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ORIGINAL

UK guidelines for the use of inhaled nitric oxide therapy in adult ICUs*

B.H. Cuthbertson
P. Dellinger
O.J. Dyar
T.E. Evans
T. Higenbottam
R. Latimer
D. Payen
S.A. Stott
N.R. Webster
J.D. Young

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B.H. Cuthbertson (✉) · S. Stott · N.R. Webster
Anaesthesia and Intensive Care, Institute of Medical Sciences, Medical School, University of Aberdeen, Aberdeen AB25, Scotland
Fax: + 44 (1224) 273 066
e-mail: b.h.cuthbertson@abdn.ac.uk

J.D. Young · O.J. Dyar
Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford, UK

T.E. Evans
Unit of Critical Care, Royal Brompton Hospital, Sydney Street, London, UK

T. Higenbottam
Department of Pharmacology, University of Sheffield, Sheffield, UK

R. Latimer
Department of Cardiothoracic Anaesthesia, Papworth Hospital, Cambridge, UK

D. Payen
Department d'Anésthésiologie Réanimation-Smur, Hôpital Lariboisière, Paris, Cedex 10, France

P. Dellinger
University of Missouri, Columbia, MO 65212, USA

Abstract *Objective:* Although unlicensed, inhaled nitric oxide (NO) therapy is now widely used in the United Kingdom. Our aim was to produce guidelines for the clinical application of inhaled NO in adult intensive care practice, based upon the current level of published information.
Methods: The published data regarding the use of inhaled NO in the acute respiratory distress syndrome and right-sided cardiac failure was presented, analysed and discussed. Recommendations based on these data as well as on current experience in the United Kingdom were formulated.
Design: An expert group comprising intensive care specialists from within the United Kingdom, representatives from the European Society of Intensive Care Medicine and the Society of Critical Care Medicine and individuals from the Departments of Health and Industry related to the field was assembled.
Results: United Kingdom guidelines for the indications, contraindications, dose, delivery, monitoring and

With support of the Consensus Conference Group:
Dr. N. Appleyard, Consultant, Intensive Therapy Unit, Northern General Hospital, Sheffield; Dr. I. Armstrong, Consultant, Intensive Therapy Unit, Royal Infirmary of Edinburgh, Edinburgh; Dr. S. Baudouin, Consultant, ITU, Royal Victoria Infirmary, Newcastle; Dr. R. Beale, Consultant, Intensive Therapy Unit, Guy's Hospital, London; Dr. A. Bodenham, Consultant, Intensive Therapy Unit, Leeds General Infirmary, Leeds; Mr. C. Gray, Medical Devices Agency, London; Dr. S. Brett, Senior Registrar, Thoracic Medicine Unit, The Royal Brompton Hospital, London; Dr. T. Clutton-Brock, Consultant, Adult Intensive Therapy Unit, Queen Elizabeth Hospital, Birmingham; Dr. S. Dean, Consultant, Intensive Therapy Unit, St. James University Hospital, Leeds; Dr. T. Gould, Consultant, Intensive Therapy Unit, Bristol Royal Infirmary, Bristol; Dr. I. Grant, Consultant, Intensive Therapy Unit, Western General Hospital, Edinburgh; Dr. K. Kelly, Senior Registrar, Intensive Therapy Unit, Western General Hospital, Edinburgh; Dr. P. Lawler, Consultant, Intensive Therapy Unit, South Cleveland Hospital, Middlesborough; Dr. K. Lowry, Consultant, Intensive Therapy Unit, Belfast, Grosvenor Road, Belfast; Dr. D. Macrae, Consultant, Cardiac Intensive Therapy Unit, Hospital for Sick Children, Great Ormond Street, London; Mr. M. McGovern, Senior Medical Officer, Department of Health, London; Dr. N. Moore, Consultant, Groby Road Hospital, Leicester; Dr. A. Oduro, Cardiac Intensive Therapy Unit, Papworth Hospital, Cambridge; Mr. D. Peel, British Standards Institution, London; Dr. A. Petros, Consultant, Paediatric ITU, The Royal Brompton Hospital, London.
Authors affiliations: Drs. Latimer and Young and Professors' Evans, Higenbottam and Webster sit on the nitric oxide advisory panel to Ohmeda. Drs. Cuthbertson and Young and Professor Webster were investigators for the AGA Ab European inhaled nitric oxide in ALI study.

scavenging of inhaled NO therapy were produced.
Conclusions: The need for additional quality research to establish evidence of efficacy and safety was emphasized. The guidelines are designed to act within the context of current practice and knowledge and should be revised as further data emerge.

Key words Inhaled nitric oxide · ARDS · Acute respiratory failure · Hypoxaemia · Pulmonary hypertension · Practice guidelines

Introduction

In recent years the use of inhaled nitric oxide (NO) therapy in adult intensive care units (ICUs) in the United Kingdom (UK) has become commonplace [1]. However, controlled studies establishing the efficacy of inhaled NO in adults are awaited, and inhaled NO is still an unlicensed therapy. Moreover, in the UK, pleas for caution regarding its use have emerged from influential sources including the Committee on Safety of Medicines [2–5].

The widespread and variable use of inhaled NO in the ICU setting in the UK suggests a clear need for national guidelines. It is recognised that guidelines do not replace clinical judgement, but rather provide a safe framework within which such judgement can be exercised. Secondly, the emphasis on the unlicensed status of this treatment and the encouragement of well designed research in this field are stressed.

Methods

From a previous survey [1], intensive care specialists using inhaled NO therapy were identified and were invited to attend a one day conference in London on 10 June 1997. A representative of the Society for Critical Care Medicine and of the European Society for Intensive Care Medicine with extensive experience with the use of inhaled NO attended on behalf of their respective societies. Representatives of the Department of Health for England and Wales, British Standards Institution and Medical Devices Agency and representatives of industry also attended as observers.

A review of current literature with emphasis on evidence to support practice in administering inhaled NO therapy in adults was presented. Thirty papers on the use of NO in the acute respiratory distress syndrome (ARDS) were reviewed and the data analysed with respect to the effects on oxygenation and pulmonary vascular resistance. The 11 papers in which dose-response data were available were analysed in detail. Evidence was examined for the use of inhaled NO as a pulmonary vasodilator and the delivery and monitoring of inhaled NO therapy. The pharmacology of inhaled NO was discussed and surveys revealing current practice for the use of inhaled NO in the UK, Europe and North America were presented. A second session involved open discussion of the indications, dose, delivery, monitoring and scavenging of inhaled NO therapy with the aim of producing UK guidelines within the adult ICU setting.

Results

Indications

Background and controversies in ARDS

The most common indication for inhaled NO is acute lung injury (ALI)/ARDS in the UK (defined according to the American/European Consensus Conference definitions) [1]. Significant evidence suggests that inhaled NO improves oxygenation and reduces pulmonary artery pressure in the majority patients with ALI/ARDS [6–8]. As yet, no prospective, randomised, controlled trials have demonstrate improved outcome for this indication. The results of two randomised trials of inhaled NO therapy in ALI have recently been presented. In a double-blind study of 19 consecutive patients randomised to inhaled NO or placebo it was demonstrated that inhaled NO may cause a delayed improvement in oxygenation not related to baseline pulmonary vascular resistance. It did not demonstrate any improvement in outcome [9]. A further randomised study of 260 patients with ALI failed to demonstrate substantial clinical benefit from inhaled NO [10].

Recommendations in ARDS

- The clinical use of inhaled NO therapy in ARDS, as defined by the American-European Consensus Conference on ALI/ARDS [11], should be limited to patients who are *optimally ventilated,* with optimal positive end-expiratory pressure, inverse ratio ventilation and positional manoeuvres as appropriate. Inhaled NO should be introduced if such patients have a partial pressure of oxygen in arterial blood (PaO_2) of < 12 kPa with a fractional inspired oxygen of 1.0.

Controversies/background for right-sided cardiac failure (RSCF)

The use of inhaled NO in patients with RSCF is also growing [1, 12–14]. RSCF can be defined as severe, acute, right ventricular dysfunction associated with pulmonary hypertension (mean pulmonary artery pressure > 24 mmHg, transpulmonary gradient > 15 and pulmonary vascular resistance > 400 dyne·s·cm^{-5}) and decreased cardiac index unresponsive to conventional

therapy. It may present during heart or lung transplantation or surgery for pulmonary embolus or severe mitral valve disease. Inhaled NO has been used in RSCF to decrease pulmonary vascular resistance and therefore right heart afterload without reducing systemic arterial pressure, which is essential for the maintenance of coronary perfusion to the right ventricle. Although there have been numerous favourable case reports, there have been no prospective controlled studies to date [12–14].

By reduction of right ventricular afterload the use of inhaled NO in biventricular failure may be associated with a increase in left ventricular preload, leading to further left ventricular dysfunction [15–18].

Recommendations in RSCF

- Inhaled NO at 20–40 ppm may benefit patients with RSCF. It should be combined with adequate support of the systemic circulation as necessary with inotropic agents and/or intra-aortic balloon pumping and possibly intravenous vasoconstrictors to maintain coronary flow to the right ventricle.

Dose

Background and controversies

The dose range used for inhaled NO therapy has changed as further investigations of dose–response relationships are published [8, 19, 20]. The dose required for the reduction of pulmonary arterial pressure seems to be significantly higher than that required to improve oxygenation in ARDS [7]. The effect of inhaled NO on pulmonary hypertension in patients with ARDS is not clear, as these effects are both modest and variable. Currently, published data suggest the majority of patients will have a maximal improvement in oxygenation with doses of 20 ppm or less, although rarely 40 ppm is required [21, 22].

Recommendations

- A dose-response test should be performed at the time of introduction of NO therapy in ARDS. We suggest an initial dose of 20 ppm for 30 min. Regardless of response, this is then reduced to 10 ppm and 5 ppm for a further 30 min at each dose and then to 0 ppm, followed by continual delivery of the lowest effective dose (see below). It should be remembered that the maximal effect of inhaled NO could take up to 4 h to occur in an optimally ventilated patient and that patients may have a response at that time that was not present at 30 min [21, 22].
- A 20 % rise in PaO_2 during the dose response test is recommended as the minimum response to continue use of inhaled NO therapy in ARDS. Due to the modest and variable effect of inhaled NO on pulmonary hypertension in ARDS, this parameter should not be used as a marker of response to treatment.
- If the dose response test dose not produce a positive response, an upward titration to a maximum dose of 40 ppm for 30 minutes is recommended [7, 23].
- With a PaO_2 response below this threshold, a dose-response test can be repeated daily while the patient fits the stated criteria for the introduction of therapy.
- The minimum effective dose of inhaled NO that brings about the maximal rise in PaO_2 should be used for continuous administration. Daily dose titration should be performed to ascertain the minimum effective dose and to ensure a minimum 20 % PaO_2 rise is still achieved.
- The dose range for the treatment of RSCF is 20–40 ppm

Delivery

Background and controversies

Inhaled NO may be delivered by either continuous injection, or using synchronised inspiratory injection systems. The latter should be considered as the optimal method, as it allows servo-controlled injection of the nitric oxide/nitrogen mixture (NO/N_2) into the inspiratory limb only during inspiration. This should reduce the bolus effect seen with continuous injection systems and may reduce nitrogen dioxide (NO_2) formation because of decreased NO and oxygen mixing time [24–27]. The continuous injection system uses a calibrated flow meter with stainless steel needle valves to deliver a continuous flow of NO/N_2 throughout the respiratory cycle [24]. Medical grade NO/N_2 is available in cylinders (ISO standard green shoulder, BOC standard gold body) with a stainless steel pressure regulator or can be piped through stainless steel medical gas piping. PIN indexed connectors are currently being developed for NO cylinders (ISO 407) and product specific outlet points are being developed for piped NO (HTM 2022).

Recommendations

- Continuous or synchronised inspiratory injection devices are appropriate for the delivery of inhaled NO.
- A calibrated flow meter with stainless steel needle valves must be used in delivering a continuous flow of NO/N_2.
- NO/N_2 mixture should be delivered into the ventilator circuit as close to the ventilator as possible. The use

of a mixing device in the inspiratory limb will reduce delivery of high peak gas concentrations and is thus desirable.
- The delivery system should be flushed thoroughly before use.
- The position of the humidifier is probably unimportant.
- Connectors and pressure regulators must be stainless steel.
- Medical grade NO/N_2 cylinders or piped medical gas must reach British Standards Institution standards for medical gases. Cylinders must be secured to avoid staff injury or cylinder damage.

Monitoring

Background and controversies

NO can be measured in gas mixtures using either chemiluminescence or electrochemical analysers. The latter can monitor both NO and NO_2 levels to an accuracy of at least 1 ppm. Both are considered adequate for clinical use. Chemiluminescence analysers monitor NO, NO_2 and other higher oxides of nitrogen to an accuracy of a few parts per billion. NO and NO_2 monitors, when placed at the distal end of the inspiratory limb at the Y-piece, give information about the delivered concentration of NO in the inspired gas, as well as on the formation and delivery of the potentially toxic NO_2.

Nitric oxide and NO_2 levels in the expiratory limb of the circuit provide little additional useful information on absorbed NO and NO_2 nor reflect environmental NO_2 levels [27, 28].

Doses of NO far greater than those used clinically are not expected to cause significant methaemoglobinaemia in adults [29]. There may be an increased risk in paediatric patients or in those with methaemoglobin reductase deficiency [30]. Only two case reports of clinically significant methaemoglobinaemia during inhaled NO therapy have been published. Both were in neonates, one of which was given an inadvertent overdose [30, 31]. Inhaled NO has now been used in many thousands of patients in doses recommended in this document without reports of clinically significant methaemoglobinaemia. Since the production of methaemoglobin at the doses recommended follows first-order kinetics, should methaemoglobinaemia occur it will be in the first few hours after starting treatment or after an upward dose titration.

Recommendations

- NO and NO_2 should be monitored continuously at the inspiratory side of the Y-piece as close to the patient as possible.
- Electrochemical monitors are considered sufficiently accurate and all monitors should be calibrated and maintained according to manufacturers' guidelines.
- Expiratory NO and NO_2 monitoring is unnecessary.
- Routine measurement of methaemoglobin should be performed prior to and at time 1 and 6 h following the introduction of inhaled NO, daily thereafter and repeated following increases in dose.

Patient and environmental exposure

Background and controversies

Environmental NO and NO_2 monitoring in the ICU can be performed using electrochemical or chemiluminescence monitors above the patient, the site of maximal environmental pollution. Control of Substances Hazardous to Health (COSHH) guidelines suggest that environmental NO levels should not exceed a time-weighted average (TWA) of 25 ppm NO over an 8-h epoch [32]. Levels of 1 ppm NO are the highest recorded in a clinical environment during the use of inhaled NO [7, 24]. These COSHH maximum exposure levels are below the maximum dose suggested for inhaled NO in ARDS and pulmonary hypertension. COSHH also suggest environmental NO_2 levels should not exceed a TWA of 3 ppm NO_2 over an 8-h epoch [32]. The maximal time that a patient can be exposed to inhaled NO therapy is unclear. Basic safety data exist up to 28 days, and there are reports of administration for up to 53 days without untoward clinical effects [33, 34]. Further data are awaited on the potential role of NO and NO_2 in mutagenesis [35].

Recommendations

- Maximal dose of inhaled NO 40 ppm (if failure to respond to lower doses).
- Maximum environmental NO concentration of 25 ppm over 8-h TWA.
- Maximum inhaled and environmental NO_2 concentration of 3 ppm over 8-h TWA.
- With adequate ventilation (see below), at the doses recommended, environmental monitoring is unnecessary.
- The minimum effective dose of NO should be used.
- NO therapy should be weaned as early as possible.
- No time limit is set for total exposure time.

Table 1 UK guidelines for the use of inhaled nitric oxide in adult ICUs (*ARDS* acute respiratory distress syndrome, *PaO_2* partial pressure of oxygen in arterial blood, *F_IO_2* fractional inspired oxygen, *RSCF* right-sided cardiac failure, *MPAP* mean pulmonary artery pressure, *TPG* transpulmonary gradient, *PVR* pulmonary vascular resistance, *NO* nitric oxide, *NO_2* nitrogen dioxide, *TWA* time-weighted average, *LVF* left ventricular failure)

Indications	1. Severe ARDS Optimally ventilated PaO_2 12 kPa on F_IO_2 1.0 2. Right-sided cardiac failure Significant RSCF: MPAP > 24 mm Hg, TPG > 15, PVR > 400 dynes-scm Must support systemic circulation: inotropes, etc. Beware adverse effects on the left ventricle
Dose	1. Maximum dose 40 ppm 2. Dose titration: 20–10–5–0 ppm for 30 min 3. A 20 % rise in PaO_2 on F_IO_2 1.0 required 4. Use minimum effective dose 5. RSCF: 20–40 ppm
Delivery	1. Continuous injection or synchronised inspiratory injection devices suitable with injection near to ventilator 2. Medical NO/N_2 gas mixture 3. Stainless steel pressure regulators, connectors and flow meter needle valves 4. Calibrated flow meter 5. Position of humidifier unimportant
Monitoring	1. Continuous inspiratory NO and NO_2 at Y-piece 2. Electrochemical monitoring adequate 3. Monitors correctly calibrated 4. Methaemoglobin levels: time 0, 1 and 6 h then daily 5. Expiratory monitoring not necessary
Exposure	1. Maximum inhaled NO < 40 ppm 2. Maximum inhaled NO_2 < 3 ppm 3. Maximum environmental NO < 25 ppm for 8-h TWA 4. Maximum environmental NO_2 < 3 ppm for 8-h TWA 5. Minimum effective dose for shortest periods advised (safety data up to 28 days available)
Scavenging	1. Not required in well ventilated unit 2. Environmental monitoring required in units with less than 10–12 air changes per hour and scavenging if exposure limits exceeded
Scavenging techniques	1. Filtration 2. Active scavenging 3. Passive scavenging
Contraindications	Absolute: methaemoglobinaemia Relative: bleeding diathesis, intracranial haemorrhage, severe LVF

Scavenging

Background and controversies

Scavenging of expired NO and NO_2 should be carried out (when appropriate) in the expiratory limb. Active scavenging systems represent ideal methods for both gases, but are expensive and are not widely available in the ICU setting [1]. Passive scavenging is effective and can be achieved by venting expiratory gas into the wall suction or out of a window. Soda-lime containing potassium permanganate is also effective, although possibly due to the reaction of the indicator and not the soda-lime [36, 37]. Industrial absorbers also scavenge NO and NO_2 [36]. The National Health Services' estate have stated that scavenging of inhaled NO therapy is not required in units that meet their guidelines for ventilation in health care premises (10–12 air changes per hour) [38].

Recommendations

- If a unit meets NHS estate guidelines [38] for ventilation within an ICU, expiratory NO and NO_2 scavenging is unnecessary.
- Units not meeting the NHS estate guidelines should monitor and/or scavenge environmental NO and NO_2, and must scavenge if the levels are above the stated environmental exposure limits (see above).
- Expiratory scavenging using filtration, active or passive scavenging is appropriate when required.

Discontinuation of inhaled NO therapy

Background and controversies

There are anecdotal reports of severe rebound hypoxaemia and pulmonary hypertension developing following withdrawal of inhaled NO therapy [39–43]. Placebo controlled data, however, do not support this as a significant clinical problem during downward titration of inhaled NO therapy [21, 22]. When used as a rescue therapy in very severe disease, however, accidental withdrawal or supply failure could have severe adverse consequences. Back-up systems in case of supply failure are therefore advisable. Following patient improvement, slow withdrawal of treatment in an incremental fashion is advisable with close monitoring of pulmonary vascular dynamics and oxygenation variables.

Recommendations

- Avoidance of accidental discontinuation or failure of supply of inhaled NO.
- Back-up NO supply and delivery equipment should be available for all patients receiving such therapy. Equipment for monitoring NO delivery should be replaced as a matter of urgency.
- Slow incremental weaning from inhaled NO at end of treatment with close monitoring of pulmonary dynamics and oxygenation variables.

Contraindications to the use of inhaled NO

Background and controversies

Patients with congenital or acquired methaemoglobin reductase deficiency are at high risk if exposed to clinical concentrations of inhaled NO [29, 30, 44]. Alterations in platelet function and bleeding time have been reported in animal and human models on exposure to inhaled NO [45, 46]. The clinical significance of this remains unclear but inhaled NO should probably be used with caution in patients with bleeding diathesis and intracranial haemorrhage [47]. Reports of worsening left ventricular failure (LVF) during inhaled NO suggests that caution should be exercised when using inhaled NO therapy in New York Heart Association grade III and IV LVF patients [15, 18].

Recommendations

- Absolute contraindications: methaemoglobinaemia reductase deficiency (congenital or acquired).
- Relative contraindications: bleeding diathesis, intracranial haemorrhage, severe left ventricular failure (NYHA grade III or IV).

Conclusions

These guidelines were compiled by a group of ICU practitioners from within the UK with advice from investigators in Europe and the United States. All contributors have knowledge in the use of inhaled NO therapy or represent regulatory authorities (Table 1). The guidelines are designed to allow the safe use of this therapy outside clinical investigations in the adult ICU environment until randomised, controlled trials have demonstrated its safety and efficacy. It must be remembered that there are potential disadvantages in the use of inhaled NO, which remains an unlicensed therapy in the UK. We hope that these guidelines will encourage the development of European and North American consensus guidelines regarding inhaled NO therapy to allow greater standardisation for its use.

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