitrogen dioxide (NO_2) concentration and FiO_2 (fraction of inspired oxygen) must also be measured at the same site using calibrated and approved (CE-marked) monitoring equipment. For patient safety, appropriate alarms must be set for INOmax (±2 ppm of the prescribed dose), NO_2 (1 ppm), and FiO_2 (± 0.05).
The power supply for the monitoring equipment should be independent of the delivery device function.

The INOmax gas cylinder pressure must be displayed to allow timely gas cylinder replacement without inadvertent loss of therapy and backup gas cylinders must be available to provide timely replacement. INOmax therapy must be available for manual ventilation such as suctioning, patient transport, and resuscitation.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available.

- The monitoring of Methaemoglobin level

A large portion of nitric oxide for inhalation is absorbed systemically. The end medicinal products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin (MetHb) and nitrate.

The concentrations of methaemoglobin in the blood should be monitored.

Neonates and infants are known to have diminished MetHb reductase activity compared to adults.
Methaemoglobin level should be measured within one hour after initiation of INOmax therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If it is > 2.5 %, the INOmax dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered. Although it is unusual for the methaemoglobin level to increase significantly if the first level is low, it is prudent to repeat methaemoglobin measurements everyone to two days.

In adults undergoing heart surgery, methaemoglobin level should be measured within one hour of the initiation of INOmax therapy. If the fraction of methaemoglobin rises to a level that potentially compromises

adequate oxygen delivery, the INOmax dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

- The monitoring of NO2 formation

NO2 rapidly forms in gas mixtures containing nitric oxide and O2, and nitric oxide may in this way cause airway inflammation and damage. The dose of nitric oxide should be reduced if the concentration of nitrogen dioxide exceeds 0.5 ppm.

Immediately prior to each patient initiation, proper procedure must be applied to purge the system of NO2. The NO2 concentration should be maintained as low as possible and always < 0.5 ppm. If the NO2 is > 0.5 ppm, the delivery system should be assessed for malfunction, the NO2 analyser should be recalibrated, and the INOmax and/or FiO2 should be reduced if possible. If there is an unexpected change in INOmax concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated.

- The potential risk of bleeding and haemostasis disorders

Animal models have shown that nitric oxide may interact with haemostasis, resulting in an increased bleeding time.

Data in adult humans are conflicting, and there has been no increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure.

Regular monitoring of haemostasis and measurement of bleeding time is recommended during the administration of INOmax for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment.

- The potential risks if used in combination with other vasodilators which act on cGMP or cAMP

A clinically significant interaction with other medicinal products used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. There may be an additive effect with INOmax on the risk of developing methaemoglobinemia with nitric oxide donor substances, including sodium nitroprusside and nitroglycerin. INOmax has been safely administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation.

The combined used with other vasodilators (e.g. sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, pulmonary artery pressure and right ventricular performance.

Inhaled nitric oxide combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.

- Medicines Authority's and Marketing Authorisation Holder's adverse drug reaction reporting details

ADR Reporting Website:
http://www.medicinesauthority.gov.mt/adrportal

MARKETING AUTHORISATION HOLDER:
Linde Healthcare AB
SE-181 81 Lidingö
Sweden

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