

CASE REPORT

Exhaled nitric oxide in chronically ventilated preterm infants

O Williams, R Y Bhat, P Cheeseman, G F Rafferty, S Hannam, A Greenough

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Exhaled nitric oxide (eNO) levels were measured in eight ventilated infants, mean gestational age 25.8 (SD 1.7) weeks and postnatal age 55 (SD 39) days, before and after three days of dexamethasone treatment. The eNO levels fell from a mean of 6.5 (SD 3.4) to 4.2 (SD 2.6) parts per billion ($p=0.031$) and the mean supplementary oxygen levels from 62% to 45% ($p=0.0078$).

Approximately 20% of very low birthweight infants develop chronic lung disease (CLD). CLD is associated with an early inflammatory response, which persists over the first weeks after birth. Analysis of bronchoalveolar lavage (BAL) demonstrated that the nitrate concentration remains elevated at 14 days after birth in those infants who develop CLD, whereas it decreases in those who recover from respiratory distress syndrome without CLD development.¹ The persistent elevation of BAL fluid nitrate may be due to increased inflammation and proinflammatory cytokines, which may stimulate the expression of the inducible form of nitric oxide synthetase (NOS). In contrast to BAL, measurement of exhaled nitric oxide (eNO) is non-invasive and results are displayed at the bedside. There are limited data on eNO in prematurely born infants, but it has been identified in their expired gases.² In adults and children with inflammatory disorders, eNO levels are reduced by dexamethasone administration.³ Dexamethasone is given to chronically ventilator dependent prematurely born infants to facilitate extubation. Our aim was to assess eNO levels in chronically ventilator dependent, prematurely born infants and whether the levels were reduced following dexamethasone administration.

METHODS

Consecutive, chronically ventilator dependent infants given dexamethasone whose parents gave informed written consent for eNO measurements were recruited. This study was approved by King's College Hospital Research Ethics Committee. eNO levels were examined in eight infants, mean gestational age 25.8 weeks (SD 1.7), birth weight 680 g (SD 103), and postnatal age 55 days (SD 39). The clinician in charge prescribed dexamethasone for infants whose respiratory failure was either not improving or had worsened over the previous week. All infants received a standard nine day course: 0.5 mg/kg/day for three days, 0.3 mg/kg/day for three days, and finally 0.1 mg/kg/day for three days. eNO was measured prior to and after three days of treatment. An NO scavenger was placed in the inspiratory limb of the ventilator to ensure ventilation with NO free gas. To measure eNO, a 4FG catheter was fed through the suction port of the manifold of the ventilator circuit and the catheter tip positioned to lie at the end of the endotracheal tube. Shouldered endotracheal tubes were used routinely on the unit and the infants supported by constant flow ventilators. The catheter was attached via a two way plastic connector to

the teflon based suction tube of a Sievers chemiluminescence analyser (Sievers Instruments Inc, Boulder CO, USA).⁴ Sampling was at a constant rate of 100 ml/min. Data were stored and analysed on a computer, using NO analysis software (Sievers Instruments Inc). The maximum eNO levels were calculated from 10 consecutive breaths and the final result was the mean of five measurements from each infant. The mean intrasubject coefficient of variability of NO levels was 11.7%.

ANALYSIS

The eNO data were normally distributed, therefore, differences in eNO levels before and after three days of treatment were analysed for statistical significance using a paired *t* test. Differences in the mean airway pressure and inspired oxygenation concentration were analysed using a paired Wilcoxon signed rank test. Spearman's correlation coefficient was calculated to assess the relationship of eNO levels and the inspired oxygen concentration.

RESULTS

The maximum mean eNO levels fell from 6.5 parts per billion (ppb) (SD 3.4) before treatment to 4.2 ppb (SD 2.6) after three days of dexamethasone ($p=0.031$), this was associated with a reduction in the median supplementary oxygen level from 59% (mean 62, range 40–93) to 41% (mean 45, range 30–80) ($p=0.0078$) and in the median airway pressure from 10 cm H₂O (mean 10.6, range 9–14) to 8 cm H₂O (mean 9, range 8–11) ($p=0.0235$). There was no significant change in the carbon dioxide tensions with a median paCO₂ of 5.75 kPa (range 4.07–7.08) prior to dexamethasone and a median paCO₂ of 6.01 kPa (range 4.84–6.35) after three days of treatment ($p=0.86$) (see table 1). Only one infant's eNO level increased following dexamethasone administration, this was the only infant whose mean airway pressure did not decrease, although there was a temporary reduction in the supplementary oxygen requirement. The infant subsequently died, never having been extubated. No significant correlation was found between the eNO levels and the inspired oxygen concentration prior to treatment ($r=0.238$, $p=0.529$).

DISCUSSION

Exhaled NO was demonstrated in all the infants studied, all were born very prematurely, that is prior to 28 weeks of gestation. In adults NO mainly originates from the paranasal sinuses. Prematurely born infants have only partially pneumatised paranasal sinuses. Nevertheless, NO levels in exhaled nasal gas have been reported to be higher than those from the lower airways in intubated prematurely born infants.⁵ In this study, eNO was sampled from the lower end of shouldered endotracheal tubes, those tubes have been

Abbreviations: eNO, exhaled nitric oxide; ppb, parts per billion; CLD, chronic lung disease; BAL, bronchoalveolar lavage; iNOS, inducible nitric oxide synthetase

Table 1 Changes in ventilatory requirements, eNO and paCO₂ levels before and after three days of dexamethasone administration (individual patient data are shown)

Patient	MAP (cmH ₂ O)		FiO ₂		eNO levels (ppb)		paCO ₂ (kPa)	
	pre	3 days	pre	3 days	pre	3 days	pre	3 days
1	11	8	0.67	0.48	8.60	3.86	5.75	5.70
2	10	8	0.41	0.34	5.12	2.48	5.92	6.01
3	14	11	0.93	0.78	11.39	8.98	7.08	6.35
4	9	8	0.54	0.33	8.98	6.60	6.62	6.08
5	9	10	0.80	0.53	1.20	4.31	5.11	6.02
6	11	10	0.59	0.40	4.70	0.94	5.30	4.96
7*	9	8	0.50	0.30	3.35	1.82	–	–
8	10	8	0.60	0.52	8.67	5.17	4.07	4.84

*Carbon dioxide tensions were not available on this patient.

shown to have minimal or no leak.⁶ In addition, the infants were ventilated with NO free gas during each measurement. Thus, we are confident we avoided nasal and environmental contamination and the eNO levels we report were from the lower airways.

We have demonstrated dexamethasone administration was associated with a significant reduction overall in eNO levels in these prematurely born, chronically ventilator dependent infants. To our knowledge, this is the first time this has been reported. Each infant acted as their own control, the infants had severe respiratory failure, thus it was felt inappropriate to withhold dexamethasone. Increasing postnatal age in prematurely born infants has been associated with increasing NO levels,² not the significant reduction we highlight. The infants were receiving different oxygen concentrations when examined. In adults, a relationship between NO levels and oxygen concentration has been demonstrated; pure oxygen inhalation during mechanical ventilation significantly decreased the concentration of exhaled NO.⁷ After three days of dexamethasone, all of the infants were receiving a lower inspired oxygen concentration, thus this did not explain the lower eNO levels seen in seven of the eight infants. Tidal eNO has been shown to be flow dependent in infants.⁸ We did not record flow, but prematurely born infants are ventilated so as to avoid either hypocarbia or a respiratory acidosis, as both can have serious sequelae. Not surprisingly then, we did not demonstrate a significant change in the carbon dioxide tensions following three days of dexamethasone, suggesting the reduction in eNO levels was not explained by changes in flow.

Glucocorticoids are thought to have an anti-inflammatory role reducing NO expression by destabilising inducible NOS (iNOS) and mRNA.⁹ iNOS is not usually present in resting cells, but is found in pathophysiological conditions (for example asthma and inflammatory bowel disease). iNOS produces high levels of NO in response to inflammatory signals (for example cytokines and lipopolysaccharides). We therefore suggest that the eNO levels overall fell in these infants with CLD in response to dexamethasone administration. That hypothesis is supported by the finding that the eNO levels did not fall in the one individual who had a poor

clinical response to dexamethasone. Whether serial eNO measurements might be helpful in monitoring the response of CLD infants to dexamethasone requires a larger study in which daily assessments are made.

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