Healthcare professional guide

Neophyr
Medicinal gas, compressed
Nitric oxide

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

Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in pulmonary artery pressure with subsequent circulatory instability.

Persistent Pulmonary Hypertension in the Newborn (PPH)
Attempts to wean Neophyr should be made after the ventilator support is substantially decreased or after 96 hours of therapy. When the decision is made to discontinue inhaled nitric oxide therapy, the dose should be reduced to 1 ppm for 30 minutes to one hour. If there is no change in oxygenation during administration of Neophyr at 1 ppm, the FiO2 should be increased by 10 %, the Neophyr is discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20 %, Neophyr therapy should be resumed at 5 ppm and discontinuation of Neophyr therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off Neophyr by 4 days should undergo careful diagnostic work-up for other diseases.

Pulmonary hypertension associated with heart surgery
Attempts to wean Neophyr should be commenced as soon as the hemodynamics 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.
Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of Neophyr.

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

The Neophyr 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). 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. Neophyr therapy must be available for mechanical and manual ventilation, during transportation of the patient and during resuscitation. The pressure of the Neophyr gas cylinder must be monitored in order to allow the gas cylinder to be changed without interruptions or changes to the treatment. There must also be a reserve supply of gas cylinders to allow changes at the appropriate moment.

The physician should have access at the bedside to a reserve nitric oxide delivery system. A back up system for the administration device must be in place, either as external device or built-in feature. The instruction for use of the device must be followed.

The monitoring of Methaemoglobin (MetHb) level
Following its inhalation, the terminal compounds of nitric oxide that arrive in the systemic circulation are primarily methaemoglobin and nitrate. The nitrate is fundamentally excreted through the urinary system and the methaemoglobin is reduced by the methaemoglobin reductase.

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Newborns and infants have diminished levels of MetHb reductase activity compared to adults; therefore the methaemoglobin concentrations in the blood must be monitored. The level of MetHb must be measured within 1 hour of the start of Neophyr therapy using an analyser that correctly distinguishes the fetal hemoglobin from the MetHb.
If the MetHb is > 2.5%, the dose of Neophyr will have to be reduced and the necessity for the administration of reducing agents such as methylene blue will be assessed.
Although considerable increases in the level of MetHb are infrequent, since the level is low during the first determination, it is advisable to repeat the MetHb measurements every 12-24 hours thereafter.

In adults undergoing heart surgery, methaemoglobin level should be measured within one hour of the initiation of Neophyr therapy. If the fraction of methaemoglobin rises to a level that potentially compromises adequate oxygen delivery, the Neophyr dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

The monitoring of NO2 formation
Nitrogen dioxide (NO2) forms rapidly in gaseous mixtures that contain nitric oxide and O2. Nitric oxide, in reaction with oxygen, will produce nitrogen dioxide (NO2) in variable quantities depending on the NO and O2 concentrations. NO2 is a toxic gas that can provoke an inflammatory reaction in the respiratory tract; it is for this reason that its production must be closely monitored.

Immediately before starting the treatment on each patient, it is necessary to apply the appropriate procedures to purge the system of NO2.

The NO2 concentration must be kept as low as possible (below < 0,5 ppm). If NO2 is > 0,5 ppm, the administration system must be checked according to the instruction for use of the device.

NO2 monitoring during the therapy must be always carried out: this is the only way to guarantee that NO2 level is kept as lowest as possible. NO delivering device should be natively equipped with NO2 continuous monitoring system.

The potential risk of bleeding and haemostasis disorders
Tests in animals have demonstrated that NO can interact with the haemostasis provoking an increase in the bleeding time. The data in adult humans is contradictory, and there has been no increase in significant bleeding complications observed in random controlled trials on new-borns.
A monitoring of the bleeding times is recommended during the course of Neophyr administration for a period of more than 24 hours in patients that suffer numerical or functional anomalies of the platelets, a deficit in the coagulation factors or that are undergoing anticoagulant treatment.

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

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie