Guidelines for the safe administration of inhaled nitric oxide

O I Miller, D S Celermajer, J E Deanfield, D J Macrae

Abstract
Inhaled nitric oxide (NO) is a selective pulmonary vasodilator, potentially useful in the treatment of pulmonary hypertension and ventilation-perfusion mismatch. High doses of inhaled NO and its oxidative product nitrogen dioxide (NO₂) may cause acute lung injury. Using a standard infant ventilator, ventilator circuit and test lung, an administration and monitoring strategy has been defined for inhaled NO and these observations validated in eight ventilated infants. In 90% oxygen, doses of inhaled NO ≥80 parts per million may result in toxic NO₂ concentrations.

(Arch Dis Child 1994; 70: F47–F49)

Methods
Medical grade NO (1000 ppm) was obtained in a balance of nitrogen (BOC Special Gases). Studies were performed using a continuous flow, pressure limited ventilator (Babylog 8000, Dräger Ltd) set to simulate neonatal ventilation, a standard disposable ventilator circuit with a compressible volume of 150 ml (Model 6057, Intersurgical), a servocontrolled humidifier with a reservoir volume of 120 ml (Model MR730, Fisher and Paykel) and a 50 ml silicone test lung. NO gas was titrated via a calibrated nitrogen flowmeter (KDG Mobrey Instruments) into the inspiratory limb of the circuit, while circuit gas was continuously aspirated for analysis of NO and NO₂ by chemiluminescence (TEI 42, Thermo Electron Ltd).

Three reproducible sites A, B, and C (figure) along the ventilator circuit were chosen for gas administration and/or analysis. Site B was used as the reference point for other comparisons as it was immediately adjacent to the patient connection which was accomplished via low (<2 ml) dead space 8.5 mm connectors. Analysis for inspired oxygen fraction was performed at B. Peak NO and NO₂ concentrations were recorded at steady state. All results are the means of three recordings.

As the standard set up, ventilator gas flow was set at 10 l/min with an inspired oxygen of 90%, NO was added at site A to achieve a NO
concentration of 40 ppm. Analysis for NO and NO\textsubscript{2} was performed at site B. An inspired oxygen of 100\% is not achievable due to dilution of the inspiratory oxygen with NO and its carrier gas, nitrogen.

The effects on inspired NO and NO\textsubscript{2} of the following manipulations to the ventilator and circuit were then tested against the standard set up. (1) Administration site: proximal extreme (PE) versus A. (2) Analysis site: inspiratory limb (A) or expiratory limb (C) versus B. (3) Ventilator gas flow rate: 5 l/min and 20 l/min versus 10 l/min. (4) Inspiratory to expiratory (I:E) ratios: 1:3 versus 1:1.

Subsequently, we performed test lung ventilation with standard settings and NO concentrations from 10–100 ppm (increments of 10 ppm) and measured NO\textsubscript{2} at B, initially in room air and then in 90\% oxygen.

Finally, identical manipulations to administration site (A or PE), analysis site (B or C), and ventilator flow rates (5, 10, 20) were applied to eight infants who were receiving inhaled NO at 20–40 ppm as part of a separate clinical trial. Hospital ethics committee approval and parental informed consent was obtained for each child.

**Results**

We found that the concentration of NO\textsubscript{2} at the patient (site B) is independent of ventilator gas flow rate or I:E ratio. Addition of NO to the circuit before the humidifier led to a small (−2\%) decrease in NO and a small rise (+2\%) in NO\textsubscript{2} at B.

Site of analysis was important. NO:NO\textsubscript{2} values at B and C were almost identical, whereas those measured adjacent to A were 22\% (NO) and 24\% (NO\textsubscript{2}) higher than at B.

During room air ventilation of the test lung, NO\textsubscript{2} production was less than 5 ppm for each NO concentration tested with NO\textsubscript{2} reaching a plateau of 1.5 ppm at 60–100 ppm NO. In contrast, in 90\% oxygen, production of NO\textsubscript{2} increased incrementally, with NO\textsubscript{2} exceeding 5 ppm between 70 and 80 ppm NO (table).

Studies of NO\textsubscript{2} production in eight ventilated infants (aged 1–19 months) gave similar, reproducible results to those predicted from the test lung studies. In each case the observed NO\textsubscript{2} was within 0.5 ppm of the predicted NO\textsubscript{2}. Proximal NO administration, ventilator flow rate, and analysis at B or C did not influence NO\textsubscript{2} production.

**Discussion**

Patients with cardiopulmonary disease who may potentially benefit from inhaled NO usually require a high inspired oxygen concentration. On the basis of a known, predictable rate of NO oxidation, other authors have also recommended the potential for toxic NO\textsubscript{2} concentrations in the presence of high oxygen.\textsuperscript{18,19} Using our ventilator circuit and 90\% oxygen, inhaled NO >80 ppm led to NO\textsubscript{2} concentrations >5 ppm and thus may be toxic. However, our data support safe extended administration of NO at lower doses with steady state NO\textsubscript{2} concentrations less than 5 ppm. The lower concentrations of NO\textsubscript{2} observed in our study compared with previously published safety guidelines is almost certainly due to gas washout by continuous flow ventilation. Therefore, the data presented here more closely reflect clinical practice.

With respect to NO\textsubscript{2} production, NO may be safely delivered proximally or distally to the inspiratory limb without needing to alter total gas flow rate. However, analysis for NO and NO\textsubscript{2} concentrations must be performed at or just distal to the patient; more proximal analysis may yield spurious data. Inspired oxygen analysis should logically occur after addition of NO, but proximal to the patient. These guidelines would also be applicable to the spontaneously breathing patient provided that a normal non-rebreathing circuit with sufficient continuous gas flow is used.

Unfortunately, the measurement of NO and NO\textsubscript{2} at site B or C does not necessarily reflect alveolar concentrations of these gases. Alveolar gases may have a higher NO\textsubscript{2} content due to a longer exposure to oxygen, water vapour, and possibly additional endogenous NO. However, the NO:NO\textsubscript{2} data from chemiluminescence analysers represent an average value during a set sampling period and with our device, a given NO or NO\textsubscript{2} value is a 10 second average sampled every 20 seconds. For this reason, chemiluminescence analysis, although accurate at steady state, is not currently suited to end tidal or alveolar sampling. A more rapid sampling rate would allow detection of phasic changes, but at a decreased level of precision. Inhaled NO is an important new treatment for a variety of disorders in infants, children, and adults. Toxic NO\textsubscript{2} production in high inspired oxygen is a major potential risk; however, careful attention to guidelines for delivery and monitoring will minimise this hazard.

Dr Miller and Dr Celermajer are supported by separate grants from the British Heart Foundation.

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