Guidelines for the safe administration of inhaled nitric oxide

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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.

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Healthy endothelium controls vasomotor tone¹ by producing vasoactive substances, including the endothelium derived relaxing factor, endogenous nitric oxide (NO).^{2,3} NO is synthesised from L-arginine in the endothelial cell⁴ and acts locally on the vascular smooth muscle cell to produce vasodilation.

In experimental pulmonary vasoconstriction, inhaled exogenous NO acts directly on pulmonary vascular smooth muscle to induce vasorelaxation.⁵ Furthermore, inactivation of inhaled NO by avid binding to haemoglobin⁶ precludes a systemic vasoactive effect. In the

clinical setting, NO is inexpensive, easy to administer in a respiratory gas mixture, and has been reported to cause selective pulmonary vasodilatation in neonates with persistent pulmonary hypertension,^{7,8} children with congenital heart disease,⁹⁻¹² and adults with pulmonary hypertension¹³ or the adult respiratory distress syndrome.¹⁴

Serious toxicity may result from high doses of inhaled NO.¹⁵ More importantly, however, in the presence of oxygen, NO is converted to nitrogen dioxide (NO₂), which may cause pneumonitis, pulmonary oedema, or emphysema.¹⁶ The Centers for Disease Control have recommended an upper limit exposure to NO₂ of 5 parts per million (ppm) in an eight hour period.¹⁷ Theoretical¹⁸ and in vitro¹⁹ work based on the rate formula for oxidation of NO to NO₂ suggests such rapid production of NO₂, that clinical use of NO would seem impractical, yet recent clinical reports have not uniformly commented on this important toxic product. We aimed to define safe and effective guidelines for delivering inhaled NO and monitoring NO₂ concentrations in ventilated infants.

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

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Ventilator circuit for inhaled NO delivery and NO/NO₂ analysis during continuous flow ventilation. A=inspiratory limb administration site, B=analysis site at patient connection, C=expiratory limb analysis site, PE=proximal extreme, H=humidifier, O₂=oxygen, N₂=nitrogen.

concentration of 40 ppm. Analysis for NO and NO₂ 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 NO₂ 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 NO₂ 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 NO₂ 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 NO₂ at B.

Site of analysis was important. NO/NO₂ values at B and C were almost identical, whereas those measured adjacent to A were 22% (NO) and 24% (NO₂) higher than at B.

During room air ventilation of the test lung, NO₂ production was less than 5 ppm for each NO concentration tested with NO₂ reaching a plateau of 1.3 ppm at 60–100 ppm NO. In contrast, in 90% oxygen, production of NO₂ increased incrementally, with NO₂ exceeding 5 ppm between 70 and 80 ppm NO (table).

Studies of NO₂ 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 NO₂ was within 0.5 ppm of the predicted NO₂. Proximal NO administration, ventilator flow rate, and analysis at B or C did not influence NO₂ production.

Discussion

Patients with cardiorespiratory 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 alerted clinicians to the potential for toxic NO₂ concentrations in the presence of high oxygen.^{18,19} Using our ventilator circuit and 90% oxygen, inhaled NO ≥80 ppm led to NO₂ concentrations >5 ppm and thus may be toxic. However, our data support safe extended administration of NO at lower doses with steady state NO₂ concentrations less than 5 ppm. The lower concentrations of NO₂ 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 NO₂ 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 NO₂ 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 NO₂ at site B or C does not necessarily reflect alveolar concentrations of these gases. Alveolar gases may have a higher NO₂ content due to a longer exposure to oxygen, water vapour, and possibly additional endogenous NO. However, the NO/NO₂ data from chemiluminescence analysers represent an average value during a set sampling period and with our device, a given NO or NO₂ 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 NO₂ production in high inspired oxygen is a major potential risk; however, careful attention to guidelines for delivery and monitoring will minimise this hazard.

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NO₂ (ppm) produced when NO is administered at concentrations of 10–100 ppm during standard ventilation in 21% and 90% oxygen. The upper limit of NO₂ to avoid pulmonary toxicity is 5 ppm (see text)

	NO (ppm)									
	10	20	30	40	50	60	70	80	90	100
Oxygen:										
21%	0.3	0.5	0.7	0.9	1.0	1.3	1.3	1.3	1.3	1.3
90%	0.6	1.2	1.9	2.4	3.1	3.9	4.5	5.1	5.7	6.1

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