Practical Approach to Pediatric Intensive Care

Editor

Praveen Khilnani
MD FAAP FCCM (USA)
Senior Consultant
Pediatric Intensivist and Pulmonologist
Apollo Centre for Advanced Pediatrics
IP Apollo Hospitals, New Delhi

Associate Editor

Rajiv Uttam
MRCP (UK)
Senior Consultant
Pediatric Intensivist and Pulmonologist
IP Apollo Hospitals, New Delhi

Editorial Board

Vinay K Aggarwal
Sandeep Chopra
RK Mani
Rajesh Chawla
Yogesh Gautam

Editorial Assistant

Kavita Sharma

Hodder Arnold
A MEMBER OF THE HODDER HEADLINE GROUP

First published in India in 2004 by Jaypee Brothers, Medical Publishers (P) Ltd,
EMCA House, 23/23B Ansari Road, Daryaganj, New Delhi 110 002, India

First published in the United Kingdom in 2005 by Hodder Arnold,
an imprint of Hodder Education and a member of the Hodder Headline Group,
338 Euston Road, London NW1 3BH

http://www.hoddereducation.com

This UK edition distributed in the United States of America by
Oxford University Press Inc.,
198 Madison Avenue, New York, NY10016
Oxford is a registered trademark of Oxford University Press

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN-10 [normal] 0 340 90582 4
ISBN-13 978 0 340 90582 1

1 2 3 4 5 6 7 8 9 10

Typeset at JPBMP typesetting unit
Printed at Gopsons Papers Ltd., Sector 60, Noida

What do you think about this book? Or any other Hodder Arnold title?
Please send your comments to www.hoddereducation.com

43

Rajiv Uttam, Reeta Singh

Inhaled Nitric Oxide (INO)

Since the discovery of endothelium derived relaxing factor and its subsequent identification as nitric oxide,[1] recognition of its potent vasodilator properties and its unique ability to be delivered as a gas to the lung, inhaled nitric oxide (INO) has become an exciting new treatment for several disorders, characterized by pulmonary hypertension and pulmonary vasoregulation.

Endogenous NO

NO is produced by L- argine by a family of enzymes called nitric oxide synthase (NOS) which exist in constitutive and inducible forms.[2] Constitutive NOS is always present, is calcium dependent and produce low levels of NO intermittently, which is a major endogenous regulator of vascular tone. In contrast the inducible NOS is activated by cytokines and endotoxins, once induced it produces large amounts of NO. The pathophysiological role of this nitric oxide is evident in a variety of disease including septic shock, asthma, and reperfusion endogenous injury, etc. (Fig. 43.2).

Clinical Pharmacology of INO

NO binds rapidly to iron in haem moiety of proteins such as guanyl cyclase, hemoglobin and electron transport chain. Activation of guanyl cyclase results in production of cyclic guanosine monophosphate (cGMP) which leads to vasodilation, and relaxation of smooth muscles of cardiovascular, respiratory, gastrointestinal and genitourinary system. Because it binds to haem, it gets inactivated in blood and does not enter systemic circulation. This accounts for selective effect of INO on pulmonary circulation.[3]

INO appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios towards regions with normal ratios.

Persistent pulmonary hypertension of newborns (PPHN).

At birth, the pulmonary circulation changes dramatically. Pulmonary blood flow increases 8-10 fold and pulmonary arterial pressure decrease to less than half systemic levels in the first 24 hours of life.[4, 5] Although release of vasoactive mediators, increased oxygenation, establishment of an airliquid interface have been shown to play a central role in transition of pulmonary circulation,[6] if postnatal adaption of pulmonary circulation does not occur, a clinical syndrome, PPHN results.

It is characterized by extrapulmonary right to left shunting across the foramen ovale and ductus arteriosus, pulmonary hypertension and severe central hypoxemia, that is not responsive to high concentrations of inspired oxygen. PPHN is often complicated by parenchymal lung injury, such as meconium aspiration, pneumonia and surfactant deficiency, further compromising efforts to improve oxygenation.

When other therapies fail neonates are treated with extracorporeal membrane oxygenation.[7] This therapy improves survival in neonates with respiratory failure, but its administration is labor-intensive and costly and

necessitates large amounts of blood products. The mortality rate in neonates treated with extracorporeal membrane oxygenation is 15-20 percent and 10-20 percent of the neonates, whose survive have substantial developmental delay.[8] Effective treatment has been limited by the absence of a selective pulmonary vasodilators. Intravenous vasodilator agents can cause non-selective vasodilation, resulting in worsening of intrapulmonary shunting and systemic Hypotension.[9] Neonates with PPHN might be hypoxemic from a combination of intrapulmonary shunting secondary to parenchymal lung disease and extrapulmonary shunting secondary to increased pulmonary vascular resistance with or without myocardial dysfunction. INO (Fig. 43.1) acutely improves oxygenation in most- term and near term neonates by reversal of extrapulmonary right to left shunting of blood secondary to pulmonary vasodilation and also improves VQ matching secondary to redistribution of pulmonary blood flow to well ventilated lung regions.[4,5]

Clinical trials indicate that need for ECMO is diminished by INO[10] (Fig. 43.4). Responsiveness to INO in these patients is dependent on the primary disease or physiologic cause of hypoxemia, with the best response rates observed in patients with idiopathic PPHN.[11] In neonates with severe parenchymal lung disease, responsiveness to INO can be improved by therapies that enhance lung recruitment, especially during high frequency oscillatory ventilation (HFOV). The combination of HFOV and INO can be efficacious in patients who fail to respond to either therapy alone.[12]

Doses

Experimental data support the notion that the minimally effective doses of INO should be used. At high concentrations INO can react with oxygen to form dioxygen nitrite (NOO), which has been shown to cause surfactant destruction.

The recommended dose is 10 to 20 part per million (ppm).[10,13] When dose is increased to 80 ppm, if the improvement in PaO_2 was less than 20 mmHg, increased incidence of methemoglobinemia occurs without any increase in PaO_2.[14] At the same time administration of a subtherapeutic (2 ppm) dose of INO may adversely affect the clinical response to a subsequent therapeutic doses of INO.[15] Clark et al used INO at 20 ppm for 24 hours followed by 5 ppm for next 96 hours and requirement for subsequent ECMO was reduced.[16] Figure 43.1 shows the Nitric oxide delivery setup with dial regulator of PPM dose of INO.

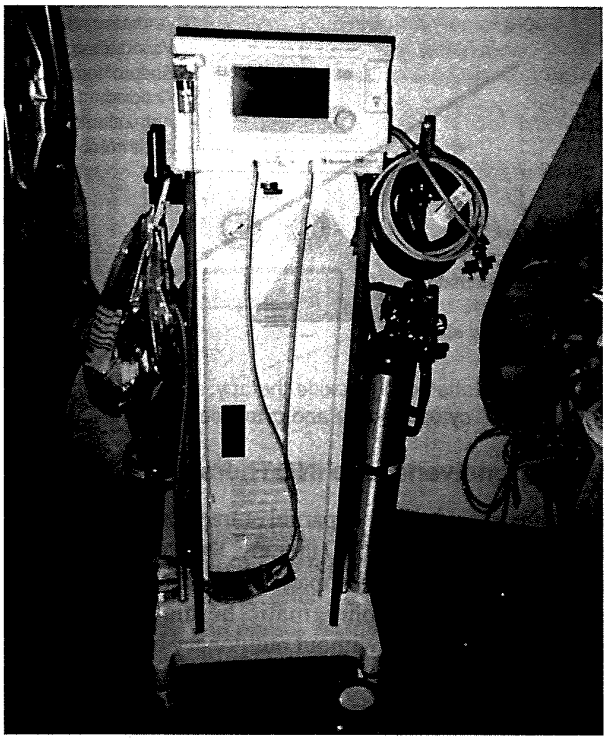

Fig. 43.1: Nitric oxide delivery system

Duration of Treatment

No controlled data are available to determine the maximal safe duration of INO therapy. In multicenterclinical trials of INO, the typical duration of INO has been less than 5 days, which parallels the clinical resolution of PPHN, 16 If INO is required for longer than 5 days, other causes like pulmonary hypoplasia must be excluded. INO can be discontinued if the fraction of inspired oxygen is less than 0.6 and PaO_2 is more than 60 without evidence of rebound pulmonary hypertension or an increase in FiO_2 more than 15 percent after INO withdrawal.[13]

Weaning

Sudden withdrawal can be associated with life-threatening elevation of pulmonary vascular resistance, profound desaturation and systemic hypotension caused by decreased cardiac output. Exogenous NO may down-regulate endogenous NO production, which contribute to severity of pulmonary hypertension after INO withdrawal. To avoid these rebound effects numerous approaches have been used and INO should be reduced in a step wise fashion.[17]

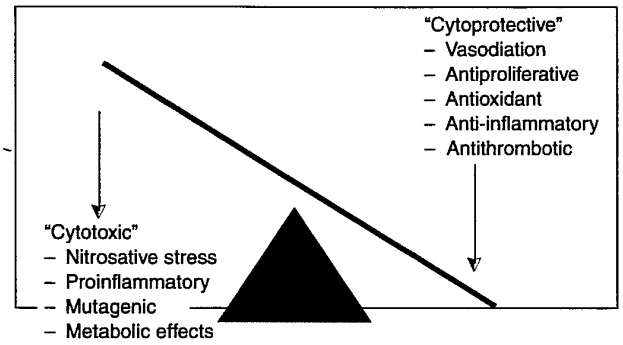

Fig. 43.2: Inhaled nitric oxide therapy: a balance between cytoprotective and cytotoxic effects

Unresponsiveness to INO Therapy in PPHN

Many neonates have only partial or transient improvement in oxygenation during INO therapy. INO tends to increase PaO_2 more readily in idiopathic PPHN than in patients with congenital diaphragmatic hernia.[17] It's use in hypoxemic neonates without pulmonary hypertension.

Unresponsiveness to INO is commonly seen in following situations:

1. INO use in hypoxemic neonates without pulmonary hypertension.
2. Inability to deliver NO due to poor lung inflation.
3. Unsuspected or missed anatomic cardiovascular lesions
4. Alveolar capillary dysplasia is a very rare cause for PPHN and is characterized by a developmental abnormality in the pulmonary vasculature. Despite aggressive therapy with NO and ECMO survival is rare.[19]
5. Advanced vascular remodeling or severe lung hypoplasia.

In some cases, INO therapy reverses right to left shunting but hypoxemia may persist due to intrapulmonary shunt, suggesting underlying disease. In these situations changes in conventional ventilator management or HFOV can further improve PaO2 by improving lung inflation and may decrease the need for ECMO.[11] In many cases greater improvement is achieved with INO in combination with either therapy alone.[19]

Monitoring

Methemoglobinemia occurs after exposure to high concentration of INO. This complication has not been reported at lower doses. However, because methemoglobin reductase deficiency may occur unpredictably, it is reasonable to measure methemoglobin level by co-oximetry within four hours of starting INO therapy and subsequently at 24 hour intervals.

Transport with INO

Although INO therapy is often effective, 30-40 percent of sick newborns do not have sustained improvement in oxygenation and hemodynamics after the initiation of therapy often require transport to ECMO center. Abrupt discontinuation may be dangerous and availability of NO during transport is vital.[20]

Long term outcomes of neonates treated by INO has been studied widely, preliminary studies show no excess adverse health or neurodevelopmental outcome among PPHN survivors treated with NO compared with those treated with conventional therapies.[21]

The premature newborns-uncertainities about use of INO.

In the preterm neonate, severe respiratory failure is, in large part, the result of surfacrant deficiency. Although treatment with exogenous surfactant can cause dramatic improvements in oxygenation. Some have suboptimal responses. Low dose INO causes immediate improvement in oxygenation in preterms.[22] It may be effective as a lung specific anti-inflammatory therapy to decrease lung neutrophil accumulation and the associated inflammatory injury and subsequent decreased incidence of chronic lung disease. INO is shown to impair platelet function in vitro, but clinical trials have not shown increased incidence of ICH,[23] and a trend in the reduced risk and severity of chronic lung disease among INO treated prematures is the main working hypothesis for most of the ongoing trials.[24]

INO in Chronic Lung Disease

Long term ambulatory use of NO via nasal canula causes decrease in PVR and improved oxygenation in adults with stable chronic obstructive pulmonary disease. It's efficacy is not proved in interstitial pulmonary fibrosis, although transient improvement occurs. It can cause bronchodilation, but not as effectively as beta agonists.[25]

INO Therapy in Children with ARDS

The management of ARDS continues to be a challenge. Clinically ARDS is characterized by pulmonary hypertension and profound hypoxemia, abnormal vasoreactivity and increased permeability. Unlike PPHN extrapulmonary shunt does not occur in ARDS and hypoxemia is primarily due to intrapulmonary shunt (perfusion of lung

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.