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General guidance on the equipment used for inhaled nitric oxide therapy

Guide général sur le matériel utilisé pour la thérapie par l'oxyde nitrique inhalé

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General guidance on the equipment used for inhaled nitric oxide therapy

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Foreword

This European Standard has been prepared by Technical Committee CEN/TC 215 "Respiratory and anaesthetic equipment", the secretariat of which is held BSI.

Introduction

It gives information on the properties and medical uses of nitric oxide and guidance on medical equipment through which this gas passes before and after administration to the patient. This report is primarily intended for those involved in the standardization and manufacture of such medical equipment and for those concerned with the practice of inhaled nitric oxide therapy.

1. General

1.1 Background

Nitric oxide for inhalation (NO) is a new medical gas. It is regarded as a new medicinal product for use in investigation and treatment of patients on a compassionate basis. It has not received marketing authorisation in any country in the European union or in the USA.

Nitric oxide in nitrogen is supplied as a ready to use mixture intended to be administered to patients together with oxygen using a suitable supply and delivery system. In this document concentrations of nitric oxide/nitrogen are given as '≤ 1000 µl/l'. At this stage of drafting, it is not possible to give a fixed value because European medicines licensing authorities have not yet registered this mixture as a medicinal product.

Nitric oxide is used in clinical studies approved by ethics committees, and those using it should be familiar with its properties and the potential problems which may arise during use. Such studies may establish dosing recommendations and may lead to regulatory approval for use in specified situations.

Before approval is granted, situations may occur where clinical use of nitric oxide inhalation outside clinical studies is considered justified by the treating physician. The format for treatment of individual patients in these cases is compassionate use. The use of unapproved medicinal products in individual patients is subject to national legislation in most countries and may require notification to or approval by the relevant Authority.

1.2 Physiology

1.2.1 General

In 1987 it was verified that the endothelium derived relaxing factor EDRF is nitric oxide (1,2). Since then there has been a considerable interest in research of the various effects of endogenously formed nitric oxide.

Endogenous nitric oxide seems to be involved in the control and action of a great number of organ functions, including platelet aggregation, neurotransmission, and antitumour and antimicrobial activity, and not only in the control of vascular tone.

1.2.2 Vascular control – Nitric oxide as a paracrine messenger

Endothelial cells produce small amounts of nitric oxide that diffuse from the endothelial cells to the smooth muscle cells causing relaxation of the vascular smooth muscle. The low pulmonary vascular tone of normal lungs appears to be partly maintained by endogenous synthesis of nitric oxide (3).

1.2.3 Inhaled nitric oxide

Based on the identification of EDRF being nitric oxide, it was thought that inhaled nitric oxide should be able to diffuse from the alveolar gas into the pulmonary vasculature of ventilated lung regions and cause relaxation of pulmonary vascular smooth muscle, thereby decreasing pulmonary hypertension in the presence of increased vascular tone. This should be able to create a selective vasodilatation of well-ventilated lung regions, causing a "steal" or diversion of pulmonary artery blood flow towards well-ventilated alveoli - lung regions, improving the matching of ventilation to perfusion and improving arterial oxygenation in hypoxaemia secondary to an increase in shunting such as in Acute Respiratory Distress Syndrome (ARDS). This hypothesis was verified in animal experiments (4,5).

1.3 Intended medical use

1.3.1 General

The most frequent indications for the clinical use of inhaled nitric oxide are:

- Severe, therapy resistant hypoxaemia in Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).
- Acute pulmonary hypertension compromising right heart function.
- Paediatric intensive care, particularly in severe persistent pulmonary hypertension of the newborn, in Respiratory Distress of the Newborn (RDS) where pulmonary hypertension is a compromising factor, and occasionally in severe meconium aspiration.
- Occasionally during and after cardiac surgery.

1.3.2 Inhaled nitric oxide in acute lung injury

Inhaled nitric oxide in concentrations between 1µl/l and 80 µl/l has been shown to improve oxygenation and to a lesser extent reduce pulmonary artery pressure in a high percentage of adult patients with acute hypoxaemia secondary to an increase in shunt. The improvement in oxygenation varies, however, between individuals as well as in each individual. Randomised studies to determine the effects of nitric oxide on the outcome of ALI as well as of ARDS have not yet been published (1998).

1.3.3 Inhaled nitric oxide in paediatric intensive care

Inhaled nitric oxide has also been used in neonates with hypoxaemia and pulmonary hypertension.

Prospective randomised studies have shown nitric oxide to be able to significantly reduce the need for extracorporeal oxygenation (ECMO) in severely hypoxic neonates. In these studies concentrations of 20 µl/l to 80 µl/l were used (6,7).

1.3.4 Inhaled nitric oxide in cardiac surgery

Inhaled nitric oxide has also been studied as a therapy for pulmonary hypertension after cardiac surgery. Limited studies have shown beneficial effects of nitric oxide as a selective pulmonary vasodilator in the post extracorporeal circulation (ECMO) period after repair of congenital heart disease.

It has been suggested that the interaction with blood platelets may be beneficial when an extracorporeal circuit is used (8).

1.4 Concentration/dose of inhaled nitric oxide in medical use

Whether an appropriate dose should be adjusted to a physiological variable such as oxygenation, or kept constant at a pre-defined level, is a matter of debate. Both the intra- and inter- individual variation in response, seen as change in P_aO_2, may call for the use of a pre-defined value over a longer time period. If, however, the indication merely is to change the pulmonary artery pressure and unload the right ventricle of the heart, a dose versus response adjustment seems justified.

The duration of therapy and combination with other substances active in the pulmonary circulation has been discussed.

Currently, concentrations up to 20 µl/l (for short time periods 60 µl/l to 80 µl/l) are being used. The higher doses are chosen when it is urgent to defuse an acute pulmonary hypertensive "crisis" during or after cardiac surgery.

1.5 Pharmacokinetics

Inhaled nitric oxide is taken up into the precapillary air spaces and alveoli at a rate many times faster than inhaled oxygen, and the diffusing capacity of the lung is 4 to 5 times higher for nitric oxide than for carbon dioxide (9).

Nitric oxide is rapidly taken up by haemoglobin and converted to nitrate and methaemoglobin, thus making part of available haemoglobin inaccessible for oxygen transport. Because of the rapid removal of nitric oxide by reaction with haemoglobin, the effects of nitric oxide inhalation are generally considered to be localised to lung tissue with an effective half-life of 2 s to 6 s (10).

The metabolites of nitric oxide are cleared from the body by the kidneys within 5 h to 8 h (11) and concentrations of methaemoglobin rarely rise above 1 % to 2 % during nitric oxide treatment with inhaled concentrations below 40 µl/l (12, 13).

1.6 Side effects of inhaled nitric oxide

Inhaled nitric oxide in concentrations below 40 µl/l is associated with few side effects. Elevation in methaemoglobin may occur. Therefore, methaemoglobin should be measured on a regular basis during administration.

Nitric oxide can be rapidly oxidized, reduced or complexed to form other oxides of nitrogen (14).

One product of the oxidation is nitrogen dioxide (NO_2) that may cause airway inflammation and cell damage. The rate of oxidation is dependent on the concentration of nitric oxide, the concentration of oxygen and the time available for the reaction.

Nitrogen dioxide may combine with water to become nitrous and nitric acid that can damage lung tissue leading to oedema (15). Supply and delivery systems should be designed to minimize the formation and delivery of nitrogen dioxide. Nitrogen dioxide levels should be kept below the order of 2 µl/l which is the occupational safety limit (20) (see also 2.4) If this is not technically achievable, appropriate monitoring should be performed to detect elevated nitrogen dioxide levels in order to make rapid intervention possible.

Withdrawal reactions such as intensified pulmonary vascular constriction and hypoxaemia have been described (16, 17, 18). See also 5.1.

Weaning from nitric oxide can be done by a step-by-step reduction of the inhaled nitric oxide dose, accepting a minor reduction in arterial oxygenation (19).

The implications of inhalation of nitric oxide are still not fully understood. Extensive research is focused on the various effects that may arise from manipulation with this intricate system. Further research regarding dose, timing and delivery systems seems necessary.

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2 Chemical and physical properties

2.1 Chemical properties

Nitric oxide, a colourless toxic gas, was first prepared about 1620 by Jan Baptist van Helmont, and was first studied in 1772 by the chemist Joseph Priestly (1).

Nitric oxide is one of the few stable compounds containing an odd number of electrons; it is remarkably inert towards most substances including water. It reacts spontaneously with oxygen (air) forming nitrogen dioxide. It is this reaction combined with the reactivity of nitrogen dioxide, which erroneously has given nitric oxide a reputation of being reactive.

The oxidation of nitric oxide with oxygen is second order with respect to nitric oxide, i.e. the reaction rate is proportional to the square of the nitric oxide partial pressure:

$$\frac{dp_{NO}}{dt} = -k \times p_{NO}^2 \times p_{O_2}$$

Table 1 illustrates the rate of this reaction.

In the presence of water, nitrogen dioxide forms liquid nitric acid (HNO_3) and liquid nitrous acid (HNO_2) that may react with traditional materials used for components of the supply systems and cause corrosion.