Should we use inhaled nitric oxide in acute respiratory distress syndrome?

THE DILEMMA

Nitric oxide produced in the lung causes pulmonary vasodilation. In acute respiratory distress syndrome, ventilation–perfusion mismatch produces arterial hypoxaemia while increased pulmonary vascular resistance causes pulmonary hypertension. In theory, nitric oxide preferentially reaches ventilated alveoli, selectively vasodilating vessels, thus improving oxygenation and reducing pulmonary vascular resistance. But should we use nitric oxide in practice?

YES

Numerous studies have reported the use of inhaled nitric oxide (NO) for patients with acute respiratory distress syndrome (ARDS). They show that up to 80% of patients will respond with a 20% improvement in the ratio of arterial oxygen tension (PaO_2) to fractional inspired oxygen and up to a 20% improvement in right–left intrapulmonary shunt and pulmonary artery pressure when inhaled NO was administered at doses of <20 ppm. The main question is whether there is an outcome improvement or not. Most trials have small patient numbers, lack controls and use varying doses of NO along with other therapies to treat ARDS.

There have been a few larger, well-designed trials, including Dellinger et al (1998). This showed significant improvements in oxygenation but no overall mortality benefit. Evidence also suggests that NO improves oxygenation when combined with other treatments, e.g. high positive end expiratory pressure and prone positioning. Inhaled NO can also lower increases in pulmonary vascular resistance caused by permissive hypercapnic ventilation (Puybasset et al, 1994), a ventilatory strategy widely used in patients with ARDS.

There is a role for the use of NO in the treatment of patients with ARDS. Evidence suggests it can reduce the damaging high oxygen concentrations required in some severe cases in the short term, especially when used with other treatment strategies as described above, and 'buy time' for recovery.

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Dellinger RP, Zimmerman JL, Taylor RW et al (1998) Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomised phase II trial. *Crit Care Med* **26**(1): 15–23

Puybasset L, Stewart T, Rouby J et al (1994) Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with ARDS. *Anaesthesiology* **80:** 1254–67

ONLY IN CERTAIN CIRCUMSTANCES

There have been four main randomized controlled trials examining the effect of NO in ARDS or acute lung injury (ALI) (Cranshaw et al, 2002). While these have shown that NO improves oxygenation in the short term, none has shown a mortality reduction, while two showed a trend towards higher mortality in the treated group. NO raises the PaO_2 (by more than 20%) in about 60% of patients with ARDS or ALI although this may take a few hours: this PaO_2 increase may seem beneficial but in several studies the control group PaO_2 has equalled that of the NO-treated patients after several days.

One of these studies in patients with ALI confirmed the short-term effects on oxygenation and pulmonary artery pressures, and also showed a decreased frequency of severe respiratory failure (2.2% *vs* 10.3% in controls $P<0.05$) but more renal impairment in the NO-treated group (Lundin et al, 1999). Along with no evidence of a mortality reduction there are other reasons not to use NO: large variation in the concentration–response relationship, rebound hypoxaemia and pulmonary hypertension after stopping treatment, and the possibility of pulmonary toxicity when NO reacts with air and water. These are not insurmountable problems, but they all cost time and money.

Evidence does not support using NO to reduce mortality in patients with ARDS or ALI, although trial data cannot exclude the possible usefulness in individual cases. If we use it because of a desire to 'do something' or because patients must be kept to pre-illness 'physiological norms' then we are only treating ourselves.

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Lundin S, Mang H, Smithies M et al (1999) Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. *Intensive Care Med* **25:** 911–19

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