Use of inhaled nitric oxide in British intensive therapy units

B. H. CUTHBERTSON, S. STOTT AND N. R. WEBSTER

Summary

The use of inhaled nitric oxide in the critically ill has increased significantly over the past few years but little published information exists on standards for current practice. Sixty-four intensive therapy units in the UK were surveyed by questionnaire from which 54 (84.4%) satisfactory replies were received. We present the survey results and put forward recommendations based on current literature and our own clinical experience for the safe use of inhaled nitric oxide. (Br. J. Anaesth. 1997; 78: 696–700).

Key words


The use of inhaled nitric oxide (NO) in intensive therapy units (ITU) in the UK has increased significantly over the past few years, despite the lack of evidence that it improves outcome.1–4 There are currently no published recommendations for delivery, monitoring and scavenging of what is potentially a dangerous gas. In light of recent reports indicating the potential dangers of this therapy to both patients and staff,5–8 we felt information was required on current British practice. In addition, we feel there is a need for recommendations regarding the safe administration and use of inhaled nitric oxide. We therefore sought to establish current practice of inhaled nitric oxide in the ITU and to compile recommendations for its safe use.

Results

Sixty-four units were identified and completed replies were received from 54 (84.4%) after two mailings. Of these, 35 were adult units with 10 performing cardiac surgery, another eight were mixed adult and paediatric ITU and 11 were paediatric ITU. Within these units there was a mean of 8.5 (range 2–22) general beds, 8.0 (1–22) paediatric beds and 8.0 (3–12) cardiac beds.

INDICATIONS

The most frequent indications for the use of inhaled nitric oxide are shown in table 1. Other less frequent indications for its use included weaning from extracorporeal membrane oxygenation (two units), ventricular off-loading in cardiac failure (two) and bronchiolitis (one). Using the American–European consensus conference definitions (appendix 2),9 we were able to establish the disease severity for which units introduce inhaled nitric oxide therapy into clinical management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (table 2). Of the 54 units which replied, the mean period that these units had used inhaled nitric oxide was 2.1 (0.1–6.0) yr. Twenty-seven units (50.0%) were carrying out research into some aspect of inhaled nitric oxide therapy and five (9.3%) used inhaled nitric oxide only as part of a study.

Table 1  Indications for use of inhaled nitric oxide therapy (%).

<table>
<thead>
<tr>
<th>Indications</th>
<th>Incidence (%)</th>
</tr>
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<tbody>
<tr>
<td>ALI/ARDS</td>
<td>91</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>70</td>
</tr>
<tr>
<td>Paediatric cardiac surgery</td>
<td>24</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>18</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
</tr>
</tbody>
</table>

Methods

Using the current Directory of Emergency and Special Care Units (1996), we phoned all adult, cardiac and paediatric ITU in the UK with more than four beds and spoke to either medical or senior nursing staff. Special care baby units were excluded. A postal questionnaire was sent to all units that used inhaled nitric oxide therapy (appendix 1). We asked about indications for its use and currently used methods of delivery, monitoring and scavenging in individual units. Units were also asked about the minimum level of monitoring that they considered satisfactory for its safe use.
Nitric oxide in the ITU

Table 2  Severity of ALI/ARDS at introduction of inhaled nitric oxide therapy (%). ALI = acute lung injury, ARDS = acute respiratory distress syndrome, SRF = severe respiratory failure

<table>
<thead>
<tr>
<th>Severity</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>26</td>
</tr>
<tr>
<td>ARDS</td>
<td>12</td>
</tr>
<tr>
<td>SRF</td>
<td>46</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 4  Use of scavenging systems with inhaled nitric oxide therapy

<table>
<thead>
<tr>
<th>Type of scavenging used</th>
<th>Incidence (%)</th>
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</thead>
<tbody>
<tr>
<td>Passive</td>
<td>19</td>
</tr>
<tr>
<td>Filtration</td>
<td>23</td>
</tr>
<tr>
<td>Active</td>
<td>23</td>
</tr>
<tr>
<td>None</td>
<td>40</td>
</tr>
</tbody>
</table>

DELIVERY AND MONITORING

Ten (18.5%) units used an inspiratory injection system which injects nitric oxide into the inspiratory limb only during the inspiratory phase of the ventilator cycle; 52 (96.3%) used a continuous flow system and eight (14.8%) used both systems. To monitor delivery of inhaled nitric oxide, eight (15.9%) units used only chemiluminescent monitoring, 48 (90.6%) units used an electrochemical monitor, and eight (15.1%) units used both systems. Two (3.8%) units monitored expired nitrogen dioxide concentrations while six (11.3%) units measured environmental nitrogen dioxide. Two (3.8%) units did not monitor the concentration of inhaled nitric oxide.

Regarding minimum monitoring standards for the safe use of inhaled nitric oxide, eight (15.1%) units believed that inspiratory chemiluminescence monitoring of nitric oxide and nitrogen dioxide was required, whereas 45 (84.9%) thought that inspiratory electrochemical monitoring of nitric oxide and nitrogen dioxide was adequate. In addition to inspiratory monitoring, 22 (41.5%) units stated that expiratory monitoring should also be used. Three (5.9%) of these stated that a chemiluminescence analyser was necessary and 19 (35.8%) thought that electrochemical monitoring was sufficient. Only nine (16.9%) units felt that environmental nitrogen dioxide monitoring was necessary. Comparison between actual use of monitoring and what the surveyed units stated to be minimum monitoring standards is shown in table 3. Methaemoglobin concentrations were measured daily in 27 (54%) units; in 16 (32.0%) it was measured with every blood-gas analysis but in seven (14.0%) units it was not measured. Four (7.6%) units stated that although they measured methaemoglobin concentrations they did not feel it was necessary.

Table 3  Current use of monitoring compared with surveyed units stated minimum monitoring standards

<table>
<thead>
<tr>
<th>Monitoring type</th>
<th>Current use (%)</th>
<th>Stated minimum standard (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory chemiluminescence</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Inspiratory electrochemical</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>Expiratory monitoring</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>Environmental monitoring</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

SCAVENGING

Table 4 shows the different methods of scavenging. Of the units using filtration systems, three (5.8%) units used the ABEK HgCONO-P3 filter, five (9.6%) units used charcoal absorbers and four (7.7%) units used soda lime.

Discussion

The potential benefits of nitric oxide are attractive to improve oxygenation and reduce pulmonary artery pressures in ARDS and act as a pulmonary artery vasodilator in pulmonary artery hypertension without systemic effects. As yet, these benefits are not proved in terms of patient outcome and thus therapy should still be thought of as experimental. We found that 50% of the units currently using inhaled nitric oxide were carrying out research in this area and thus nitric oxide is being used widely in research designs. Only 9.4% of responding units were using it solely for research purposes. Until the risk/benefit ratio has been established it would seem logical to use inhaled nitric oxide therapy in more severely ill critical care patients. No evidence is yet available to allow recommendations to be made for the introduction of inhaled nitric oxide. Our opinion is that in ARDS, ventilation should be optimized with an arbitrary partial pressure of arterial oxygen to fractional inspired oxygen concentration ratio (P_{A\text{O}_2} : P_{F\text{O}_2}) of less than 14 kPa (106 mm Hg) before introduction of inhaled nitric oxide for clinical purposes.

DELIVERY

There are essentially two ways to deliver inhaled nitric oxide, either continuously or by intermittent flow. The gold standard for nitric oxide delivery is a Servo controlled inspiratory injection device such as the NODOMO system (Dräger Medical UK, Hemel Hemstead, Herts, UK) which allows injection of nitric oxide into the inspiratory limb of the system during inspiration only. This technique reduces the bolus effect seen with continuous flow systems and reduces nitrogen dioxide formation because of decreased nitric oxide and oxygen mixing time.9 10 The continuous flow system uses a calibrated flowmeter delivering a continuous flow of nitric oxide–nitrogen 10–800 ml min⁻¹ throughout the respiratory cycle.9 Medical quality nitric oxide–nitrogen is available in cylinders for direct patient use or can be delivered through stainless steel medical gas piping. Medical quality nitric oxide–nitrogen gas cylinders with a stainless steel pressure regulator, connectors and calibrated stainless steel flowmeter needle valves are the minimum required for the safe delivery of inhaled nitric oxide. Polytetrafluoroethylene (PTFE) tubing for the delivery of inhaled nitric oxide is safe (personal communication, Nigel Wadsworth, BOC Special Gases,
Cylinders of nitric oxide—nitrogen are available in 10- and 40-litre sizes and must be secured in the ITU so as to avoid injury. Methods of delivery for inhaled nitric oxide in the UK vary but the majority (96.3%) use nitric oxide cylinders and a continuous flow system. Some units did not monitor the delivery of nitric oxide; we would strongly discourage this practice.

**MONITORING**

Nitric oxide in gas mixtures can be measured either with chemiluminescence or electrochemical analysers. Electrochemical analysers monitor both nitric oxide and nitrogen dioxide concentrations to an accuracy of at least 1 part per million (ppm) while chemiluminescence analysers monitor nitric oxide, nitrogen dioxide and other higher oxides of nitrogen to an accuracy of a few parts per billion. When placed at the distal end of the inspiratory limb, nitric oxide and nitrogen dioxide monitors provide information on the delivered dose of nitric oxide to the patient and information on the formation and delivery of the potentially toxic nitrogen dioxide. Few clinical indications require delivery of greater than 80 ppm of inhaled nitric oxide and this should be regarded as a maximum dose, but it should be noted that the Control of Substances Hazardous to Health (COSHH) guidelines for inspired nitric oxide concentrations are 25 ppm over an 8-h time-weighted average (TWA) and 35 ppm over a 15-min TWA. Maximum nitrogen dioxide concentrations should be less than 3 ppm over an 8-h TWA and 5 ppm over a 15-min TWA. There is evidence that concentrations as low as 5 ppm of nitrogen dioxide cause surfactant damage in rats. Nitric oxide monitoring in the expiratory limb of the system provides some information on the amount of nitrogen dioxide being exhausted from the system but this does not reflect environmental nitrogen dioxide concentrations. We recommend that inspiratory electrochemical or chemiluminescence monitoring of nitric oxide and nitrogen dioxide is the minimum requirement. Expiratory monitoring of nitrogen dioxide does not provide any useful information on atmospheric nitrogen dioxide concentrations and thus we do not feel its measurement is routinely required.

Environmental nitric oxide and nitrogen dioxide monitoring in the ITU can be performed using chemiluminescence or electrochemical analysers at the patient bedside. Environmental nitric oxide concentrations should not exceed the COSHH guidelines, but concentrations of 1 ppm of nitric oxide are the highest recorded in a clinical environment during the use of inhaled NO. In light of the current published data, environmental nitric oxide and nitrogen dioxide monitoring is not routinely required.

The reaction of nitric oxide with haemoglobin produces the compound methaemoglobin. Doses of nitric oxide far greater than those used clinically do not cause significant methaemoglobinaemia in adults. To date there are only two case reports of significant methaemoglobinaemia during inhaled nitric oxide therapy. Both were in babies and in one case there was an overdose of nitric oxide. Inhaled nitric oxide has now been used in many thousands of patients without further reports of methaemoglobinemia. We suggest that methaemoglobin measurements may be unnecessary, but until further evidence is available they should be measured daily.

A surprisingly high percentage (41.5%) of respondents thought that expired nitrogen dioxide monitoring was a minimum requirement but there is no current evidence to support this practice. Otherwise, the minimum monitoring standards from the surveyed units broadly agreed with our recommendations for inspiratory nitric oxide and nitrogen dioxide and daily methaemoglobin measurement being the minimum requirement. Although we do not feel that exhaled or environmental nitrogen dioxide measurements are required, we would not discourage this safety orientated approach. Environmental electrochemical nitrogen dioxide monitors are now readily available at an affordable price.

**SCAVENGING**

Scavenging can be used both in the inspiratory limb of the system to scavenge inspired nitrogen dioxide or on the expiratory limb to scavenge expired nitric oxide and nitrogen dioxide. Active scavenging systems would be the gold standard for nitric oxide and nitrogen dioxide scavenging, but are expensive and are not commonly available in the ITU. Active scavenging can also affect the performance of the expiratory valve of the ventilator. Because of the high moisture content of both inspired and expired gases, passive scavenging, which usually involves a length of hose being placed out of a window, is often associated with excess moisture collection in the tubing. Expiratory scavenging of nitric oxide or nitrogen dioxide with soda lime has been reported to be ineffective and although soda lime containing potassium permanganate indicator has been shown to scavenge inspired nitric oxide and nitrogen dioxide, this was probably because of the reaction of the indicator and not the soda lime. Two stage permanganate and charcoal filtration devices are also available but there is no clinical evidence regarding efficiency. The lack of evidence for effectiveness of soda lime in expiratory scavenging implies that we are unable to recommend its clinical use at this time. Charcoal type absorbers are ineffective absorbers of nitric oxide or nitrogen dioxide.

The ABEK HgCONO-P3 filter (Dräger Industrial Ltd., Hemel Hempstead, Herts, UK) which is used industrially appears to scavenge nitric oxide and nitrogen dioxide effectively. Two stage permanganate and charcoal filtration devices are also available but there is no clinical evidence regarding efficiency. The lack of evidence for effectiveness of soda lime in expiratory scavenging implies that we are unable to recommend its clinical use at this time. Charcoal type absorbers are ineffective absorbers of nitric oxide or nitrogen dioxide.

More than half (59.6%) of responding units used some type of scavenging system. Health Technical Memorandum 2025 states that in units with adequate ventilation in clinical areas (10–12 air changes per hour), scavenging of nitric oxide or nitrogen dioxide is not necessary but recommends scavenging in units that do not reach this standard. Expiratory scavenging using the ABEK HgCONO-P3 filter, active or passive scavenging are appropriate in units that do not meet the above guidelines. We would not discourage the practice of scavenging exhaled nitric oxide and nitrogen dioxide and would recommend scavenging in poorly ventilated units. It should be
noted that there is little evidence to support the use of soda lime or charcoal absorbers in the scavenging of exhaled nitric oxide and nitrogen dioxide.

In summary, inhaled nitric oxide is a new form of therapy in the ITU. The use of this potentially toxic compound should be supervised closely by experienced clinicians and its delivery and monitoring standardized to acceptable minimum levels. At present there is wide variety in the standards of clinical practice for using inhaled nitric oxide in the UK. We have put forward recommendations (appendix 3) for its use with the belief that this will promote discussion and research into nitric oxide therapy and with the hope that national guidelines may soon become available.

Acknowledgements
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Appendix 1
SURVEY OF THE USE OF INHALED NITRIC OXIDE IN THE ITU

Dear Colleague

We believe that your unit uses inhaled nitric oxide therapy. As you are probably aware there has been concern stated by the CSM on the use of inhaled NO in clinical practice. We are conducting a postal survey of all the units in the UK that use inhaled NO. We would appreciate if you could complete this short questionnaire and return it to us in the enclosed STA as soon as it is convenient.

Thank you for your help.

Brian H Cuthbertson and Steve Stott, Intensive Care Unit, Aberdeen Royal Infirmary, Aberdeen.

A.
Name of unit____________________________________________________
Name of person filling in questionnaire _______________________
Grade____________________________________________________
Bed number:- total general paediatric cardiac
B. How long have you used it:-____years_____months

What indications do you use inhaled NO for in your hospital:-

a. ALI/ARDS
b. Secondary pulmonary hypertension
c. Pulmonary vaso dilator during adult cardiac surgery
d. Cardiac transplant surgery
e. Paediatric cardiac surgery
f. RDS of the newborn
g. Others -please state___________________________________

If you use inhaled NO for ALI/ARDS, what criteria do you use for its use? (American–European consensus conference definitions).

a. Consensus conference definition for ALI
   *(P_{A}O_{2}/F_{I}O_{2} \text{ ratio } < 300 \text{ mm Hg, infiltrates on CXR, PCWP } < 18 \text{ mm Hg})*
   □

b. Consensus conference definition for ARDS
   *(P_{A}O_{2}/F_{I}O_{2} \text{ ratio } < 200 \text{ mm Hg, infiltrates on CXR, PCWP } < 18 \text{ mm Hg})*
   □

c. Severe respiratory failure (ECMO) criteria
   *(P_{A}O_{2} \text{ before NO } < 8 \text{ kPa on } F_{I}O_{2} 1.0 \text{ for } >8 \text{ h})*
   □

d. Other (please state) ____________________________________

Are you undertaking research in the subject of inhaled NO:- Yes / No

Are you using inhaled NO only as part of a trial:- Yes / No

What equipment do you use for administration of inhaled NO

What equipment do you use for measurement of inhaled NO levels

What monitoring do you feel is the minimum necessary for the safe use of inhaled NO:-

a. Inspired NO and NO_{2} levels-
   - chemiluminescent monitor □
   - electrochemical monitor □

b. Expired NO and NO_{2} levels-
   - chemiluminescent monitor □
   - electrochemical monitor □

c. Methaemoglobin levels:-
   - Daily □ Every gas □
   - Not required □

d. Other (please state) ____________________________

What means of scavenging of NO do you use:- None □

Passive □

Active □

Soda lime □

Other □

Thank you for your time.

Appendix 2
AMERICAN–EUROPEAN CONSENSUS CONFERENCE DEFINITION FOR ALI AND ARDS AND THE SEVERE RESPIRATORY FAILURE CRITERIA

Abbreviations: ECMO = extracorporeal membrane oxygenation, PCWP = pulmonary capillary wedge pressure, CXR = chest x-ray.

Acute lung injury

\(\text{Pa}_{O_{2}}/\text{Fi}_{O_{2}} \text{ ratio } < 39.5 \text{ kPa (300 mm Hg) }\)

Acute respiratory distress syndrome

\(\text{Pa}_{O_{2}}/\text{Fi}_{O_{2}} \text{ ratio } < 26.3 \text{ kPa (200 mm Hg) }\)

Severe respiratory failure criteria

\(\text{Pa}_{O_{2}}/\text{Fi}_{O_{2}} \text{ ratio } < 8 \text{ kPa (60.8 mm Hg) for } >8 \text{ h}\)

Appendix 3
RECOMMENDATIONS FOR THE USE OF INHALED NITRIC OXIDE IN THE ITU

Abbreviations: NO = nitric oxide, NO_{2} = nitrogen dioxide, PTFE = polytetrafluoroethylene, COSHH = Care of Substances Hazardous to Health, ppm = parts per million, TWA = time-weighted average.

<table>
<thead>
<tr>
<th>Table A1</th>
<th>Recommendations for the use of inhaled nitric oxide in the ITU</th>
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</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>1. Medical NO/\text{N}_{2} gas mixture</td>
</tr>
<tr>
<td></td>
<td>2. Stainless steel pressure regulators, connectors and flowmeter needle valves</td>
</tr>
<tr>
<td></td>
<td>3. Calibrated flowmeter</td>
</tr>
<tr>
<td></td>
<td>4. Stainless steel/PTFE tubing</td>
</tr>
<tr>
<td>Monitoring</td>
<td>1. Inspiratory NO and NO_{2}</td>
</tr>
<tr>
<td></td>
<td>2. Chemiluminescence or electrochemical monitor</td>
</tr>
<tr>
<td></td>
<td>3. Daily methaemoglobin concentrations</td>
</tr>
<tr>
<td>Exposure</td>
<td>1. Maximum inhaled NO &lt; 80 ppm</td>
</tr>
<tr>
<td></td>
<td>2. Maximum inhaled NO_{2} &lt; 3 ppm</td>
</tr>
<tr>
<td></td>
<td>3. Maximum environmental NO &lt; 25 ppm for 8 h TWA</td>
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<td></td>
<td>4. Maximum environmental NO_{2} &lt; 3 ppm for 8 h TWA</td>
</tr>
<tr>
<td>Scavenging</td>
<td>1. Not required in well ventilated unit</td>
</tr>
<tr>
<td></td>
<td>2. Required in units with less than 10–12 air changes per hour</td>
</tr>
<tr>
<td>Scavenging techniques</td>
<td>1. ABEK \text{HgCONO-P3 filter}</td>
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<td></td>
<td>2. Active scavenging</td>
</tr>
<tr>
<td></td>
<td>3. Passive scavenging</td>
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References


