Serum nitrogen oxides during nitric oxide inhalation

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Summary

A patient with acute respiratory failure secondary to leptospirosis was treated with 40 and 90 volumes per million inhaled nitric oxide. His serum nitrogen oxide concentration (nitrates and nitrites combined) increased 13-fold. The mechanisms for the formation and elimination of nitrates are discussed. (Br. J. Anaesth. 1995; 74: 338–339)

Key words

Pharmacology, nitric oxide. Toxicity.

Case report

A 43-yr-old, 69-kg male presented with a 4-day history of fever, limb cramps, weakness, nausea, diarrhoea and epistaxis. On the day of admission he also developed jaundice, abdominal pain and intracranial vomiting. He had been working in contact with rat-infested water and a clinical diagnosis of leptospirosis was made. This was confirmed later with antibody titres. Three days after admission he developed severe pulmonary haemorrhage requiring tracheal intubation and artificial ventilation. The bleeding gradually decreased although lung function remained very poor. On day 9 after admission, because of worsening arterial oxygenation and increasing pulmonary hypertension, we administered 40 volumes per million (vpm) of inhaled nitric oxide in 100% oxygen. This markedly improved the patient’s arterial oxygenation and reduced pulmonary arterial pressures (table 1). Inhaled nitric oxide was continued at 40 vpm for 3 days; however, arterial oxygenation continued to deteriorate despite increasing nitric oxide to 90 vpm. He subsequently developed a nosocomial Pseudomonas aeruginosa lung infection and systemic sepsis and died 14 days after admission.

Sixteen blood samples were obtained for measurement of total serum nitrates and nitrites (serum nitrogen oxides or sNOx) while the patient was receiving nitric oxide. After deproteination with zinc sulphate solution 25 mmol litre⁻¹, serum nitrogen oxides were determined by conversion to nitric oxide using hot acidic vanadium (III) chloride. Nitric oxide was eluted in a stream of nitrogen and measured using a chemiluminescent analyser (CLD 700, Eco Physics, Durnten, Switzerland). The method is identical to that described by Braman and Hendrix [1]. The results are shown in figure 1.

The basal sNOx concentration before administration of inhaled nitric oxide (81 μmol litre⁻¹) was twice our laboratory value for normal volunteers (39 (sd 7) μmol litre⁻¹). A plateau concentration (350 μmol litre⁻¹) was reached after 21 h and a second increase in sNOx concentration to 791 μmol litre⁻¹ was observed after increasing the inspired nitric oxide from 40 to 90 vpm. The maximum concentration (1060 μmol litre⁻¹) occurred after the patient developed acute renal failure and anuria. Blood methaemoglobin concentrations never exceeded 3.2% during inhalation of nitric oxide.

Discussion

Inhaled nitric oxide is being used increasingly as a selective pulmonary vasodilator in adults [2] and children [3], both to reduce pulmonary arterial pressures and decrease ventilation–perfusion mismatching. It has no direct systemic vasodilator action because it is bound avidly to haemoglobin, forming methaemoglobin which is in turn reduced back to haemoglobin and nitrates mainly by the NADH–methaemoglobin reductase pathway. The stable end-products of nitric oxide metabolism in mammals are nitrogen oxides [4]. The only report of sNOx concentrations in humans inhaling nitric oxide [5] observed a 46 % increase in sNOx, after inhalation of 25 vpm for 1 h. There are no reports of the effect of long-term nitric oxide inhalation on serum nitrogen oxide concentration in humans.

Measured sNOx concentrations result from the balance between nitrogen oxide intake, production...
and elimination. The initial sNOx concentrations were raised because of increased endogenous nitric oxide synthesis caused by the leptospirosis infection which activated inducible nitric oxide synthases [6]. The only exogenous source of nitrates was inhaled nitric oxide; all of the fluids that this patient received were tested and were free of nitrates. Thus during nitric oxide inhalation the increase in sNOx must have been caused by biotransformation of the inhaled nitric oxide. Assuming 90% absorption of inhaled nitric oxide [7], inhaling 40 vpm nitric oxide would result in a daily nitrogen oxide load of about 25 mmol.

Nitrates and nitrates are eliminated principally via the kidney, both directly and after conversion to urea [8–10]. Any impairment of renal function would thus be expected to cause an increase in sNOx and, as this patient became anuric, sNOx concentrations did increase.

The highest sNOx concentration observed in this patient breathing nitric oxide was 13 times the basal concentration, and about 27 times the mean concentration recorded in normal subjects. It is not known if this has any deleterious effects. In the past high doses of oral ammonium nitrate were used as a diuretic (10–15 g or 120–190 mmol per day) and the only reported problem was transient methaemoglobinaemia [11]. This has been reported also in infants ingesting high levels of nitrates in drinking water [12] and after direct systemic absorption of nitrates through burns [13,14]. Oral sodium nitrate 470 μg kg⁻¹ caused plasma nitrates to increase transiently to 1.85 mmol litre⁻¹ in normal subjects, apparently without ill effects [8]. No other consequences of increased blood nitrate concentrations in humans have been reported, but in animals reduced thyroid function, vitamin A deficiency and increased spontaneous abortion rates have all been attributed to high nitrate ingestion [15]. The World Health Organization has defined a recommended maximum daily nitrate intake of 3.65 mg kg⁻¹ and a nitrite intake of 0.4 mg kg⁻¹ [16]. This patient probably absorbed a total of about 0.7 g per day of nitric oxide while inhaling nitric oxide 40 vpm which, if converted to nitrates, is about three times this value.

The patient had considerably increased nitrate concentrations while inhaling nitric oxide, and these concentrations increased further when he developed renal failure. Further work is needed to determine if elevated nitrate concentrations have any deleterious effects.

Acknowledgement

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References

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