Farmacia Hospitalaria
ISSN: 1130-6343
ISSN: 2171-8695
Grupo Aula Médica

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Farmacia Hospitalaria, vol. 41, no. 2, 2017, March-April, pp. 292-312
Grupo Aula Médica

DOI: https://doi.org/10.7399/fh.2017.41.2.10533

Available in: https://www.redalyc.org/articulo.oa?id=365962268010

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REVISIÓN

Inhaled nitric oxide in adult patients with acute respiratory distress syndrome

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Farmacia Hospitalaria, vol. 41, no. 2, 2017

Grupo Aula Médica

Received: 03 April 2016
Accepted: 07 November 2016

DOI: 10.7399/fh.2017.41.2.10533

Abstract: In some patients, acute respiratory distress syndrome (ARDS) leads to life-threatening refractory hypoxemia developing. Physicians may consider hypoxemic rescue therapies in an attempt to improve oxygenation in these patients while on conventional mechanical ventilation support. Use of inhaled nitric oxide (iNO) in ARDS is one of the most widely-studied pharmacological interventions over the past two decades. Its efficacy was examined in several randomized clinical trials and has undergone meta-analyses. Although iNO treatment was associated with improved oxygenation, researchers unfortunately never demonstrated a concomitant decrease in mortality or any improved outcome. Hence the current evidence suggests that iNO should not be routinely used in patients with ARDS however may be considered as adjunct therapy to tentatively improve oxygenation while other therapies are being considered in patients with severely hypoxemic ARDS.

This review focuses on the therapeutic use of iNO in adult ARDS patients. We set out some recommendations for its use as rescue therapy against refractory hypoxemia.

KEYWORDS: Acute respiratory distress syndrome, Acute lung injury, Hypoxemia, Nitric oxide.

Resumen: En algunos pacientes, el síndrome de distrés respiratorio agudo (SDRA) provoca el desarrollo de una hipoxemia refractaria que compromete la vida. En este contexto pueden considerarse terapias de rescate en un intento de mejorar la oxigenación mientras los pacientes permanecen en ventilación mecánica. El uso de óxido nítrico inhalado (NOi) en el SDRA ha sido una de las terapias farmacológicas más estudiadas en las últimas dos décadas. Diversos ensayos clínicos y metaanálisis han evaluado su eficacia, y aunque se ha demostrado un aumento en la oxigenación, no se ha podido demostrar un descenso en la mortalidad o una mejora en el pronóstico. La evidencia actual sugiere que aunque el NOi no debe usarse de forma rutinaria en pacientes con SDRA, puede considerarse su uso para mejorar la oxigenación en pacientes severamente hipoxémicos. Esta revisión examina la aplicación terapéutica del NOi en pacientes adultos con SDRA. Se propone un esquema con diversas recomendaciones para su uso como terapia de rescate frente a la hipoxemia refractaria.

PALABRAS CLAVE: Síndrome de distrés respiratorio agudo, Lesión pulmonar aguda, Hipoxemia, Óxido nítrico.

Introduction

Acute respiratory distress syndrome (ARDS) is defined by acute-onset hypoxemia (PaO_2/FiO_2 ratio ≤ 300 mm Hg) in conjunction with the presence of bilateral pulmonary infiltrates not due to cardiac insufficiency or hydrostatic edema.

This hypoxemia occurs as a result of an alteration in the ventilation/perfusion ratio, due both to alveolar inflammation and alteration of pulmonary vascular reactivity, which sometimes becomes refractory, when persistent respiratory insufficiency is maintained under pneumoprotective measures with PaO_2/FiO_2 < 100 mm Hg or plateau pressure > 30 cm H_2O_2[1].

Despite the advances in managing ADRS patients, their mortality rate still continues to be high. Since pneumoprotective ventilation revolutionized the ventilation strategy for ARDS patients, numerous therapies have been studied for correcting the hypoxemia, and although many of these interventions improve arterial oxygenation, unfortunately very few are associated with a benefit relating to survival[1].

Since the role of nitric oxide (NO) in vascular biology was first discovered, its administration in inhaled form was incorporated into the treatment of ARDS due to the belief that selective pulmonary vasodilation in the ventilated alveoli would improve gas exchange and hence the prognosis of these patients. Its efficacy has been evaluated by numerous randomized clinical trials, and it has undergone several meta-analyses, having demonstrated its effect on the transient increase in arterial oxygenation, albeit no clinically-relevant benefit has been demonstrated in prognosis parameters (i.e. survival rate or ventilator-free days). Nevertheless, inhaled nitric oxide (iNO) continues to be used in critical adult ARDS patients, and although its routine use is not recommended, its use as a rescue therapy in patients with severe refractory hypoxemia seems reasonable.

The objective of this review is the clinical evaluation of the role of iNO in ARDS, by setting out the currently-available evidence, the usage-related controversies concerning and the current recommendations for use. A scheme is detailed for its use as a rescue therapy against refractory hypoxemia, which includes aspects such as the indications for administration and withdrawal, dosage and monitoring.

Methodology

A non-systematic search was conducted for articles in the PubMed/ MEDLINE base, confined to the English and Spanish languages, without any time limit, using the MeSH terms: "Respiratory Distress Syndrome, "Adult/ therapy" and "Nitric Oxide". The articles most relevant with regard to their relationship to the aforesaid topic were selected. A manual search was also conducted in the references of the articles selected.

NO is nitrogen monoxide, one of the nitrogen oxides in conjunction with nitrogen dioxide (NO_2), nitrogen tetroxide (N_2O_4) and nitrogen protoxide (N_2O), the last of which has anesthetic properties. Under atmospheric conditions, nitric oxide is a gas which is produced in combustion processes and comprises part of air pollution, it having been considered merely a toxic substance until its role in the regulation of animal physiology was discovered. In the human body, it is synthesized in the vascular endothelium from L-arginine amino acid by means of an enzyme called nitric oxide synthase (NOS), of which several types of different cells in the organism in addition to the vascular endothelium has been characterized and identified[2].It is an unstable molecule with a very short average lifetime (3-5 seconds) and is highly lipophilic, giving it the special ability to pass through membranes. When it is administered via the inhaled route, it passes through the alveolar epithelial cell barrier and into the smooth muscle cells, where it directly stimulates the guanylyl cyclase enzyme, creating cyclic guanosine monophosphate (cGMP), which is the mediator in smooth muscle relaxation and vascular dilation[2,3].

In turn, NO spreads through the endothelial cell toward the vessel lumen, where it quite avidly combines with the hemoglobin and is inactivated, forming meta-hemoglobin, which is reduced by the meta-hemoglobin reductase of the erythrocytes[4]. iNO flows solely in the well-ventilated regions of the lung, and this inactivation on spreading to the blood is what makes it possible to cause selective pulmonary vasodilation without causing systemic vasodilation. Another two main reactions stem from the NO reacting with the oxygen in the blood forming the toxic nitrogen dioxide (NO_2) molecule and from the reaction with the pl asma proteins to form S-nitrosothoioles or thionitrites with vasodilating properties and possible extra-pulmonary effects[2-4].

A modulation of bronchial tone with iNO has also been observed, although even in large doses (80 parts per million (ppm) the bronchodilating response is less than that of inhaling a standard beta-2 agonist[5]. iNO can also have other pulmonary effects (pro-inflammatory or anti-inflammatory properties) and extra-pulmonary effects, although its clinical relevance must be investigated[2-4].

Inhaled nitric oxide in ARDS

Historic perspective and current evidence

In 1980, it was discovered that stimulating endothelial receptors with acetylcholine triggered the production of a substance which spread to the vascular smooth muscle cells and caused vasodilation, this substance having been termed the endothelium-derived relaxing factor (EDRF). Some years later, in 1987, this molecule was proven to be NO[6,7], the authors of said studies having been the 1998 Nobel Prize for their discoveries of this molecule.

Following the promising results of studies on the use of iNO in animals and later in humans with pulmonary hypertension[8], its use was broadened to ARDS patients. Rossaint et al[9] were the first to study the effects of iNO in ARDS patients, having found there to be a reduction of the pulmonary arterial pressure and an increase of the oxygenation at doses of 18-36 ppm. Despite the limitations of their study, the findings justified the dissemination of numerous studies for evaluating iNO in ARDS, which were burgeoning in the 1990's, demonstrating that when inhaled in small doses (5-80 ppm), it rapidly caused selective pulmonary vasodilation of the ventilated alveoli, hence entailing an improvement in the pulmonary hypertension and an increase in the arterial oxygenation[10-12]. These findings provided renewed encouragement to researchers such as Gerlach et al.[31], who evaluated the response of severe ARDS patients to iNO by means of dose response curves. The results showed an improvement in the oxygenation and reduction in the use of extracorporeal membrane oxygenation in the iNO group, there however having been no differences in the length of time of the mechanical ventilation. Despite the belief that the improvement in the gas exchange would have a bearing on the prognosis of these patients, this encouraged different randomized clinical trials subsequently being conducted[13-22] (Table 1). These studies demonstrated the inhalation of NO in ARDS to tentatively improve the arterial oxygenation, although they failed to confirm an improvement in the survival rate or in the morbidity of critical patients. Different meta-analyzes and systematic reviews have also confirmed the increase in oxygenation but nevertheless have not provided evidence of a reduction in the mortality or in the number of ventilator-free days[23-(30].

Table 1

Characteristics of the main clinical trials on inhaled nitric oxide (iNO) in adult patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

Study	Patients/ Centers	Randomized Study	Inclusion Criteria	iNO administration details	Ventilation Strategy
Dellinger et al., 1998[13]	177 adults/ 30	Yes	ARDS < 72h, AECC criteria, FIO2 ≥ 0.5, PEEP ≥ 8	n = 120 Dose 1.25, 5, 20, 40, 80 ppm, for 28 days or until extubation	Standardized protocol (Pplat <35; PEEP until compliance is optimized)
Michael et al., 1998[14]	37 adults y 3 children/ 1	Yes	AECC criteria for ARDS, PaO2/ FIO2 ≤ 150 and FIO2 ≥ 0.8 ≥ 12h or ≥ 0.65 ≥ 24h	n = 20 Adjustment every 6h (5, 10, 15, 20 ppm) for 24h, afterward in clinical judgment Average dose 13 ppm.	Ventilating mode unchanged throughout study, similar PEEP for 72 h
Troncy et al., 1998[15]	30 adults/ 1	Yes	Lung injury score ≥ 2.5	n = 15 Initial adjustment (2.5, 5, 10, 20, 30, 40 ppm every10 min) and daily adjustment up to oxygenation and PEEP Average dose 5.3 ppm. Average duration 8 days.	Standardized protocol (TV: 10 mL/kg, PaCO2 ≤ 35–45, PEEP ≤ 15, PaO2 > 85)
Lundin et al., 1999[16]	180 adults/ 43	Yes	Responding to iNO with infiltrates on radiographs, mechanical ventilation 18-96h, PaO2/FIO2 < 165, PEEP >5, Pplat >10	n = 93 1–40 ppm, smaller effective dose Average dose 9 ppm. Average duration 9 days	In clinical judgment. Ventilation controlled by pressure or volume, I:E ratio 1:2 to 2:1
Payen et al., 1999[17]	203 adults/ 23	Yes	AECC criteria for ARDS, Lung injury score 2-3 after 24h of "treatment optimization"	n = 105 10 ppm, up to oxygenation and PEEP criteria. Median for 5 days	Variable
Cuthbertson et al., 2000[18]	30 adults/ 1	Yes	Infiltrates on radiographs, PaO2/FIO2 ≤ 22 kPa, PEEP ≥ 5, Pplat >10, POAP <18	n = 15 Dose adjustment (0, 2, 10, 40 ppm) up to increase in PaO2/FIO2 ≥ 25%. Average dose 10 ppm. Median duration 10.6 days	Standardized protocol
Mehta et al., 2001[19]	14 adults/ 1	Yes	ARDS ≤ 5 days, bilateral infiltrates on radiographs, PaO2/FIO2 < 200, PEEP ≥ 8, PAOP <18	*n* = 8 Daily adjustment (5, 10, 20 ppm every 30 minutes) for 4 days for higher PaO2/FIO2 up to PaO2/FIO2 > 200 or FIO2 < 0.5. Median dose 5-10 ppm. Average duration 8 days	In clinical judgment
Gerlach et al., 2003[20]	40 adults/ 1	Yes	AECC criteria para ARDS, duration of mechanical ventilation ≥ 48 hours FIO2 ≥ 0.6, PaO2/FIO2 ≤ 150, PEEP ≥10, PAOP ≤ 18	n = 20 10 ppm, adjustment daily response dose up to start of weaning	Standardized protocol
Park et al., 2003[21]	23 adults/ 1	No	AECC criteria for ARDS A prior recruitment maneuver (pressure 30-35 cm H2O for 30 seconds)	n =6 5 ppm, average duration 8.2 days	Standardized protocol (TV 6 mL/kg, FR 20–25, PLAP ≤ 30 cm H2O, PEEP for optimizing PaO2/FIO2)
Taylor et al., 2004[22]	385 adults/ 46	Yes	AECC criteria for ALI modified, duration ≤ 3 days, PaO2/FIO2 ≤ 250, bilateral infiltrates on radiographs, PAOP ≤ 18, FIO2 0.5–0.95 con PEEP ≥ 8	n = 192 5 ppm up to oxygenation or PEEP criteria or end of study (28 days)	Standard protocol (optimized PEEP, Ppla ≤ 35)

ALI: Acute Lung Injury. Pplat: Pressure plateau or mean airway pressure. AECC: American European Consensus Conference. POAP: Pulmonary Artery Occlusion Pressure (in cm H2O). PEEP: Positive End-Expiratory Pressure (in cm H2O). PaO2/FiO2: Ratio of partial pressure arterial oxygen and fraction of inspired oxygen (in mm Hg). TV: Tidal Volume. RR: Respiratory Rate.

Limitations of the available evidence

The increase in oxygenation substantiated with the iNO has not meant an improvement in prognosis in clinically-relevant terms such as the survival

rate. Some authors assert that these results obtained in small-scale, low-powered clinical trials may have significant limitations, and their results may serve better for giving rise to rather than confirming hypotheses[4]. In fact, the greatest criticism of these studies is that they do not distinguish between severe and moderate ARDS, in the belief that the greatest benefit is achieved in patients with severe hypoxemia and that this sub-group has been poorly represented in the clinical trials[32,33]. However, a meta-analysis[30] recently examined the effect which iNO has on mortality by sub-groups defined by the degree of severity of the hypoxemia for 9 clinical trials and 1,142 patients, no benefit having been found according to the severity of the group. The analysis of sub-groups showed that the therapy with iNO does not reduce the mortality in patients with baseline $PaO_2/FiO_2 \leq 100$ mm Hg (RR 1.01 (95% CI, 0.78-1.32); p = 0.93; n = 329; 6 trials) or those with a baseline $PaO_2/FiO_2 > 100$ mm Hg (RR 1.12 (95% CI, 0.89-1.42); p = 0.33; n = 740; 7 trials). Nor was any PaO_2/FiO_2 threshold (increments of 10 mm Hg within 70-200 mm Hg range) identified in which the mortality of the patients treated with iNO was lower than in the controls. One limitation of this study, according to the authors, is that it included solely 329 patients in the severe ARDS sub-group, which limits the statistical power for detecting actual differences in mortality among sub-groups.

Other limitations of these reviews are due to the lack of homogeneity of the patients included in one trial and another, due in part, up to relatively a few years ago, to there being no universal definition of ARDS to improve the coherence between research and clinical practice. Furthermore, there is a lack of homogeneity in the indication and in the treatment, with different methods for administering iNO and differing doses from one trial to another[3], which complicates their comparison for drawing any significant conclusions (Table 1). Furthermore, it is currently known that the ventilating strategy employed for managing a patient with acute respiratory insufficiency has a significant bearing on the evolution of the disease, although this finding was discovered after many of these studies had been conducted, in which the patients were ventilated with a tidal volume above the recommended volume of 6 ml kg^{-1}. The slight improvements in oxygenation due to the iNO may be masked by the deleterious effects of a non-protective ventilating strategy used in most trials, which limits neither the tidal volume nor the airway pressure. A protective ventilation within the context of the use of iNO might perhaps have provided more positive results as far as prognosis-related parameters are concerned[4,34].

On the other hand, the mortality of ARDS patients is related more to events such as sepsis or multiple-organ dysfunction than to hypoxemia per se[35]. The fact that the improvement in oxygenation substantiated with the use of iNO has not meant an improvement in the mortality rate may be influenced for this reason[4]. Furthermore, most of the treatments researched for ARDS are focused on short-term prognosis parameters, such as mortality. However, the patients who survive ARDS may have

long-range pulmonary sequelae, such as obstructive, restrictive disorders and alterations in gas exchange, which may compromise their quality of life. The actual impact which iNO may have on these parameters is unknown[36]. In 2004, Taylor et al.[22] evaluated the efficacy of small doses of iNO (5 ppm) in 385 critical patients with moderate/severe lung damage ($PaO_2/FiO_2 \leq 250$) from 46 hospitals, finding a transient increase in the PaO2 without any benefit on the mortality or ventilator-free days. A later follow-up carried out as part of the original study however showed better values in functional respiratory tests at 6 months among the ARDS patients who had been treated with iNO than those treated with placebo[36]. Nevertheless, the validity of the study is limited by the loss of follow-up of most of the survivors and the lack of information on smoking. The effects of iNO on long-term pulmonary function of ARDS patients and hence their morbidity and quality of life are still as yet to be determined. Nevertheless, the improvement in oxygenation demonstrated with the use of iNO could suffice in itself to justify iNO being used in some severely hypoxemic ARDS patients[34].

Use and current recommendations

Following the burgeoning number of articles published concerning iNO in the mid-1990's, the use of therapy employing iNO began expanding to different disorders such as persistent neonatal pulmonary hypertension, pediatric and adult heart surgery and ARDS[34].

In fact, at the end of the 1990's, a working group on using iNO in the ICU of the European Society of Intensive Care Medicine (ESICM) explored the clinical practice of the use of iNO in the ICU by means of a questionnaire which was answered by 310 physicians from 21 countries[37]. More than 60% of said physicians reported using iNO therapy (63.2%), the specialists among whom were mainly intensive care specialists, pediatricians and anesthesiologists.

However, in ARDS patients, its clinical and prognosis-related repercussion has not met with the anticipated degree of success. In 2005, a group of experts organized by the EISCM and by the European Society of Cardiothoracic Anesthesiologists set out some recommendations regarding iNO therapy in adults within the perioperative and critical care realm. In the specific case of ARDS, they mention that its routine use cannot be recommended, although its use as a rescue treatment in patients with severe refractory hypoxemia is considered reasonable[32]. The recent publication of the results of a meta-analysis which seem to reject the belief that the greatest benefit is achieved in patients with severe hypoxemia[30] continue fostering the idea of relegating the use of iNO in patients with ARDS to extreme situations[1,30].

The treatment indications approved by Spain's Medicines Agency for the use of iNO are the treatment of newborns born with more than 34 weeks of gestation who have hypoxic respiratory insufficiency associated with clinical or echocardiography evidence of pulmonary

hypertension, and the treatment of perioperative and postoperative pulmonary hypertension in heart surgery[38]. There is currently no indication approved for its use in adult ARDS patients, the use thereof hence requiring informed consent (Figure 2). Despite the foregoing, it continues to be used extensively (off-label indication) as a rescue therapy against refractory hypoxemia. For example, it was used in over 20% of the patients included in a large-scale clinical trial published in 2010 concerning the use of neuromuscular relaxants in ARDS patients[39]. Similarly, it was used as a treatment during the 2009 influenza-A (H1N1) virus pandemic in 32% of the patients with refractory hypoxemia prior to the administration of ECMO in Australia and New Zealand[40] and as rescue therapy in up to 14% of critical patients in Canada[41], although scarcely any use was documented in Spain and some series from Latin America[42].

INFORMED CONSENT FOR THE COMPASSIONATE USE OF INHALED NITRIC OXIDE

What is nitric oxide and what is it used for?
Nitric oxide is a molecule found in many cells in all mammals that is involved in functions such as in the process of relaxing the blood vessels in the human body. It is a gas and is used for treating newborns that have a lower than normal amount of oxygen in their bloodstream due to a pulmonary insufficiency associated with high arterial pressure in their lungs. It is also used at any age in patients with pulmonary hypertension related to heart surgery.

Why do we want to use inhaled nitric oxide?
When a person inhales, they can improve their blood flow by means of their lungs, which can help to increase the amount of oxygen reaching the blood.
This increase in oxygen is what we are aiming to achieve.

How is inhaled nitric oxide administered?
Inhaled nitric oxide is administered continuously as a gas into the air and oxygen mixture which is supplied to the patient by means of the ventilator during artificial ventilation. This is done by means of a system designed to guarantee the correct amount. The medical personnel on the unit will determine the most suitable dose.
The treatment may last for several days. The minimum effective dose will be sought, however inhaled nitric oxide does not always turn out to be effective, in which case the treatment will be suspended if the desired effect is not being achieved.

What side-effects may be involved?
Just as all other medications, this medication may cause adverse effects, although not everyone experiences these effects. At the doses normally used, it is considered to be a safe drug, no severe side-effects having been reported.
- It may affect the blood's ability to transport oxygen due to the increase in a substance called methemoglobin, which will be monitored by blood tests, and the dose will be lowered if necessary.
- It may react with the oxygen and form nitrogen dioxide, which can cause severe irritation of the respiratory airways. Monitoring is done for nitrogen dioxide and, if higher than normal values are detected, the treatment will be reduced.
- Decrease in the number or aggregation of platelets (components which help to coagulate the blood) or alteration in coagulation.
- Some studies have shown an increased risk of renal insufficiency.
- When the treatment is interrupted suddenly, arterial hypotension, a rise in the pressure in the lungs or a worsening of the oxygenation may occur, so the precaution will be taken of reducing the dose progressively.

AUTHORIZATION
I, Mr./Ms. ..... , holding Spanish National I.D. Card No..... fully understand the information provided and **authorize** my being treated with inhaled nitric oxide as an alternative treatment beyond the officially-approved indications.

I, Mr./Ms. ....., holding Spanish National I.D. Card No..... as the **legal representative** of Mr./Ms. ..... fully understand the information provided and **authorize** him/her being treated with inhaled nitric oxide as an alternative treatment beyond the officially-approved indications

Informing member of the medical team: .....

Physician's signature Patient / representative's signature

In , on .... , ...

REVOCATION

I, Mr./Ms. ....., holding Spanish National I.D. Card No., as the patient/legal representative of Mr. /Ms.....
Revoke my consent to be treated with inhaled nitric oxide as an alternative treatment beyond the officially-approved indications.

The physician's signature The patient / representative's signature

In , on .... , ...

Figure 2
Proposed informed consent form for compassionate use of inhaled nitric oxide (iNO) in adult patients with acute respiratory distress syndrome (ARDS) with severe refractory hypoxemia.

Based on the foregoing, inhaled nitric oxide therapy seems reasonable as a medication for compassionate use as an off-label therapy in ARDS patients who present severe refractory hypoxemia.

Combined treatment

iNO improves the ventilation/perfusion ratio in the aerated pulmonary regions, as a result of which the use of recruitment maneuvers to get previously-atelectatic terminal alveoli opened up improves their usefulness with a synergetic effect on the increase of the PaO2(43) These recruitment maneuvers include the use of appropriate PEEP (positive end-expiratory pressure) (making it possible to turn patients not responding to iNO into responding patients)[44], ventilation in prone position[45] and high-frequency ventilation[46]. Although the repercussion of this synergism on the prognosis of ARDS patients has not been evaluated, the importance of the maneuvers affording the possibility of preventing atelectasis is relevant to allowing iNO to improve the gas exchange by means of selective pulmonary vasodilation in the largest possible number of aerated alveoli.

As far as the use of catecholamines is concerned, it has been hypothesized that septic patients may have an inadequate response to iNO due to the influence of the endogenous and exogenous catecholamines on the pulmonary vasculature, although some studies have revealed that the sepsis condition does not modify the response to the iNO in PaO_2/FiO_2[14], and that the effect of the iNO is not influenced by the administration of vaso-pressors such as noradrenalin[47].

Dosage

In adults, for the treatment of the pulmonary hypertension associated with heart surgery, the initial dose of iNO recommended on technical data sheet is of 20 ppm of inhaled gas. This dose can be increased up to 40 ppm as a maximum dose if the minimum dose has not caused sufficient clinical effects[38]. However, in the case of ARDS patients, the dosage is a source of controversy. Within this context, different studies have delved into the response in the oxygenation following the administration of different iNO concentrations. The results differ from one another, such that the response observed (increase in the oxygenation or decrease in the pulmonary arterial pressure) varies widely with different doses and treatment times evaluated[11,20,31,48-52].

The maximum benefit on the oxygenation has been documented with doses of 0.1 - 2 ppm[48,49], and with doses of under 20 ppm[31] or under 40 ppm[11,50]. On the other hand, a worsening of oxygenation has also been substantiated with doses above 20 ppm[52] or even 10 ppm[20,31]. Nor is the relationship between the dose of iNO and the response in the oxygenation (dose response curve) concordant, in contrast to small-

scale trials in which both a dose-dependent effect[48,49] and a non-dose-dependent effect has been described with the improvement in the variable oxygenation([11,50)] or with interpatient differences[51,52]. Gerlach et al.[20] found there to be a progressive shifting of the dose-response curve toward the left in ARDS patients who were given iNO continuously for several days. A small percentage of ARDS patients are non-responders to iNO on not increasing the oxygenation relevantly with doses of up to 20 ppm[52].

Furthermore, the parameter which must be taken into consideration as a favorable response is not made clear in literature, ranging from a 15% reduction in the FiO2[14], a higher than 10% increase[3] or 20% increase[13] in pO2 or at least a 20% increase in the PaO2/FiO2[33]. Nevertheless, taking into account its fast-acting quality, this clinically-significant improvement in the oxygenation must be noticeable within the first hour of the therapy in order to justify continuing its use[33]. This lack of concordance in seeking the optimum iNO dosage in ARDS patients is patent in a recently-published meta-analysis evaluating the effect of iNO on in-hospital mortality of severe ARDS patients[30]. The nine clinical trials analyzed show variability in the doses of iNO used. Four trials used a set dose of 5[21,22] and 10[17,20] ppm, one trial randomized patients to different does (1.25-80 ppm)[13], the rest of the studies having used smaller doses, thus achieving a response in the oxygenation (average dose of 5.3[15], 9[16], 13[14] or 5-10[19] ppm).

It is therefore complicated to draw any conclusions regarding the ideal dose of iNO in ARDS patients, which should be adjusted daily in each patient[33], the minimum effective dose being administered by means of slow-paced reductions, provide that the systemic arterial oxygenation continues to be appropriate with reach reduction[32,53].

Safety

Administering therapeutic doses of iNO seems safe in terms of NO_2 and toxic methemoglobinemia forming. There is no direct evidence of direct iNO toxicity or severe side-effects at clinically-relevant doses[27-29]. Nevertheless, some safety precautions must be taken, and the administering technique must minimize the amount of NO_2 administered to the patient and the environmental exposure to the healthcare workers[32,49].

Methemoglobin

In healthy volunteers, inhaling iNO in much larger than therapeutic doses (up to 128 ppm) was not associated with clinically-significant methemoglobinemia levels (over 5%), the elevation of the maximum levels at 3.5 hours after starting the iNO having been substantiated[54]. In critical ARDS patients, methemoglobin levels of higher than 5% can be detected with high concentrations of iNO (40 and 80 ppm), severe methemoglobinemia being extremely rare, which has not be found to be the case with therapeutic doses (< 20 ppm) in Cochrane reviews[27-29].

Using iNO must be avoided in patients with a methemoglobin reductase deficit, it being necessary to monitor the baseline methemoglobinemia and at 4-6 hours after starting the therapy as well as on a daily basis, the dose being lowered in the event of finding a methemoglobinemia < 5%[32,38,49]. The methemoglobinemia which does not cease to exist after cutting back on or halting the therapy or which is compromising oxygenation can be treated with vitamin C, N-acetylcysteine, tocopherol, methylene blue or exchange transfusion, depending on the clinical situation[38].

Nitrogen dioxide (NO_2)

NO oxidizes in the presence of oxygen to form NO_2, a highly toxic gas, levels higher than 2 ppm of which can increase alveolar permeability, and which can cause severe lung damage at levels above 10 ppm[3]. The NO to NO_2 conversion rate is directly proportional to the NO concentration, to the O2 concentration and to the length of time NO and O2 are in contact with one another, it therefore being necessary for iNO to be administered using a continuous or synchronized release system with the inspiratory outlet near the patient's circuit (on the inspiratory limb) and monitored distally from the point of administration[32,55]. In one clinical trial, an increase was found to exist in the NO_2 concentrations in three patients who had received concentrations higher than 80 ppm over the course of several days' time[13]. Nevertheless, no increased risk of NO_2 formation was found to exist with doses lower than 80 ppm[27-29].

In long-term treatments, is it recommended to reduce the iNO concentration to 10 ppm or less in order to reduce exposure to the potentially toxic NO_2[32]. According to the technical data sheet the highest exposure limit (average exposure) to NO on the part of the personnel determined by the labor legislation is of 25 ppm for 8 hours (30 mg m^3-1) in most countries, the respective limit for NO2 being 2-3 ppm (4-6 mg m^3-1)[38].

Renal insufficiency

Two meta-analyses showed an increased risk of renal dysfunction with the use of iNO[27,29]. Nevertheless, the authors proper state there not to have been any generally-accepted classification such as RIFLE or AKIN which would have increased the validity of the results, and that this must be interpreted cautiously on the basis of the fact that the result stems from a post hoc analysis and it's potentially being biased on publishing as a result of no renal function data having been obtained in some of the trials analyzed.

Coagulopathy

Although alteration of hemorrhaging time with the use of iNO has been documented[56], as well as an attenuation of platelet aggregation in patients with ARDS (which did not change the bleeding time even with iNO fractions above 100 ppm)[57], the data in adult humans is contradictory, no increase in the risk of bleeding or in hemorrhaging

events having been found in recent meta-analyses and Cochrane reviews[27-29].

Rebound phenomenon

Withdrawing iNO suddenly should be avoided[32], given that a rebound phenomenon has been found to exist in some patients with acute pulmonary hypertension, hemodynamic collapse and worsening oxygenation[58], which is due to a reversible inhibition of the endothelial NOS by the iNO[3]. Withdrawal must therefore be gradual, at least every 12 hours, once the oxygenation has improved and the patient is stable, with a low dose of iNO (5 ppm). The dose should then be progressively reduced to 1 ppm over a period of 6-12 hours, to then be maintained for 30 minutes, continuously monitoring the arterial tension, heart rate and the O2 sat, to then finally disconnect the system[38] (Figure 1).

INDICATION
- ARDS patients on invasive mechanical ventilation who present severe refractory hypoxemia, when persistent respiratory insufficiency is maintained with a $PaO_2/FiO_2 < 100$ or a Pplat > 30 cm H_2O, once the respiratory support has been optimized with a ventilation strategy under pneumoprotective measures and ventilation in prone position.
- May be individualized under certain circumstances in which the patient is at a high risk of death or damage due to hypoxemia despite other available treatments or when other therapeutic alternatives such as ventilation in prone position are contraindicated[30,32,34].

INFORMED CONSENT
- An informed consent form will be furnished to the legal representative for the authorization thereof.

ADMINISTRATION
- During the invasive mechanical ventilation process, following its dilution with an oxygen/air mixture using an approved system, which must provide a constant concentration of iNO into the inspiratory limb of the ventilating circuit.
- The therapy must be available both for manual ventilation (i.e. during transport or resuscitation) and for emergency system (electric power supply and backup system)[32,38,49].

DOSAGE
- Start at 5 ppm, increasable to 10-20 ppm, adjusting each dose after 10 minutes at least. The maximum dose of 40 ppm shall never to exceed[32,33,38,49].
- The positive response (increase in PaO_2 > 20%) must become patent within the first hour of the therapy. In the event of not finding there to be any improvement despite having increased the dose, its use is not justifiable:
  - Start at 5 ppm and take arterial blood gas in 30 minutes. Response to 5 ppm:
    - PaO_2 increases > 20%: continue at 5 ppm.
    - PaO_2 increases < 20%: increase to 10-20 ppm and check arterial blood gas in 30 minutes.
- The dose must be adjusted daily, the minimum effective dose which maintains adequate systemic arterial oxygenation being administered. Try a reduction of 5-10 ppm:
  - Postweaning PaO_2 decreases < 20% of the preweaning PaO_2: Maintain dose and wait the time interval for trying to lower to the next value.
  - Postweaning PaO_2 decreases > 20% of the preweaning PaO_2: Increase the iNO dose up to preweaning.
- The iNO dose must be reduced if the methemoglobinemia is > 5% or the NO_2 is > 1 ppm.

MONITORING
- The continuous monitoring system with alarms for iNO (±2 ppm of the prescribed dose) and NO_2 (0.5 ppm)[32,38,49,56].
  - If the NO2 is >0.5 ppm in the dose interval of < 20 ppm iNO, the administration system must be checked in case it were to be malfunctioning, the NO2 analyzer must be recalibrated and, if possible, the dose and/or the FiO2 must be reduced.
  - If the NO2 concentration exceeds 1 ppm at any point in time, the iNO dose must be reduced immediately.
- O_2 sat, invasive AT, CF
- Arterial blood gas check at 30 minutes after starting the therapy and every 8-12 hours.
- Maintain methemoglobinemia < 5% and NO_2 < 1 ppm
- Daily control analysis (platelets, renal function and coagulation times)

WITHDRAWAL

It shall be attempted to gradually withdraw the iNO treatment once the oxygenation has improved and stabilized. Its final withdrawal must be considered if the patient has a PaO_2/FiO_2 > 150 with use of FiO_2 < 0.8.
- From 20 ppm to 5 ppm, reducing by 5-10 ppm (sequence 20-10-5): reduce every 8-12 hours.
- From 5 ppm to 1 ppm, reducing by 2 ppm (sequence 5-3-1): reduce every 6-8 hours.
- Maintain for 30 minutes at least at 1 ppm, constantly monitoring O_2 sat, invasive AT , FC and AT to them finally turn off completely.

Figure 1

Proposed scheme of recommendation for the use of inhaled nitric oxide (iNO) in adult patients with acute respiratory distress syndrome (ARDS) with severe refractory hypoxemia.

Others

Although no interaction studies have been conducted, a clinically-significant interaction with NO donor substances (local anesthetics,

nitroprussiate, nitroglycerin, etc.) or with other vasodilators which act through the GMPc or AMPc systems which must be used cautiously cannot be ruled out completely[38].

The treatment with iNO can elevate the transpulmonary gradient in certain situations and worsen cardiac insufficiency in situations of left-right blood shunting, it therefore having to be used cautiously in these patients and in those with deteriorated left ventricular function and an elevated baseline pulmonary capillary pressure[4,32,38].

Proposed scheme of use

Based on current evidence, the routine use of iNO in adult ARDS patients is not recommended. The use thereof should be considered under certain circumstances in which the patient has a high risk of death or damage due to hypoxemia despite other available treatments[30,32,34]. The benefit in increasing the oxygenation can provide valuable time necessary for remedying the process which caused the damage in order to optimize the ventilation strategy or establish other treatment modalities such an extracorporeal membrane oxygenation. Furthermore, there are certain patients with severe refractory hypoxemia who could also benefit from an increase in oxygenation by means of treatments such as iNO, in which some therapies which improve the gas exchange (PEEP, prone position) cannot be used as a result of being contraindicated or involving excessive risk (i.e. intracranial hypertension or instability of the cervical spine). The use thereof for this indication, as a rescue therapy against refractory hypoxemia in optimally-ventilated adult ARDS patients requires informed consent (Figure 2).

Figure 1 provides a scheme of recommendations for using iNO in ARDS patients with severe refractory hypoxemia which includes aspects such as the indications for administration and withdrawal, dosage and monitoring. The implementation of a protocol for use and withdrawal can reduce the direct costs associated with iNO use[59].

Prospects of future research

The prospects are not good of finding future clinical trials evaluating iNO therapy in ARDS[30]. Although numerous pharmacological therapies are currently continuing to be researched for the treatment of ARDS patients, in the case of iNO, in view of the evidence available showing no benefit on parameters such as mortality or duration of mechanical ventilation[23-30], its high cost (markedly higher following its approval as a pharmaceutical product and its patenting by the industry)[60], the possible associated risk of renal dysfunction[27,29], the number of patients with severe hypoxemia being small to detect an effective treatment[30], and the existence of therapeutic alternatives which have clearly shown clinical benefits such as protective ventilation or ventilation in prone position[1],

it is unlikely that future clinical trials will be conducted evaluating iNO dosage and duration strategies in severely hypoxemic patients, if it is not in conjunction with other interventions which have clearly shown a benefit on ARDS[30,34].

Conclusions

In ARDS patients, iNO causes on-the-spot pulmonary vasodilation by improving arterial oxygenation, although an improvement in the survival rate or in the morbidity of critical patients has not been demonstrated. Although its routine use cannot be recommended, iNO still continues to be used as a safe option, and its administration is reasonable as a rescue treatment in patients with severe refractory hypoxemia.

Acknowledgements

None

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Conflict of interest declaration

Conflicts of interest: No conflict of interest