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Letter to the Editor

Massive hyperhomocysteinaemia as a complication of nitrous oxide inhalation

Stanislas Faguer,[1,2] Jean Ruiz[1] & Arnaud Mari[1]

[1]Service de Réanimation, Département d'Anesthésie – Réanimation, CHU de Toulouse, Toulouse, France and [2]Département de Néphrologie et Transplantation d'organes, Unité de Réanimation, CHU de Toulouse, Toulouse, France

Here, we report two cases of venous thromboembolic events associated with massive hyperhomocysteinaemia (7 to 10 fold the normal values) induced by a prolonged use of inhaled 50% nitrous oxide/oxygen premix during sickle-cell disease (SCD)-related acute pain disease. Given that SCD patients are at risk of deep vein thrombosis, we suggest that inhaled nitrous oxide should be use with caution in these patients and serum level of homocysteine should be monitored.

Inhaled 50% nitrous oxide/oxygen premix is a potent analgesic with amnesic properties and a safe profile linked to its rapid onset and elimination. Its main complication is megaloblastic anaemia that occurs after long exposures (>24 h) [1]. Here, we present two cases of massive hyperhomocysteinaemia after prolonged but intermittent therapeutic use of inhaled nitrous oxide. Two women (36 and 30-years-old), followed for SCD and receiving hydroxyurea because of recurrent vaso-occlusive disease, were hospitalized in the intensive care unit for severe acute pain disease requiring multimodal analgesia including non-steroidal anti-inflammatory drugs, tramadol, nefopan chlohydrate, paracetamol, pregabalin, ketamine and intravenous oxycodone. Because of refractory pain, inhaled 50% nitrous oxide/oxygen premix was given (10 to 20 min every 4 to 6 h for 7 to 9 days) allowing a substantial decrease of the opioid use. Neither of these patients had a previous history of venous thromboembolism and both received prophylaxis including a low molecular weight heparin. In both patients, deep vein thrombosis was recognized during their hospital stay. In one of them, thrombosis progressed despite curative anticoagulation with low molecular weight heparin (enoxaparin). In the second, iliac occlusive thrombosis (*phlegmasia caerulea dolens*) developed and required *in situ* intravenous thrombolysis. In both, no oral contraception was used. Apart from the intrinsic risk of venous thromboembolism in SCD patients [2], thrombophilia screening identified a massive hyperhomocysteinaemia (153 and 99 μmol l^{-1}, respectively; normal 5–15 μmol l^{-1}). Concomitantly, serum folic acid and vitamin B12 were normal. After inhaled nitrous oxide withdrawal and oral folic acid supplementation, serum homocysteine level normalized within 3 weeks suggesting the lack of an underlying inherited hyperhomocysteinaemia.

Nitrous oxide inhibits methionine synthetase and thus potentially leads to mild hyperhomocysteinaemia (<40 μmol l^{-1}) with uncertain clinical significance when used as an anaesthetic agent for less than 3 h [3, 4]. In our patients, the cumulative time of nitrous oxide exposure was 10 to 15 h, spread over 7 days, and nitrous oxide was the only factor that may have induced hyperhomocysteinaemia.

These cases highlight the potential for transient massive hyperhomocysteinaemia, an independent risk factor for venous thrombosis and cardiac morbidity potentially through causing endothelial dysfunction and procoagulation [5], after prolonged therapeutic use of inhaled 50% nitrous oxide/oxygen premix. In patients with sickle cell disease, other adverse events related to a direct effect of the prolonged use of this premix have also been described, including severe neuropathy [6]. Thus, we consider that prolonged use of inhaled 50% nitrous oxide/oxygen premix should be used with caution in patients with SCD, a condition at risk of venous thrombosis, and that homocysteinaemia should be monitored in cases of prolonged use.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the

previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Authors contributions

SF, JR and AM managed the patients in the ICU, SF, JR and AM designed the study and SF wrote the manuscript.

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CORRESPONDENCE
Dr Stanislas Faguer MD, PhD, Département de Néphrologie et Transplantation d'organes, INSERM U1048 (équipe 12, I2MC), Hôpital Rangueil, 1, avenue Jean Poulhes, 31000 Toulouse, France.
Tel.: +33 5 6132 3288
Fax: +33 5 6132 2351
E-mail: faguer.s@chu-toulouse.fr