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Inhaled nitric oxide applications in paediatric practice

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Abstract

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The nitric oxide pathway plays a pivotal, yet diverse, role in human physiology, including modulation of vascular tone, neural transmission and inflammation. Inhaled nitric oxide is a selective pulmonary vasodilator that has emerged rapidly as an important therapeutic agent. It finds its best applications in paediatrics; the use of iNO in term neonates with hypoxaemic respiratory failure, in the assessment of pulmonary vascular reactivity and in the treatment of postoperative pulmonary hypertension in congenital heart disease is well recognised and accepted. This review details the delivery and monitoring aspects of inhaled nitric oxide, its potential toxic and side effects and its applications in several cardiopulmonary disorders in paediatrics.

MeSH: Heart defects, congenital, Hypertension, pulmonary, Infant, premature, Newborn, Nitric oxide, Paediatrics

Introduction

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Inhaled nitric oxide (iNO) therapy is nowadays recognised as an important tool for the treatment and diagnosis of pulmonary vascular and airspace disease. Nitric oxide (NO) is a naturally occurring gas with multiple biological actions. Endogenous NO plays a role in the modulation of vascular tone,[1,2] the regulation of platelet function, neuronal transmission and the inflammatory response.[3] NO is formed, in the endothelial cell, from L-arginine and molecular oxygen in a reaction catalysed by the enzyme nitric

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NOS 3, identified in endothelial cell also called eNOS. Even if very similar in structure, they show some differences. NOS 1 and 3 are constitutively expressed and are calcium calmodulin dependent. NOS 2, in contrast, is seen after induction by inflammatory stimuli, and is calcium independent. Nitric oxide synthase 2 can produce large amount of NO measured in nanomoles, instead of the picomoles produced by the nitric oxide synthase 1 and 3. NO thus formed is a small reactive molecule which diffuses readily to adjacent vascular smooth muscle. In the vascular smooth muscle NO activates guanylate cyclase, which transforms GTP into cyclic guanylate monophosphate (cGMP), which in turn induces vasodilatation.[5] As NO exists as a gas, it can be delivered by inhalation, hence NO can vasodilate constricted blood vessels in close proximity to the ventilated lung. The rapid inactivation of NO by haemoglobin, when NO reaches the intravascular space, limits its effects on the pulmonary circulation.[6]

In this review, we will first describe the delivery and monitoring of inhaled NO (iNO) as well as its potential adverse effects and toxicity. These aspects are essential to the safe use of iNO. We shall then discuss its different applications in paediatric practice.

Rationale for the use of inhaled nitric oxide

For many years, physicians involved with the care of patients with pulmonary hypertension were in search of the ideal pulmonary vasodilator, which should be easy to administer, have a short duration of action and above all, be selective for the pulmonary circulation. Approaches to manipulate the pulmonary vascular tone were limited to oxygen supplementation[7,8] and respiratory or metabolic alkalosis.[9,10] Drug therapy included several intravenous vasodilators such as prostaglandins,[11,12] tolazoline[13] and magnesium sulphate.[14,15] All were characterised by their lack of selectivity, leading to a fall in systemic arterial pressure and an increase in intrapulmonary shunt. The introduction of inhaled NO and other recent advances in vascular biology have drastically changed the therapeutic approach of pulmonary hypertension.

As nitric oxide exists as a gas, it can be easily administered by inhalation. The anatomical proximity of the airspaces to the muscular arterioles allows NO to diffuse. Nitric oxide is lipophilic and thus crosses the membranes easily. By inducing vasodilation of aerated airspaces, NO can redirect blood flow from poorly ventilated areas, atelectatic or diseased lung regions, to better aerated air spaces and improves oxygenation and ventilation perfusion mismatch. This effect is the so-called microselective effect of iNO. As for endogenous NO, this vasodilator effect is induced through the cyclic cGMP pathway, as demonstrated by an increase in plasma cGMP during iNO therapy.[16,17] When it reaches the vascular lumen, NO avidly binds to haemoglobin and is thereby inactivated with a half-life of 2-6 seconds.[18] This rapid inactivation limits its effects on the pulmonary circulation and accounts for its selective action.[6,19] This is the macroselective effect of iNO. Indeed, red blood cells act as scavengers of iNO as demonstrated by Deem et al.[20] Between 75 and 90% of iNO is absorbed during inhalation. The metabolic fate of iNO is indeed similar to endogenous NO with the formation of nitrites and nitrates eliminated in the urine,[21] and more than 70% of the inhaled gas will appear in the urine as nitrates within 48 hours of

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In summary, iNO fulfils most of the properties required to be the ideal pulmonary vasodilator; thus its use has become of major clinical interest.

Delivery and monitoring

The potential toxicity of iNO calls for reliable modes of delivery and availability of monitoring systems. Large and extensive reviews of the diverse modes of iNO delivery have been published.[24–32] The exact method of delivery and monitoring of NO may vary with the clinical indication and duration of treatment as well as the type of ventilator used. NO source tanks should be medical grade quality gas manufactured by a process accepted by the medical administration and is available in different concentrations of NO in N_2, from 100 to 10000 ppm. By using continuous flow ventilators, stable NO concentrations can be easily delivered by titrating NO directly from the tank into the inspiratory limb of the ventilator. The theoretical concentration can be calculated using the following formula: $NO_{conc} = NO_{tank} x (Flow_{NOtank}/Flow_{ventilator})$. However, as demonstrated by Betit et al.[32] NO concentrations can be underestimated and direct measurement of NO is mandatory during therapy.

NO can also be administered with demand valve systems using a similar technique but a stable concentration of NO may be difficult to obtain. It has been proposed to deliver NO with a synchronised inspiratory injection technique to avoid the inconvenience of delivery during expiration.[33] Ventilators equipped with in-built NO delivery and monitoring systems are currently available. They simplify delivery and improve safety. The recent development of new ventilatory techniques such as high frequency oscillation ventilation (HFO) in newborns or infants with respiratory failure open new challenges for iNO deliveries, but because HFO is also delivered at constant flow, it seems possible to obtain stable NO concentrations.[34,35] Fujino et al reported that mixing NO during HFO was acceptable at all injection sites with a preference for the prehumidifier injection, which offers less fluctuation of NO concentration.[36] However, with this latter ventilatory technique, measurements may not be accurate, as a prolonged residency time of NO in the airways is possible; also the concentrations measured at the inspiratory limb of the ventilator do not accurately reflect the effective NO concentrations in the alveoli.

In spontaneously breathing patients NO can be administered by mask or hand ventilation with a bag.[37–39] Administration through nasal prong is also possible, opening the possibility of long-term treatment with iNO.[40]

The appropriate dose of iNO to assess pulmonary vascular resistance or treat pulmonary hypertension is not completely defined. Dose response studies have been performed in persistent pulmonary hypertension of the newborn (PPHN) and ARDS[41–46] and in congenital heart disease.[47,48] Inhaled NO doses required to treat pulmonary hypertension are higher than those required for improvement of ventilation perfusion mismatch and oxygenation.[41] The recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm. Recently, Tworetzky et al suggest an initial dose of 20 ppm for the treatment of PPHN, as it produced an improvement in the pulmonary to systemic arterial pressure ratio, even though 5 ppm iNO was enough to produce peak improvement in oxygenation.[49] The

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et al. showed that the effective dose (the smallest dose effective to obtain a beneficial response) decreases as therapy continues.[50]

It has been shown that there is little haemodynamic benefit obtained above 20 ppm. The dose used to assess pulmonary vascular reactivity varies between 10 and 40 ppm, rarely 80 ppm, but higher doses had no further effect. The same may be applied for postoperative cardiac patients with a starting dose between 10 and 20 ppm. If there is no response, a trial at 40 and 80 ppm may be attempted but questions about the diagnosis must be raised. Higher doses give little or no benefit but may be associated with an increased risk of toxicity, in particular NO_2 and methaemoglobin formation. When a response is obtained, the dose must be decreased progressively to the lowest effective dose to avoid potential toxic effects. Slightly higher doses may be required for PPHN but Finer et al. showed that maximal response was obtained with 5 ppm.[44] Adequate ventilation and lung recruitment is necessary in these patients to deliver NO in the alveoli and obtain a result. ARDS patients sometimes respond to very low doses of some hundreds ppb.

Guidelines on the use of NO with an emphasis on safety have emerged from a NHLBI workshop.[51] An ideal delivery system uses medical grade NO, limits to the maximum the residency time of NO in the ventilatory circuit, allows for precise concentrations of NO with a uniform mixing, has alarms notifying when excessive concentrations of NO are administered or if inadvertent discontinuation of NO occurs. Most important of all, it allows on line monitoring of NO and NO_2.

The formation of NO_2 is in part correlated to the amount of NO administered and a correct measurement of NO concentrations is of utmost importance. Two systems are currently available for monitoring NO and NO_2 concentrations. Chemiluminescence technique remains the gold standard with an accuracy of some ppb.[52] Manufacturers have adapted industry materials to the requirement of medicine with rapid response analysers requiring small amount of air sampling and therefore not interfering with ventilation. However, these devices are expensive and one may prefer the electrochemical devices that are somewhat inaccurate to measure very low amount of NO (such as for measurement of exhaled NO) but accurate enough by far for treatment monitoring.[53]

Toxicity

There has been proper concern about the potential toxicity of NO therapy. NO is a common pollutant. The US Occupational Safety and Health Administration has set a limit of NO exposure time to 25 ppm when breathed for 8h/day in the workplace.[54]

No severe side effects of iNO have been described, using concentrations up to 40 to 80 ppm (the maximal doses used in clinical practice). Studies in rats have shown that inhalation of NO up to 1500 ppm for 15 min caused no demonstrable injury.[55] Moreover cigarette smoke contains NO concentrations up to 1000 ppm[56] and no acute toxic effects have been reported. However, NO may be one of the substances involved in long-term lung toxicity of cigarette smoke. If extreme doses are used it seems to lead rapidly

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transformation of NO to NO_2than to a direct effect of NO.[57] Therefore, particular attention has been focused on the possible acute toxic effects such as the production of NO_2 (a pulmonary toxin), methaemoglobinemia (which should remain < 5%), and cellular toxicity.

NO_2

One of the main concerns of iNO therapy is the chemical reaction of NO to NO_2 in the presence of oxygen within the ventilatory system or the airways. NO_2 is thought to be responsible for the pulmonary injury caused by exposure to NO. NO_2 is clearly cytotoxic[55] and in aqueous solutions is transformed to nitric and nitrous acids. It causes pulmonary epithelial cell damage, interstitial atrophy and fibrosis.[55] It is generally accepted that concentrations of NO_2 over 5 ppm are toxic.[54,58] Production of NO_2 is function of the NO concentration squared, the fraction of inspired oxygen and the time of residency in the ventilatory system.

Based on these findings guidelines should be followed to minimise the risk of toxicity related to the formation of NO_2:

1. Administer the lowest effective dose of iNO with a maximal dose of 40 to 80 ppm
2. Administer the lowest possible concentration of O_2
3. Monitor O_2 , NO and NO_2 concentrations
4. Minimise the transit time in the ventilator by using high gas flow rates to flush out alveolar gases
5. Minimise the exposure time of NO to oxygen before it reaches the patient

Methaemoglobin

Inhaled NO is quickly absorbed into the blood stream, avidly bound to haemoglobin and thereby, inactivated with the formation of methaemoglobin. This oxidised form of haemoglobin has impaired oxygen transport function. Methaemoglobin is restored to its oxygen carrying capacity by methaemoglobin reductase. Increased levels of methaemoglobin in patients receiving iNO therapy are unusual, and remain for the great majority in a safe range (<5%). High levels of methaemoglobin have rarely been reported.[59,60] Neonates have an immature methaemoglobin reductase system and may be more susceptible to increased levels.[61] Of note, methaemoglobin reductase deficiency is common in Native Americans.[62]

Methaemoglobin will indeed remain in a safe range with doses of iNO of 40 ppm and less. If necessary, excess methaemoglobin may be treated by reducing the iNO concentrations, or administrating vitamin C or methylene blue.[24,63–65] Particular caution must be taken when intravenous nitrovasodilators are associated with iNO, i.e. in the postoperative cardiac patient, where in our experience higher levels of methaemoglobinemia might be encountered.

Cellular effects

NO reacts with O_2^- and superoxide anion (O_2^-) to form peroxinitrite. Peroxinitrite is a potent oxidant that

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