Inhaled nitric oxide, methemoglobinemia, and route of delivery

Sir,

Inhaled nitric oxide (INO) has emerged as one of the most important therapies for pulmonary hypertension.[1] It is also beneficial in patients with acute respiratory distress syndrome. Methemoglobinemia is a well-known potential complication of INO in patients with methemoglobin reductase deficiency and overdose of INO. However, do we need to be careful in using low dose INO even in patients without deficiency of methemoglobin reductase?

Nitric oxide oxidizes heme iron to the ferric state, resulting in the formation of methemoglobin.[2] Methemoglobin has higher oxygen affinity and decreased oxygen-carrying capacity of the blood due to fewer hemes to bind oxygen. This causes leftward shift of oxyhemoglobin dissociation curve and reduced unloading of oxygen to the tissues. Methemoglobin is converted back to hemoglobin by enzyme methemoglobin reductase in the blood. Normal methemoglobin level in body is <2% of normal hemoglobin. Raised production (overdosing of INO, inadvertent faulty delivery) or reduced clearance of methemoglobin (methemoglobin reductase deficiency) results in its accumulation - methemoglobinemia.

When NO is delivered during mechanical ventilation with variable mainstream flow, there is periodic accumulation of NO in the inspiratory limb of the ventilator circuit as NO is delivered continuously into the inspiratory limb. The patient is delivered NO bolus with each breath from such NO pools in inspiratory limb of circuit. Such NO fluctuations may not get detected by slow response chemiluminescent analyzers.[3,4]

Yamaguchi *et al*. showed that higher concentration of delivered NO was seen by lower ventilator flow rates and by more distal instillation of the gas.[5] Taylor *et al*. reported two cases of methemoglobinemia with moderate- and even low-dose delivered NO due to inadvertent overdosing during phasic flow ventilation.[6]

Methemoglobinemia is fatal if not detected early as hypoxia due to it is refractory to oxygen therapy. In critically ill, ventilated patient receiving INO, even lower dose may produce severe tissue hypoxia as the patient may be in hypoperfused state. Alteration in dosing should be considered if methemoglobin level more than 5%. High level with clinical findings of severe lactic acidosis and tissue hypoxia warrants treatment with intravenous methylene blue 1–2 mg/kg, which will rapidly convert ferric iron back to ferrous form with resultant unloading of oxygen to tissues.[7]

It is essential to know how NO is administered and analyzed. Methemoglobinemia can be underestimated even if low concentration of NO is delivered. It is suggested to administer NO through continuous flow ventilator to avoid NO pooling in the circuit.[6] Delivery and analysis of NO should be done near the mouthpiece of the ventilator circuit with less dead space for accumulation.

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Conflicts of interest

There are no conflicts of interest.

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