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REVIEW ARTICLE

Inhaled nitric oxide in pediatrics

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Abstract

Objective: To review the literature on inhaled nitric oxide and to describe its main clinical applications in pediatrics.

Sources of data: A 10 year literature review with selection of the most important publications on inhaled nitric oxide, using the Medline and Cochrane Systematic Review databases.

Summary of the findings: This review was organized as follows: introduction; metabolism and biological effects; clinical applications; dosage, gas administration and weaning; precautions and side-effects. Inhaled nitric oxide use was described in persistent pulmonary hypertension and hypoxia of the newborn, acute respiratory distress syndrome, primary pulmonary hypertension, heart surgery, chronic obstructive pulmonary disease, sickle cell anemia, and bronchospastic disease.

Conclusions: Inhaled nitric oxide is a therapeutic approach with wide clinical applications in pediatrics. Its use is safe when administered in pediatric intensive care units under strict monitoring. As a pulmonary vasodilator, nitric oxide has beneficial effects on gas exchange and ventilation. Controlled trials, focusing on early gas administration should be performed under many clinical conditions, especially acute respiratory distress syndrome.

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Introduction

In 1980, Furchgott and Zawadzki[1] demonstrated that relaxation of the aorta of rabbits in response to acetylcholine was dependent upon the presence of intact endothelial cells. If the endothelium was removed, the vessel would still contract in response to noradrenaline and would still relax in the presence of vasodilator agents, but would not relax in response to acetylcholine. The authors demonstrated that vascular relaxation that was dependent on acetylcholine was controlled by the liberation of a humoral factor, described as endothelium-derived relaxing factor. Later it was demonstrated that endothelial liberation of nitric oxide (NO) was responsible for the biological activity of the endothelium-derived relaxing factor, stimulating intense research into the biological effects of the gas.[2]

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Nitric oxide is a 1:1 combination of two of the most abundant gasses in the atmosphere. It is highly soluble and exercises paracrine effects over many tissues, regulating a number of different functions, such as vasomotor tone, neurotransmission, immunoresponse and the adhesion of inflammatory cells to the vessel walls.[3,4]

The physical characteristics of NO, its role in the evolution of organic systems, its universal distribution and its participation in fundamental biological functions meant that the scientific community attempted to better understand the biochemistry, physiology, neuroscience and immunology of the gas. Such was the interest generated by the first studies that Science awarded NO the title of "molecule of the year", in 1992.[2]

Metabolism and biological effects

Nitric oxide is synthesized from the L-arginine amino acid by the action of NO synthase (NOS) and is liberated after chemical and mechanical activation.

To date, three isoforms of NOS have been described and denominated, depending on cell type or the conditions under which they were identified, constitutive forms (endothelial and neuronal) and inducible or macrophagic,[2,4] in that macrophages appear to be the main source of inducible NOS.[5] All three isoforms of NOS have been identified within the airways of human beings. Additionally, arterial and venous endothelial cells, epithelial cells, inflammatory cells (macrophages, neutrophils, labrocytes), fibroblasts, smooth muscle cells and non-adrenergic and non-cholinergic cells have all been identified as sources of endogenous NO.

High levels of NO are continually produced within the airways and inhaled with every breath. The NO produced by the lungs maintains pulmonary artery pressure (PAP) low while at rest and during exercise, controls the distribution of pulmonary blood flow, combats hypoxic pulmonary vasoconstriction and regulates the pulmonary response to both endogenous and exogenous vasoconstrictors. The NO that is liberated by the nerves can control bronchomotor tone, while that liberated by the bronchial epithelium may reduce submucosal edema.[2]

Once inhaled, NO easily disperses across the alveolar-capillary membrane reaching pulmonary circulation and vascular smooth muscle, increasing intracellular concentrations of Cyclic GMP and provoking vascular relaxation.[6] Consequentially, PAP and pulmonary vascular resistance (PVR) reduce and gas exchange is improved resulting in an improved ventilation/perfusion ratio (V/Q).

Once absorbed by the organism, NO passes through the pulmonary capillary bed where it combines with hemoglobin saturated at 60% to 100% with oxygen. At this oxygen saturation, the gas bonds, predominantly with oxyhemoglobin to produce methemoglobin and nitrate. The nitric oxide is rapidly and specifically inactivated by hemoglobin, meaning that its vasodilator effect remains restricted to pulmonary vasculature and has no systemic effects. Due to its short half-life in biological systems, NO does not affect the extravascular compartments. Stable derivatives, however, may prolong its effects which is consistent with the finding that nitrate concentrations are increased an hour after administration of the gas is stopped.[6]

In addition to the hemodynamic effects, inhaled nitric oxide (iNO) may exercise generalized antiinflammatory and anti-thrombotic effects of leukocytes and platelets. These effects are dose-dependent in that both excesses and deficiencies of the gas have been implicated in the genesis or evolution of many significant diseases. At high concentrations (> 80 - 100 parts per million) iNO has proinflammatory and prooxidant effects, increasing macrophage production of tumor necrosis factor alpha, interleukin 1 and reactive oxygen species.[7,8] Up to 80 parts per million (ppm) the gas appears to reduce the number and activity of pulmonary neutrophils. The dose of 50 ppm appears, also, to reduce the migration of neutrophils from the vascular compartment to the airways and inhibits chemotaxis.[9] Inhaled nitric oxide can directly inhibit the adhesion of neutrophils to the endothelial cells. It was recently demonstrated that iNO reduces leukocytic adhesion and recruitment within the mesenteric vasculature, providing evidence that the action of the gas on circulating neutrophils may have implications beyond pulmonary vasculature.[10]

Inhaled nitric oxide also inhibits platelet aggregation. Studies that have investigated whether the exposure of platelets to the gas within the alveolar-arterial membrane alters its ability to regulate homeostasis have returned conflicting results.[11]

Clinical applications of inhaled nitric oxide

In clinical practice, pulmonary hypertension (PH) and hypoxemia are two pathophysiological conditions which often complicate many diseases and which can be treated with iNO.

Pulmonary hypertension is characterized by increased PVR, thickening of the pulmonary artery wall and right side cardiac failure. The priority objective in these conditions is to increase right ventricle output without increasing the load, impeding the liberation of oxygen to tissues or compromising hemodynamic functions or the integrity of systemic circulation. For this reason, the selectivity of pulmonary vasodilators, when compared with systemic ones, is fundamental.[2] The decrease in endogenous NOS expression observed in PH states, contributes to pulmonary vasoconstriction and to excessive arterial tunica media growth.

The vascular reactivity of iNO in PH situations varies widely, possibly because the more chronic cases lead to

varying degrees of vascular remodeling and hypertrophy of the tunica media of small pulmonary arteries. Furthermore, it has been observed that the degree of acute PH predicts the degree of response to iNO.[2]

Under normal conditions, pulmonary circulation is finely controlled, with the proportion between ventilation and perfusion being regulated by hypoxic pulmonary vasoconstriction. The attenuation of hypoxic pulmonary vasoconstriction results in areas of low V/Q ratio and the diversion of blood from the right to the left via the lungs. Imbalances in the V/Q ratio are the most important cause of gas exchange disorders and of hypoxemia in cases of acute hypoxemic respiratory failure, chronic obstructive lung disease and the extrapulmonary diversion of blood from the right to the left that is characteristic of certain congenital cardiopathies.[2]

The administration of iNO results in both micro and macroselective effects on the pulmonary vasculature.[12] The macroselective effect is obtained from direct vasodilation of pulmonary arteries and the microselective effect is due to its action being limited to the aerated areas of the lungs. This selective vasodilation directs the blood flow from badly ventilated areas (intrapulmonary shunt areas) to better ventilated areas and those with diminished perfusion optimizing the V/Q ratio and improving oxygenation. This is the greatest advantage of iNO over intravenous vasodilators. The latter may worsen the V/Q ratio by non-selective vessel dilation of the pulmonary vasculature. Additionally, the alveolar dead space is reduced by NO inhalation.[2]

Inhaled nitric oxide has proven useful in the treatment of a number of different clinical conditions which will be discussed immediately below.

Persistent pulmonary hypertension and hypoxemic respiratory failure of the newborn

Persistent pulmonary hypertension (PPH) of the newborn (NB) is a process which evolves rapidly and which results in high mortality rates and which by meconium aspiration syndrome, respiratory distress syndrome, asphyxia, shock or infection.[13] In addition to vasoconstriction, its pathogenesis involves lesions of the peripheral pulmonary arteries, with structural remodeling. Histological alterations include, initially, muscular hypertrophy, intimal hyperplasia and, later, plexiform lesions.[14]

Inhaled nitric oxide has been used with children with PPH and hypoxia for its inhibitory effects on the cellular growth of smooth muscle and on the synthesis of proteins from the extracellular matrix and for its reduction of hypoxic arterial remodeling, demonstrated in rat lungs.[6]

Preliminary uncontrolled studies showed improved oxygenation in NBs with PPH treated with iNO.[15] Despite these animating results, randomized and placebo controlled studies of full or near term NBs with respiratory failure and PPH, did not reveal any significant reduction in mortality among the children treated with iNO, although fewer patients in the group treated with the gas required the use of an extracorporeal oxygenation membrane (ECOM).[16] In premature infants with respiratory failure and hypoxemia, iNO improves oxygenation, although without consistent results in terms of reducing mortality.

In 1999, a collaborative Franco-Belgian study was performed[17] in which premature infants with gestational ages of less than 33 weeks and near-term NBs, with respiratory failure and moderate hypoxemia were randomly separated to receive treatment with 10 ppm of iNO. There was significant oxygenation improvement among the near-term NBs during the second hour of inhalation and a reduction in the number of days on mechanical ventilation for the survivors in the group. In the same year, Kinsella et al.[18] performed a double-blind controlled study involving premature NBs (< 34 weeks) with severe hypoxemic respiratory failure. The premature infants were randomly divided to either receive 5 ppm of iNO or inhalation with air. Inhalation of NO improved oxygenation after 60 minutes. However, as with the Franco-Belgian study, the authors did not demonstrate a significant reduction in mortality and neither was there a reduction in events such as intracranial hemorrhage, pulmonary hemorrhage or evolution to chronic pulmonary disease.

Another aspect studied was the question of the best dosage of iNO. There are reports that high doses can worsen surfactant function, while low doses can improve it and even alleviate oxidative stress, resulting in a reduced risk of NBs developing chronic pulmonary disease[19]. O Clinical Inhaled Nitric Oxide Research Group Initiative (CINRGI) study published in 2000,[20] a placebo-controlled, double-blind study to determine whether the employment of low-dose iNO would reduce ECOM usage in a group of NBs born at more then 34 weeks gestational age, suffering from PH. The NBs received an initial dose of iNO at 20 ppm for a maximum of 24 hours and, after, if the response was maintained, the dose was reduced to 5 ppm. The authors demonstrated that low-dose iNO reduces the need for ECOM.

Recently, the Cochrane Neonatal Review Group, in two publications, studied the effects of iNO on full term NBs and premature NBs (< 35 weeks gestational age) with respiratory failure.[21,22] For premature NBs, a met-analysis of three randomized, controlled studies did not demonstrate that the gas had any effect on mortality or on the appearance of bronchopulmonary dysplasia. Only one of the studies analyzed demonstrated reductions in the number of days of mechanical ventilation use in the group treated with iNO. Furthermore, there was no effect on the incidence of intraventricular hemorrhage. In contrast, a meta-analysis of 12 studies of full term NBs found evidence that iNO, at an initial dose of 20 ppm, improves final results, reducing the incidence of the combined outcomes, death and the need for ECOM. The authors commented that the results were basically due to a reduction in the need for ECOM, without

reduced mortality. The only subgroup of patients that returned worse results was made up of NBs with diaphragmatic hernias.

In 2000, the Neonatal Inhaled Nitric Oxide Study Group (NINOS)[23] evaluated the effects of the gas on neurological development and behavior. Full or near-term NBs were evaluated at 18 and months of age. The children were randomized to receive 20 ppm of iNO or 100% oxygen. It was observed that the iNO therapy did not result in an increased incidence of neurological development or behavioral disorders.

Summing up, data available to date indicate that the use of iNO in cases of PPH and respiratory failure of full or near-term NBs should be considered effective. However, its use should remain restricted to clinical trials, within which any adverse effects, especially with premature infants, can be sufficiently monitored.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS), described by Ashbaugh et al. in 1967,[24] is the most severe clinical form and the final aspect of acute pulmonary lesions. The disease, initially viewed as simply a surfactant abnormality, similar to neonatal respiratory failure, is nowadays characterized by the inflammatory process which leads to the rupture of the alveolar-capillary barrier and development of interstitial and alveolar edema, reduced pulmonary compliance, and V/Q imbalance (intrapulmonary shunt) and hypoxemia refractory to oxygen therapy.[25] Furthermore, there is an increase in PVR produced by a complex combination of the primary pulmonary lesion resulting from the inflammatory response to pulmonary aggression, and the complications of treatment, primarily pulmonary lesions induced by mechanical ventilation (MV). Furthermore, pulmonary hypertension puts an additional load on the right ventricle limiting cardiac output.[25]

Despite improved understanding of the pathophysiology of the disease and technological advances in the treatment and monitoring of severely ill patients, ARDS mortality remains high, varying from 43% to 62% in children.[25,26]

Mechanical ventilation is one of the pillars of ARDS treatment to the extent that it improves oxygenation by alveolar recruitment, reestablishing the V/Q ratio. However, while ventilatory maneuvers can improve arterial oxygenation, they do not reduce PH. Furthermore, with the progression of respiratory failure large tidal volumes and high inspiratory pressures may become necessary.[25]

Observation of the lungs using tomographic studies has aided greatly in understanding the disease in that it has afforded the observation that pulmonary parenchyma compromise is not homogenous in ARDS, and that normal areas of the lung remain.[27] In parallel, a number of different publications (28-30) have drawn attention to the pulmonary lesion induced by MV if large tidal volumes (10-15 ml/kg) and high peak inspiratory pressure (> 40 cmH_2O), that had previously been employed routinely, are used.

The idea that predominates currently is that the use of large tidal volumes which generate high inspiratory pressures results in structural lesions in areas of the lung that had been healthy, aggravating hypoxemia and worsening the evolution of ARDS patients. More aggressive MV can also result in inflammatory alveolar lesions, mimicking the anatomical and pathological lesions of the syndrome in healthy areas.[31] The current MV recommendations for ARDS[32] are to use tidal volume up to 6 ml/kg, limiting PIP to 35 cmH_2O, allowing arterial oxygen saturation to remain between 88 and 90% (permissive hypoxemia) and $PaCO_2$ to reach values of up to 100 mmHg (permissive hypercapnia).

As was described above, the local effects of iNO on PH and consequentially on right ventricle dysfunction, on oxygenation, inflammation, edema and capillary permeability make it attractive for use with ARDS.

Rossaint et al.,[33] in 1993, published the first reports of the effects of iNO on ARDS, demonstrating reduced intrapulmonary shunt and improved arterial oxygenation in adult patients. Abman et al., in 1994,[34] described beneficial effects on oxygenation, PH and cardiac index in children with the syndrome. Later, studies conducted on adults[35,36] and children,[37,38] while confirming the immediate beneficial effects, were not capable of demonstrating a prolonged response to iNO therapy. Dobyns et al.,[39] however, observed a prolonged response to iNO as compared to therapy with a placebo in subgroups of patients; those with the most serious respiratory failure (oxygenation index ≥ 25) and among immunodepressed patients. The authors admitted that treatment with iNO did not sustain improved oxygenation in all patients because of the inclusion of patients in the final stages of the disease (after 5 to 7 days).

The hypothesis that the response to iNO depends on the moment of its introduction was put forward by other authors, introducing the concept that early treatment with the gas may be more effective.[40] Recently,[41] attempting to establish a protocol for early iNO administration, we demonstrated an immediate and sustained effect on oxygenation. In this study, the median of the time passed between establishing a diagnosis of ARDS and starting treatment with the gas stands out, being 12 hours. Despite the study not having been developed to evaluate mortality rates, the fact that only one of the ten children died attracted our attention.

In 2002, The Cochrane Library[42] published a systematic review of the effects of iNO on acute hypoxemic respiratory failure in adults and children. Five randomized and controlled studies evaluating 535 patients were analyzed. The review concluded that iNO can only be useful as a rescue therapy, during the first 24 hours of the disease. However, it is worth pointing out that of the five studies involved, only one was performed with children[39] and that the final conclusion was that none of the studies enabled the effects of the gas on mortality to be defined. The influence of iNO treatment on

the length of stay in an intensive care unit was also not thoroughly evaluated. Thus, the potential effect of therapy with iNO on ARDS patients is yet to be defined, particularly with children.

This data leads us to continue to study the use of iNO for ARDS and, now test the hypothesis that early iNO administration reduces mortality, the length of pediatric intensive care unit stay (PICU) and the duration of MV. To this end we compared a group of pediatric patients with ARDS treated with iNO associated with conventional therapy, with a group of children, who were studied in the period between August 1996 and August 1998 and who were treated with conventional therapy only.[26] The preliminary results showed that iNO, when administered as soon as one hour after the establishment of a diagnosis of ARDS, at an average dose of 4 ppm, has immediate and prolonged beneficial effects on the PaO_2/FiO_2 ratio and on the oxygenation index. Additionally, there was reduced mortality, which was 47.62% for the group that received conventional therapy and 16.67% in the group that received conventional therapy associated with iNO.[43] No side effects were observed. These results should be received with due care since the study was a prospective observational one.

A recently published study, substantiating the hypothesis that early iNO administration can be beneficial in ARDS, looked at the effects of iNO on acute pulmonary lesions induced by sepsis, in an experimental model with rats. The authors concluded that early exposure to iNO during the course of acute pulmonary lesions induced by sepsis was associated with reduced leukocytic infiltration and smaller oxidative lesions, and that NO may be of great benefit if administered earlier during the natural history of acute pulmonary lesions.[44]

In view of the pathophysiological complexity of ARDS, we believe that it is extremely unlikely that a single method of treatment will be found which, in isolation, will solve the therapeutic dilemma posed by the syndrome. On the contrary, many different studies have focused on the use in conjunction of a number of different form of treatment, such as the prone position, high frequency oscillatory ventilation, protective and optimized mechanical ventilation and ECOM.[45,46] These studies have demonstrated that iNO has a synergetic effect with these forms of treatment.

It is possible that the iNO therapeutic failures observed in a number of different studies are related, not just to late introduction of the gas, but also to the employment of, mechanical ventilation with insufficient positive expiratory pressure (PEEP). It is already understood that the response to iNO is strongly influenced by the application of adequate PEEP[16,47] and, according to recent recommendations,[48] clinical iNO usage for ARDS should be limited to well-ventilated patients with PEEP.

Taking this data into account, in 2000 the Intensive Care Department of the Sociedade de Pediatria de São Paulo published recommendations for the use of iNO for ARDS. The use of the gas can be considered when, after optimization of mechanical ventilation with PEEP (generally above 10 cmH_2O), the patient maintains $SaO_2 \leq 88\%$ at $FiO_2 \geq 60\%$, and is hemodynamically stable.[49]

Summing up, there are a variety of factors which interfere with a prolonged response to iNO from ARDS patients, such as the dosage, differences between patients, severity of the primary disease, different definitions of a positive response to iNO, duration of respiratory failure before treatment, level of alveolar recruitment during mechanical ventilation and, additionally, whether it is primary or secondary ARDS. Difficulties demonstrating prolonged effects from iNO therapy may be related to these factors which are not easily controlled in clinical studies.

We believe that iNO therapy should be used early and in conjunction with other, established, treatments. It is clear that future controlled studies should concentrate on the treatment of ARDS with early use of iNO as one more treatment weapon.

Primary pulmonary hypertension of the young

Primary pulmonary hypertension is a progressive disease characterized by an increase in PVR which leads to a deterioration of right-side cardiac function as a result of the increased post-load of the right ventricle. It is rarely diagnosed during infancy. However, the number of children diagnosed with primary PH and are referred for treatment has been increasing since it has become apparent that even infants can benefit from treatments used for adult patients.[50]

In children the disease is restricted to severe medial hypertrophy of the pulmonary artery with pronounced proliferation of the tunica intima, which are potentially reversible lesions. The causes of this process are as yet unknown.

Primary PH was the first hypertense pulmonary syndrome for which iNO proved of benefit. Its use is restricted to cases that do not respond to systemic vasodilators. In this context, iNO has been use used with success for patients with acute pulmonary vascular crises, as a testing substance, to select patients for further therapy with oral vasodilators.[6]

Heart Surgery- congenital heart disease and heart transplantation

The pathogenesis of the organic dysfunction which occurs after extracorporeal circulation involves the inflammatory cascade and cellular components of the immune system. Pulmonary hypertension is characteristic of the post-operative period of heart surgery for the repair of congenital heart conditions in children, of myocardial revascularization surgery and of valve surgery on adults or heart transplantation post-op.

When PH occurs after surgery for congenital heart disease, it characteristically occurs during immediate post-op and presents as a PH crisis with acute PVR increase, which begins a cycle of right ventricle failure and low cardiac output and which, if untreated, will lead to death.[6]. Despite traditional intervention, including parenteral vasodilators, hyperoxic hyperventilation, alkalosis and inotropic support, the morbidity and mortality associated with condition remain high.[51]

As has been described previously, advances in vasomotor tone control have given prominence to the role of iNO as a key vasodilator. The basic liberation of endogenous NO by the pulmonary endothelium is fundamental to constant active vasodilation in this circulation. Failure of NO liberation has been described in children with congenital cardiac lesions with left to right blood diversion. Furthermore, a pre-existing endothelial dysfunction may be exacerbated by heart surgery to correct a congenital heart defect. This deficit in pulmonary NO availability, may, therefore, be pathophysiologically linked to the PH crises that occurs with surgery for congenital cardiopathy.[51]

In 1994, the efficacy and safety of iNO administered for short periods was described for children with clinical PH crises after corrective surgery for congenital heart defects.[52] More recently, a placebo-controlled, randomized study assessed 124 children with widespread intraventricular communication or atrioventricular canal defect. The children received iNO at a dose of 10 ppm, and it was demonstrated that routine use of the gas, after corrective heart surgery, can reduce the risk of PH crises and shorten post-op, without toxic effects.[51]

After heart transplantation, PH resulting from chronic heart failure is the major cause of right ventricular dysfunction. Treatment objectives in these clinical situations include the preservation of coronary perfusion to maintain systemic arterial pressure, optimizing pre-load and reducing right ventricle post-load. Thus, iNO is the treatment of choice, even before leaving the operating theatre. There is increasing evidence of the efficacy of iNO in this context. In a study of cases and controls, 16 adults receiving heart transplants, who presented pulmonary artery pressure > 25 mmHg, were prospectively allocated to receive 20 ppm of iNO and were compared with an historic group with the same degree of PH. The authors observed a significant reduction in post-op PVR and improved right ventricular function.[53]

Inhaled nitric oxide has also been used as a method to diagnose the reversibility of PH and establish indications for heart or heart/lung transplantation.[2] However, cases of pulmonary edema were observed among patients chosen for heart transplantation when iNO had been used as a test of PH reversibility.[54]

Chronic obstructive lung disease and pulmonary fibrosis

Chronic obstructive pulmonary disease (COPD) in adults often complicates with the appearance of PH. The increase in pulmonary artery pressure is almost always mild to moderate, but some patients may suffer from severe PH and follow a most unfavorable clinical course, with right ventricle failure. Under these conditions, the cause of PH is an extensive remodeling of the walls of the pulmonary arteries, which results in hypoxic pulmonary vasoconstriction.[6]

The efficacy of iNO for reducing PH observed in COPD and pulmonary fibrosis is well known. However, its effects on gas exchange have sometimes been disappointing, meaning that the use of iNO in these situations remains controversial. The safety and efficacy of mixing NO (25 ppm) and oxygen administered via nasal cannula, for a period of 24 hours, has been demonstrated for adult patients adults with COPD, when stable and oxygen dependent. Those patients who had been on oxygen for longer demonstrated greater benefit from treatment with 5 ppm of iNO. In contrast patients with acute exacerbation of their COPD do not seem to respond to the gas. The improvement in oxygenation during iNO therapy is not constant, and can depend on the type of lung disease and the degree of response from the bronchi.[6]

Currently, iNO is understood to be a form of treatment for PH among selected groups of adult patients with advanced COPD and right-side heart failure.

Further studies are necessary to determine its true efficacy as a long-term treatment for this group of patients. In pediatrics there have been not studies evaluating the role of iNO in COPD or pulmonary fibrosis.

Sickle-cell anemia

Sickle-cell anemia covers a group of diseases which alter hemoglobin, causing hemolytic anemia and recurrent episodes of vascular occlusion characterized by painful crises and chronic and acute organic lesions.[55] The painful crises may be precipitated by surgical stress or by inadequate post-operative pain control.

The traditional treatment for patients with sickle-cell anemia who will undergo surgery includes pre-operative transfusion and the use of opioids during post-op. Inhaled nitric oxide, by reducing vascular resistance and pulmonary pressures may be of benefit to acute cases.

In 2003 a double-blind, randomized study was published which evaluated 20 patients (between 10 and 21 years of age) with sickle-cell anemia and severe vaso-occlusive crises. The patients received either placebo or iNO (80 ppm), and it was demonstrated that iNO can be of benefit during acute vaso-occlusive crises.[55]

Other clinical studies are in progress to establish whether iNO is capable of significantly reducing the morbidity and mortality of these patients.

Bronchospasm

In animal models of induced bronchospasm, iNO has been shown to be a potent bronchodilator, with effects comparative and additional to ß2-agonists.[56] In healthy adults, 80 ppm of iNO shows a modest bronchodilator effect, when compared with beta sympathomimetic drugs, and had a weak effect on asthmatic patients.[2]

The use of iNO for this condition remains experimental.

Extrapulmonary uses of iNO: future applications

One of the most intriguing applications for iNO is with lesions provoked by ischemia-reperfusion. This pathophysiological condition involves an orchestrated sequence of cellular and molecular events which have only recently been explained.[6]

Ischemia-reperfusion lesions occur over a period of a few hours (2 - 4 hours) and involves two distinct, interrelated events: the endothelial trigger and neutrophilic amplification. The primary, early stage event which leads to endothelial dysfunction is the loss of endothelial NO liberation and the second phase of the process is the amplification of polymorphonuclear cells which, in the final analysis, controls cellular adherence to the endothelium. As reduced NO liberation is an early pathophysiological event and relevant to the reperfusion lesion, it has been proposed that NO should be replaced as a means of alleviating the effects of the endothelial lesions of a number of different clinical conditions, such as acute coronary occlusion.[6]

Dose, administration and withdrawal of iNO treatment

Inhaled nitric oxide administration begins with the performance of a four-hour response test. In the protocol we published in 2001,[41] administration began with a test dose of 20 ppm of iNO for 30 minutes and, whatever the response, the concentration was reduced to 10 ppm and, after 30 minutes to 5 ppm, which dose was maintained for a further three hours top complete the four hours of the response test. Such care is important since literature describes that an iNO response may only be manifest after four hours.[48] In the past, patients were maintained on the lowest dose which was associated with a positive response (an increase greater than or equal to 10 mmHg in the PaO_2/FiO_2 ratio). The maximum dose, in the majority of clinical situations, is 20 ppm to begin the response test. If the patient does not respond, the initial dose may be raised to 40 ppm, bearing in mind that the objective of the test is to keep the patient on the lowest dosage that is associated with a beneficial effect on oxygenation. A time limit for usage has not yet been established in published literature.

The definition of a positive response to treatment with the gas remains controversial. There are authors who state that any improvement in oxygenation should be considered a positive response, particularly in severe ARDS. The Intensive Care Department of the Sociedade de Pediatria de São Paulo recommend that a positive response be considered an increase of 10% to 20 % in PaO_2 or in the PaO_2/FiO_2 ratio.[49]

Administration follows previously established standards.[41,48] In brief, a fraction of iNO is continuously liberated to the patient, via flowmeter, directly into the inspiratory limb of the mechanical ventilation circuit, forward of the humidifier, 30 cm from the endotracheal tube. Concentrations of iNO and of NO_2 (nitrogen dioxide) are continually measured by means of electrochemical sensors or chemoilluminescence of gas samples obtained from as close as possible to the endotracheal tube. The audiovisual alarm should be set at a ppm above the iNO dose being administrated and at the maximum level for NO_2 of 3 ppm. The electrochemical sensor should be calibrated for each patient immediately prior to administration of iNO and the entire gas system should be cleaned before use.

Precautions and adverse effects

The main problems related to the administration of iNO are the formation of NO_2, methemoglobinemia and the rebound effect.[6]

Nitrogen dioxide is produced from NO and oxygen. It causes oxidative pulmonary damage, resulting in the generation of free radicals which can oxidize amino acids and start lipid peroxidation of the cellular membrane. The pulmonary lesion is characterized by an increase in pulmonary extravascular water, erythrocyte migration, hyperplasia of type II pneumocytes and alveolar fibrin, polymorphonuclear cell and macrophage accumulation. The NO_2 can also compromise the efficiency of pulmonary defenses.[2] The level of NO_2 production depends on the iNO dose and the FiO_2 used and the duration of gas treatment, with the quantity of NO_2 formed being 1.1% of the iNO dose.[57] Therefore monitoring the levels of iNO and NO_2 is fundamental.

Another problem to be avoided is worsening oxygenation and increased pulmonary artery pressure which can occur after abrupt withdrawal of the gas (rebound phenomenon).[41] This phenomenon can be explained by the fact that exogenous NO can reversibly inhibit NOS that is present in the airways and pulmonary circulation and reduce endogenous pulmonary production of the gas, resulting in an amplified rebound in pulmonary arterial pressure when the drug is abruptly suspended. The development of a protocol for slow withdrawal and avoidance of accidental interruption of supply or failures in administration are fundamental and reserve systems

should be planned, as should systems for NO inhalation during periods when the ventilator is disconnected.

When NO reacts with hemoglobin, methemoglobin is produced. Levels over 2% of total hemoglobin may compromise the liberation of oxygen and worsen tissue hypoxia. Doses of iNO much greater than those used clinically do not cause significant methemoglobinemia in adults.[58] In work we have published we did not observe methemoglobin above 2% of total hemoglobin.

Methemoglobin levels should be evaluated before starting administration of the gas, after one hour and on any increase of dosage. After stabilization, monitoring may be daily. A methemoglobin level less than or equal to 2% is considered normal. Levels of up to 5% do not demand treatment.

Despite worries, therapy with iNO doses varying from 5 to 80 ppm has been shown to be safe in the majority of clinical studies.

Interactions with other drugs

There have not been any studies assessing the interaction of iNO with other drugs. Clinical interactions with other medication used in the treatment of respiratory failure cannot be ruled out. Inhaled nitric oxide has bee administered together with dopamine, dobutamine, corticoids, surfactant and high frequency ventilation without any interactions being detected.[6]

Contraindications

Both relative and absolute contraindications have been described. Among the absolute ones it is worth highlighting methemoglobin reductase deficiency and use with newborns who are known to be dependent on left-right shunts. Relative contraindications described include bleeding diathesis, intracranial hemorrhage and severe left-side heart failure (class III or IV on the NYHA).[2,6]

Conclusions

Inhaled nitric oxide is a therapeutic technique with wide possibilities for pediatric clinical applications. Its use is safe in an intensive care environment under rigorous monitoring. As a selective pulmonary vasodilator, NO has beneficial effects on gas exchange and ventilation, improving children with hypoxia rapidly. Controlled studies which focus on early administration of the gas are necessary into a number of conditions, primarily ARDS, and until such are completed its use should be considered to be investigational.

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