Intensive Care Med (2005) 31:1029–1041
DOI 10.1007/s00134-005-2675-4

SPECIAL ARTICLE

Peter Germann
Antonio Braschi
Giorgio Della Rocca
Anh Tuan Dinh-Xuan
Konrad Falke
Claes Frostell
Lars E. Gustafsson
Philippe Hervé
Philippe Jolliet
Udo Kaisers
Hector Litvan
Duncan J. Macrae
Marco Maggiorini
Nandor Marczin
Bernd Mueller
Didier Payen
Marco Ranucci
Dietmar Schranz
Rainer Zimmermann
Roman Ullrich

Inhaled nitric oxide therapy in adults: European expert recommendations

Received: 8 November 2004
Accepted: 24 May 2005
Published online: 23 June 2005

Peter Germann, Roman Ullrich: Both autors contributed equally in preparing and editing the manuscript.

This article refers to the article available at http://dx.doi.org/10.1007/s00134-005-2674-5

This conference was supported by an unrestricted grant from INO-Therapeutics.

P. Germann (✉) · R. Ullrich
Department of Anaesthesiology and General Intensive Care,
Medical University of Vienna,
Waehringerguertel 18–20, 1090 Vienna, Austria
e-mail: peter.germann@meduniwien.ac.at
Tel.: +43-1-404004181
Fax: +43-1-404004183

A. Braschi
Department of Anaesthesia and Intensive Care,
University of Pavia,
IRCCS Policlinico S. Matteo,
P.le Golgi 2, 27100 Pavia, Italy

G. Della Rocca
Policlinico Universita Udine,
Via Colugna 50, 33100 Udine, Italy

A. T. Dinh-Xuan
Service de Physiologie-Explorations Fonctionnelles,
Hôpital Cochin,
27 rue du Faubourg Saint-Jacques,
75679 Paris cedex 14, France

K. Falke
Department of Anaesthesiology and Intensive Care Medicine,
Charité Campus Virchow Klinikum,
University Medical Center,
Augustenburger Platz 1, 13353 Berlin, Germany

C. Frostell
Department of Anaesthesia and Intensive Care,
Karolinska Institutet, Danderyd Hospital,
18288 Danderyd, Sweden

L. E. Gustafsson
Physiology and Pharmacology at Berzelius Lab,
Karolinska Institutet,
17177 Stockholm, Sweden

P. Hervé
Service d'Explorations Fonctionnelles,
Centre Chirurgical Marie Lannelongue,
133 avenue de la Résistance-Le Plessis Robinson, 93350 Orsay, France

P. Jolliet
Division of Medical Intensive Care,
University Hospital of Geneva,
1211 Geneva 14, Switzerland

U. Kaisers
Department of Anaesthesiology and Intensive Care Medicine,
Charité Campus Virchow Klinikum,
University Medical Center,
Augustenburger Platz 1, 13353 Berlin, Germany

H. Litvan
Cardiac Anestesia and Postoperative Intensive Care Unit,
Hospital Santa Creu i Sant Pau,
C/San Antoni Mª Claret 167,
08025 Barcelona, Spain

D. J. Macrae
Paediatric Intensive Care,
Royal Brompton Hospital,
Sydney Street, London, SW3 6NP, UK

M. Maggiorini
Intensive Care Unit,
Department of Internal Medicine,
Universitätsspital,
Ramistrasse 100, 8091 Zurich, Switzerland

N. Marczin
Heart Science Centre,
Harefield Hospital,
Harefield, UB9 6JH, UK

B. Mueller
Laboratory of Respiratory Cell Biology,
Division of Pneumology,
Philipps University,
Baldingerstrasse, 35033 Marburg, Germany

D. Payen
Département d'Anesthésie-Réanimation Chirurgicale,
Hôpital Lariboisière,
2 Rue Ambroise Paré,
75475 Paris cedex 10, France

M. Ranucci
Department of Cardiothoracic Anaesthesia and Intensive Care,
Istituto Policlinico S. Donato,
Via Morandi 30, 20097 S. Donato Milanese, Italy

D. Schranz · R. Zimmermann
Abteilung Kinderkardiologie,
Univ.-Kinderklinik Giessen,
Klinikstrasse 36, 35392 Giessen, Germany

Abstract *Background:* Inhaled nitric oxide (iNO) has been used for treatment of acute respiratory failure and pulmonary hypertension since 1991 in adult patients in the perioperative setting and in critical care. *Methods:* This contribution assesses evidence for the use of iNO in this population as presented to a expert group jointly organised by the European Society of Intensive Care Medicine and the European Association of Cardiothoracic Anaesthesiologists. *Conclusions:* Expert recommendations on the use of iNO in adults were agreed on following presentation of the evidence at the expert meeting held in June 2004.

Keywords Inhaled nitric oxide · Pulmonary hypertension · Acute respiratory distress syndrome · Acute lung injury · Cardiac surgery · Lung transplantation

Introduction

Inhaled nitric oxide (iNO) has been used in Europe for treatment of acute respiratory failure and pulmonary hypertension for several years, both in the operating room and the intensive care unit. In the middle 1980s Higenbotham and his group [1, 2] were the first to demonstrate that iNO selectively decreases pulmonary artery pressure (PAP) in a series of patients with primary pulmonary hypertension. Then it was demonstrated that iNO can selectively reverse experimental pulmonary arterial hypertension [3]. In the early 1990s it was shown that iNO selectively decreases pulmonary arterial hypertension and improves arterial oxygenation in patients with acute respiratory distress syndrome (ARDS) [4, 5, 6, 7, 8, 9]. The rationale for the treatment of critically ill patients with iNO was based on these studies [1, 2, 3, 4, 5, 6, 7, 8, 9]. However, subsequent randomised controlled trials (RCTs) failed to confirm an improvement in survival or morbidity in critically ill patients treated with iNO [10, 11, 12, 13, 14, 15]. In addition, to date there is no drug approval for these indications in adults, although iNO is still extensively used as an off-label drug, and many clinicians consider it an important treatment, combining effective selective pulmonary vasodilatation with a favourable pharmacological profile [16]. iNO has been approved for treatment of term and near-term neonates with hypoxic respiratory failure. The provision of a pharmaceutical product has led to high drug costs and an increased need for justification of the clinical use of iNO in adults in daily practice. This suggested to our group that recommendations should be established on the use of iNO in adults covering all aspects of current and potential applications based on expert opinion.

Methods

An Advisory Board was established under the auspices of the European Society of Intensive Care Medicine and European Association of Cardiothoracic Anaesthesiologists to coordinate the scientific program of the meeting. The board consisted of experts with proven scientific or clinical expertise relevant to the clinical use of iNO. The board identified a further panel of experts who were invited to act as section leaders whose role was to review the literature in their designated subject area, taking special care to ensure the presence of different opinions. Section leaders were asked to produce written summaries of their subject area, which were then circulated to delegates prior to the meeting and which formed the basis of the evidence presented to delegates at the expert meeting itself. A further panel of opinion leaders were invited to attend the meeting on the basis of their known interest in the use of iNO or their status as opinion leaders in the field of adult intensive care. The European Society of Intensive Care Medicine and the European Society of Cardiothoracic Anaesthesiologists were officially represented at the meeting. At the expert meeting each subject area was presented in summary by the section leader(s), following which open discussions led to the composition of draft expert recommendations statements. These were then edited and re-presented to delegates with further discussion and reading leading to final agreement on the individual recommendations.

The first part of this program was built upon discussions among a core group of experts, and this led to draft recommendations covering areas such as clinical pharmacology, toxicity, dosing, administration and various indications supported by appropriate literature and clinical data analysis. These draft recommendations were made available to a wider group of physicians through a dedicated restricted website. Following discussions based upon these statements revisions were published online. A 2-day conference was then organised, enabling 58 experts from different specialties and coming from 14 European Union countries to openly discuss all related issues and jointly agree on recommendations. During this conference an Editorial Committee was formed to summarise expert recommendations. These statements were then published anew on the dedicated, restricted website for final review and comments by all participants. Following a last round of online discussions the Editorial Committee prepared the final article which is presented in this contribution. The cost of this project, including hotel and accommodation, travel, online conferencing facilities, IT support and website, expenses for preparation work, was approx. €218,000 (€20,000 for the first part and €198,000 for the second part of the program) which was supported through an unrestricted grant from INO Therapeutics. The process of producing the present

expert recommendations was entirely independent of the sponsoring company, and the contributors specified their potential conflicts of interest. The sponsor has no authorship or editorial control over the content of the meetings or any subsequent publication. Most of the expense for this effort has been time by the Committee.

Results

Clinical pharmacology

iNO acutely relaxes constricted vascular smooth muscle leading to vasodilatation of the pulmonary circulation with no measurable haemodynamic action outside the lung ('selective pulmonary vasodilatation'). In addition, iNO potentially dilates constricted bronchial smooth muscle, and it may improve arterial oxygenation in hypoxaemic patients by reducing the intrapulmonary shunt leading to enhanced matching of ventilation and perfusion. The selective pulmonary vasodilator action of iNO has been confirmed in various animal models [3], in a human model of acute alveolar hypoxia [17] and in patients with pulmonary arterial hypertension resulting from pulmonary vascular constriction [1, 2, 18, 19]. However, due to its short half-life sustained vasodilatation requires the continuous delivery of iNO to the lungs. Sudden disruption of iNO therapy can therefore result in a severe withdrawal reaction with rebound and possibly severe vasoconstriction [20]. The bronchodilator effect of iNO is dose dependent in anaesthetised animals [21] and in volunteers or patients with active bronchoconstriction [22]. Even at the high doses of iNO used in these studies (80 ppm) the bronchodilator response of iNO was less effective than a subsequent inhalation of a standard β_2-agonist [22].

Several clinical studies have tested the use of iNO for treatment of acute pulmonary hypertension or hypoxaemia employing doses between 3 and 80 ppm. However, these acute physiological effects did not alter clinical outcome parameters, such as mortality or morbidity, and a high proportion of patients do not respond to iNO therapy (non-responders). There is some evidence from experimental and human studies for potential pharmacodynamic effects outside the pulmonary circulation, mainly on diuresis and natriuresis [23, 24], platelet function [25, 26], and modulation of the immune response [27].

Expert recommendations:

- It has been conclusively demonstrated in human experimentation and clinical studies that exposure to iNO causes a concentration-dependent and immediate selective pulmonary vasodilatation in the presence of pulmonary vasoconstriction in most patients.
- Nitric oxide induces vasorelaxation in ventilated portions of the lung and redistributes pulmonary blood flow, thus reducing intrapulmonary shunting in most hypoxaemic patients, at concentrations ranging from 0.1–10 ppm iNO. However, the optimum dose may vary over time and between different subjects.
- iNO is believed to have other pulmonary and extrapulmonary effects. Their clinical relevance and concentration-response relationships remain to be investigated.

Synergistic effects

The rationale for combining iNO with other therapeutics, either pharmacological or nonpharmacological, is to obtain a synergistic or additive effect on pulmonary vascular tone in patients with pulmonary arterial hypertension or hypoxaemia. Most proposed synergistic drugs are effective in influencing only one or the other of these two potential therapeutic aims. For example, prostacyclin [28] and adenosine [29] directly stimulate the synthesis of cyclic adenosine monophosphate (cAMP) whereas phosphodiesterases inhibitors inhibit the breakdown of cAMP and cyclic guanosine monophosphate (cGMP), thereby effecting pulmonary vascular relaxation through signalling pathways that are different from those which are directly brought about by NO.

Expert recommendations:

- The rationale for combining iNO with other drugs is to obtain an additive (or synergistic) effect and to induce an additional reduction in pulmonary vascular tone and/or further optimisation of pulmonary gas exchange than is obtained by use of iNO alone.
- There are clinical reports of the co-administration of 'synergistic' drugs with iNO. The majority of synergistic drugs are effective in influencing only one or another of these desired therapeutic aims [30, 31, 32, 33, 34, 35, 36, 37].
- Only the association of iNO and inhaled nebulised prostacyclin has shown, in a limited number of patients, positive effects on both pulmonary hypertension and gas exchange [36]. The therapeutic benefit of this synergistic response has yet to be determined.
- Published studies on the use of potentially synergistic drugs in association with iNO report effects on small populations or are methodologically inadequate.
- Dose-response studies with both iNO and the associated drugs are incompletely defined.
- The underlying molecular mechanisms of interaction between NO and potentially synergistic drugs and the cross-talk pathways of the two drugs acting together are only partially understood.
- The interpretation of clinical data in individual patients and from small published experiences must therefore be made with caution.

– On the basis of current evidence the clinical use of synergistic drugs in adults in association with iNO cannot be recommended outside the confines of clinical trials.

Toxicology, monitoring, delivery, transport

Over the course of the past decade iNO has been administered to numerous patients without any apparent major side effect [10, 11, 12, 13, 14, 15]. Although the use of iNO is considered to be safe, and there is no evidence of direct NO toxicity at clinically relevant doses, precautions and safety regulations must be taken into account, especially the risk of exposure to higher oxides of NO (i.e. nitric dioxide). Therefore care should be taken to use iNO in humans that has been manufactured according to agreed good manufacturing practice standards (medical grade iNO). These issues have been reviewed in detail previously, including toxicology, monitoring of iNO therapy, delivery and procedures for transport of patients on iNO together with environmental issues and considerations on staff training [38].

Toxicology and monitoring

Expert recommendations:

– There is no evidence of direct NO toxicity at clinically relevant doses.
– Methaemoglobin should be measured 4 h after commencing iNO and daily thereafter.
– Clinically significant levels of methaemoglobin are unlikely to result unless iNO concentrations over 20 ppm are administered.
– Administration of iNO is associated with NO_2 formation which is potentially toxic.
– Environmental exposure limits exposure to NO_2 to a 2-ppm 8 h time-weighted average in non-intubated patients and staff.
– Clinically significant levels of NO_2 are unlikely to occur when iNO is delivered by an efficient delivery system at concentrations of 20 ppm or less.
– If long-term iNO treatment is to be undertaken, attempts should be made to reduce the concentration of iNO to 10 ppm or less to further reduce exposure to potentially toxic NO_2.
– Use of iNO is associated with accumulation of nitrate and nitrite. The significance of these increases is uncertain.
– There are no long-term follow-up studies from which freedom from late adverse effects following iNO therapy can be ascertained.

Delivery

Expert recommendations:

– INO should be delivered by a system approved for clinical use, conforming to appropriate CE standards and capable of meeting the following specifications.
– It should be able to deliver a constant concentration of iNO to the patient.
– The design should minimise the generation of NO_2 and should have continuous monitoring and alarms for inspired NO, NO_2 and O_2.
– A backup system for hand ventilation should be immediately available to ensure continuous iNO delivery in the case of delivery device malfunction.
– The delivery device should be compatible with the type(s) of ventilator(s) in use, which at present does not include closed-circuit, rebreathing systems during anaesthesia.

Transport

Expert recommendations:

– iNO therapy must be delivered without interruption when patients are transferred within or between hospitals.
– An iNO delivery and monitoring system which is of low weight and is designed and approved for use during transport in road and air ambulances is urgently needed.

Contraindication

– Methaemoglobin reductase deficiency (congenital or acquired)

Diagnostic assessment

Heart failure

The frequently elevated PVR in patients with chronic left ventricular failure may be a result of dysregulation of vascular smooth muscle tone and structural remodelling [39]. There is growing evidence that the dysregulation of pulmonary vascular tone in disease states, such as chronic heart failure involves vascular endothelial dysfunction with impaired endogenous NO availability in the pulmonary circulation. Endothelial cell dysfunction predisposes the vessel wall to vasoconstriction, leucocyte adherence, platelet activation, mitogenesis, thrombosis, impaired coagulation and vascular inflammation [40]. In addition, endothelial function testing may serve as a

useful biomarker of pulmonary circulatory function [41]. Bocchi and colleagues [42] reported sudden development of pulmonary oedema in patients with severe congestive heart failure treated with iNO, which was most probably due to a sudden increase in left atrial filling caused by pulmonary vasodilatation rather than a direct negative inotropic effect of iNO [43]. iNO may be used as a test for pulmonary vasoreactivity before cardiac transplantation.

Expert recommendations:

- Response to iNO treatment may identify patients still suitable for heart or heart/lung transplantation or to help to identify patients with congenital heart disease suitable for further intervention.
- iNO decreases PVR but potentially increases left ventricular preload which may be dangerous in left ventricular dysfunction. In the presence of left heart dysfunction it is increasingly recognised that iNO testing should be performed only after optimising heart failure therapy immediately prior to testing.
- iNO testing is useful to demonstrate the remaining reactivity of the precapillary component of postcapillary pulmonary hypertension. Reduction in PAP/PVR shown by iNO testing does not imply that long-term iNO therapy should be instituted

Pulmonary arterial hypertension

Pulmonary arterial hypertension, previously known as primary pulmonary hypertension, is a rapidly progressive disease of the pulmonary vasculature with consecutive right heart failure [44]. Prognosis may be improved in adult patients responding to calcium channel blocker and/or anticoagulation [45] and in patients treated with continuous prostacyclin [46]. The response to acute vasodilator testing has important implications both for the choice of therapy and for prognosis [28, 47, 48]. For example, only patients with a positive response to acute vasodilator testing remain suitable for long-term treatment with calcium channel blocker. Those who do not are treated with long-term intravenous epoprostenol. Today intravenous epoprostenol adenosine or iNO is recommended for acute vasodilator testing in adults, defined as a decrease in the mean PAP of at least 10 mmHg to less than 40 mmHg with an increased or unchanged cardiac output [49]. iNO has been shown to be superior to prostacyclin for this use [50] whereas aerosolised iloprost is more effective in improving oxygenation and haemodynamics in patients with primary pulmonary hypertension [51]. Combining oxygen and iNO can identify a greater number of appropriate candidates for corrective cardiac surgery or transplantation during preoperative testing [52].

Expert recommendations:

- iNO is a potent selective pulmonary vasodilator which used alone or in combination with other vasodilators may be useful in revealing the extent of reversibility (if any) in selected patients with pulmonary arterial hypertension.
- iNO clearly identifies responders suitable for long-term treatment with calcium channel blockers.
- iNO dose recommended for acute vasodilator testing should be 10–20 ppm. iNO does not have relevant adverse effects during short-term acute testing.
- iNO combined with additional O_2 may lead to further pulmonary vasodilatation.
- There is insufficient data to recommend iNO for long-term therapy of pulmonary arterial hypertension.

Medical conditions complicated by pulmonary arterial hypertension

Thromboembolism

iNO, which decreases PAP [2], is likely to unload the right ventricle in pulmonary embolism and chronic thromboembolic pulmonary hypertension. Furthermore, its platelet anti-aggregate property could prove beneficial [53, 54]. iNO for severe pulmonary embolism or chronic thromboembolic pulmonary hypertension has not been investigated in randomised controlled trials. Animal studies have shown that iNO decreases PVR [55] and platelet aggregation [54]. Use of iNO has been reported in case reports from patients with massive pulmonary embolism leading to cardiogenic shock. iNO decreased right ventricular afterload, improved cardiac output (CO) and increased arterial oxygen content [56, 57, 58]. After thrombendarterectomy iNO significantly improved arterial oxygenation but had a negligible effect on PAP. In one case postoperative hypotension progressively reversed with iNO [59].

Expert recommendations:

- There are no controlled trials which support the routine use of iNO in patients with thromboembolic disease.
- iNO might be of benefit in selected patients with thromboembolic disease who have severe right ventricular failure and/or severe hypoxaemia.

Sickle-cell disease

Stiffened red blood cells lead to impaired blood flow in the microcirculation, veno-occlusive phenomena, inflammation and haemolysis [60]. Given the depletion of endogenous NO by cell-free haemoglobin iNO may restore endothelial homeostasis by enhancing pulmonary vasodilatation and inactivation of cell-free haemoglobin.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.