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# Delayed neurologic sequelae following anoxic-anoxia related to nitrous oxide by pipeline mix-up during anesthesia

Jaouad Laoutid, Nabil Jbili, Lotfi Bibiche, Hicham Kechna, Moulay Ahmed Hachimi

## ABSTRACT

**Introduction: Pipeline mix-up is a rare situation in anesthesia and may engender hypoxic event with severe complications. Delayed neurologic sequelae may appear after anoxic and or ischemic event. We report a case of delayed neurologic sequelae following prolonged anoxia related to nitrous oxide after pipeline mix-up in a newly operation room. Case Report: A 36-year-old female, the first patient admitted for abdominoplasty under general anesthesia in a newly opened operating room. The patient was exposed to hypoxia-anoxia for several minutes due to crossing of oxygen and nitrous oxide pipelines. Nitrous oxide became the drive gas on anesthesia machine. The diagnosis of pipeline mix-up was unthinkable and delayed because of oxygen analyzer on anesthesia machine was non functional. The gas analyzer was very useful to suspect the pipeline mix-up when it showed 99% of inhaled fraction of nitrous oxide while anesthesia machine was set to deliver 100% oxygen. After complete recovery, she presented at the second postoperative day a paraparesis and dysarthria. Nitrous oxide myelopathy was eliminated because of normal vitamin B12 and homocysteine and delayed neurological sequelae (DNS) were retained. The patient has fully recovered under supratherapeutic dose of vitamin $B_{12}$ therapy. Conclusion: In a newly opened operation room, gas pipelines should be verified before beginning any anesthetic procedure. Our finding suggests that vitamin B12 may have a place in the treatment of delayed neurological sequalae.**

**Keywords: Delayed neurologic sequelae, General anesthesia, Nitrous oxide, Pipeline mic-up, Vitamin $B_{12}$**

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## INTRODUCTION

Neurologic deficits following acute anoxic insults are well recognized. However, severe neurologic dysfunction may occur in patients sometime after they recovered from initial hypoxia, generalized ischemia which was caused by severe hypotension, or both [1, 2]. Delayed neurologic sequelae (DNS) is usually caused by carbon monoxide (CO) poisoning [1, 2]. DNS induced by other types of anoxia and ischemia has rarely been reported, including complications of surgery and anesthesia, respiratory

depression, cyanosis, shock [1, 2], drug over dosage [3] and strangulation [4]. The present case illustrates delayed neurologic sequelae following prolonged anoxia related to nitrous oxide ($N_2O$) who exhibited a rapid recovery under vitamin $B_{12}$ (cobalamin) therapy.

## CASE REPORT

A 36-year-old female, ASA 1, weighing 76 kg for 1.68 m (BMI = 30 kg/m²), admitted to the operating room for abdominoplasty. The operation was planned in a newly opened operating room and the patient was the first one to be admitted in. After standard monitoring, a 20 Gauge venous route was taken. Preoxygenation was provided by anesthesia machine: Dräger Fabius® Plus (Figure 1) which was not equipped by gas analyzer and whose oxygen analyzer was not functional due to its expiration, oxygen flow meter was opened to deliver 10 liters of oxygen. Anesthetic induction was achieved by propofol (2 mg/kg), fentanyl (3 µg/kg) and mask ventilation was initiated after curarization by rocuronium (0.6 mg/kg). Four minutes after the induction when mask ventilation, cyanosis of the extremities and desaturation were observed and the patient was rapidly intubated and connected to the anesthesia machine in controlled ventilation with 50% mixture of each $O_2$ and $N_2O$. That allowed an improvement of the pulse oximetry values. Maintenance of anesthesia was provided by isoflurane 0.9%. Chest auscultation and insufflation pressures were normal. Ten minutes after of the onset of the procedure, pulse oximetry ($SpO_2$) decreased to 92%, oxygen flow was increased but $SpO_2$ values continued to decline. The respiratory auscultation and parameters was always without abnormalities. Oxygen flow was opened to 10 l/min and $N_2O$ flow stopped without improvement of the situation, and pulse oximetry values continue decreasing showing sometimes 0%, hypotension and reactive semi-mydriasis appeared.

After calling for help, we decided to change to ventilator machine, and we brought another one, same Dräger Fabius® Plus which was equipped by external gas analyzer Dräger Vamos monitoring capnography ($CO_2$), Halogens and $N_2O$ but not the $O_2$ (Figure 2). Once the gas analyzer started it showed signs of low cardiac output with deep hypocapnia to 14 mmHg and an expired fraction of $N_2O$ to 99% while the patient was connected to the anesthesia machine set to deliver 100% oxygen. Error during installation of sources and crossing of oxygen and nitrous oxide pipelines was suspected.

It was not possible to ventilate the patient with 100% oxygen because we had to set flow meter, on the anesthesia machine, to deliver 100% $N_2O$ and when it was done, the ventilator machine stopped delivering any gas (security setting of the machine to avoid ventilation without oxygen "$O_2$ failsafe"). So, for that the anesthesia machine works, we were obliged to open $O_2$ flow meter which contains $N_2O$ ($N_2O$ became the drive gas,).

In order to stop exposure to nitrous oxide, we ventilated the patient with Ambu bag using room air and once we received Oxygen bottle we connected it to the anesthesia machine permitting 100% $O_2$ ventilation to the patient. That allowed gradual rise of the $SpO_2$ and $CO_2$ with regression of the semi-mydriasis. Then the Surgeons were allowed to continue the procedure under $O_2$ 60%–air 40% mixture and 0.8% isoflurane for maintenance. The duration of hypoxic-anoxia and hypotension was about 15–20 minutes.

Error of source installation was confirmed by following through gas pipelines, oxygen pipeline of the respiratory was connected to wall oxygen source but this one was relied to $N_2O$ source, the colors of such pipelines was confounded by the installer of the new operating room.

The duration of surgery was one hour. The awakening was restless and the patient was sedated for 24 hours by midazolam-fentanyl at the ICU. Non contrast cerebral scan was without anomalies. The patient was extubated the next day without neurological deficit. At the night of the second postoperative day, the patient presented symmetrical paresthesia on the feet, ascending to the trunk, chest and both arms. This was followed by weakness and clumsiness of all limbs, loss of their use and dysarthria, mental status was normal. Before any specific therapy, vitamin $B_{12}$ and homocysteine (HC) was tested. Methylmalonic acid

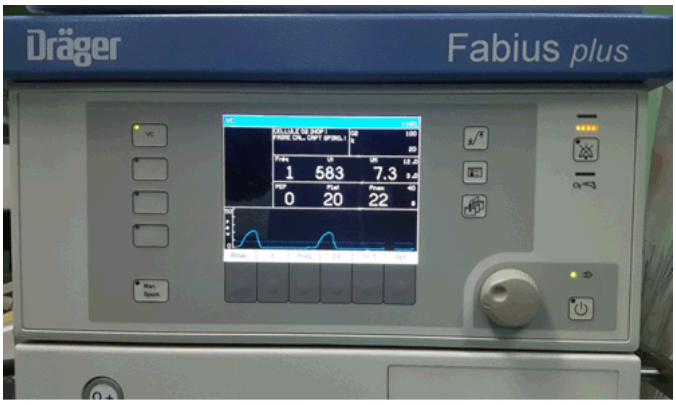


Figure 1: Drâger Fabius® Plus, the anesthesia machine in use in our operating theater ($O_2$ analyzer unfunctional).


Figure 2: External gas analyzer without analyze oxygen fractions.

(MMA) was not tested. Cerebrospinal MR Imaging was normal. Delayed neurologic sequelae due to the anoxic-anoxia were suspected and neuropathy secondary to $N_2O$ toxicity was evocated too. Before receiving results of laboratory, we decided to begin a course of vitamin $B_{12}$ (hydroxocobalamin) injections: 5 g/day. Biological exams received, two days after, showed normal vitamin $B_{12}$ at 785 pg/mL (normal 193–982 pg/mL) and normal HC level at 7 μmol/L (normal < 10 μmol/L) what permitted us to eliminate the diagnosis of nitrous oxide myelopathy. Amelioration was noted from the second injection, the numbness decreased, so we decided to maintain vitamin $B_{12}$ therapy 5 grams/day for one week then 5 grams/week for two months. The patient could walk within five days and she was discharged from the hospital after one week with a light dysarthria. She has fully recovered in two months. One year later, the patient was healthy without any sequela.

## DISCUSSION

The diagnose of nitrous oxide induced myeloneuropathy was suspected because of prolonged exposure to pure $N_2O$ but the short delay of apparition of symptoms and normal HC have made this diagnosis less probable. Even if radiologic imaging were unremarkable, in both, $N_2O$ myelopathy and DNS, early MRI scan may be normal [5, 6]. We think that the only role of nitrous oxide was as its function as an asphyxiating gas and retained the diagnosis of DNS.

There is no known neurological toxicity threshold for nitrous oxide exposure. In the last several years, multiple case reports have appeared in the medical literature regarding nitrous oxide ($N_2O$) induced myelopathy, a condition mimicking the myelopathy seen in spontaneous vitamin $B_{12}$ deficiency. Both clinically presented as a symmetrical paresthesia of the limbs ascending to the trunk and followed by weakness and clumsiness of all limbs [7, 8], and radiographically with generalized increased T2 signal seen most prominently in the dorsal and, to a much lesser extent, lateral and anterior columns of the cervical and, occasionally, thoracic cord [7–9].

For some authors, $N_2O$ toxicity is related not to the frequency or level of nitrous oxide exposure, but to the patient's levels of vitamin $B_{12}$ [4, 5]. For others, level can be normal with non-functioning vitamin $B_{12}$ evidenced by measuring MMA and HC levels, which would be decisive investigations to make the diagnosis. In our case, vitamin $B_{12}$ and HC were normal.

Delayed neurologic sequelae (DNS) is a demyelinating syndrome characterized by acute onset of neuropsychiatric symptoms days to weeks following apparent recovery from coma after a period of prolonged cerebral hypo-oxygenation [10]. DNS normally develops within 1–4 weeks of acute anoxic exposure, though the interval may be as short as one day to as late as 47 days and that the corresponding radiological findings may be delayed even later [10]. The syndrome of delayed neurologic deterioration with cerebral demyelination has been reported in the literature several times as occurring in the setting of carbon monoxide poisoning [10]. DNS unrelated to CO are reported in the literature, caused by hemorrhagic shock, prolonged hypoxia and hypotension, anoxic anoxia, cardiac arrest, drug overdose and in other situations that lead to severe hypoxia [3, 4, 10].

DNS classically conforms to one of two general categories of clinical presentation: parkinsonism or akinetic-mutism [11]. In addition to characteristic parkinsonian motor features (masked facies, rigidity, short stepped gait, tremor) dystonic posturing, agitation, apathy, hallucinations, or odd behaviors may also be present, extremely slow verbal responses with varying degrees of impaired cognition or emotional lability [12].

Akinetic-mute patients were profoundly apathetic and developed functional bowel and bladder incontinence, minimal primitive responses to pain, and pathologic laughter or crying. A near clinical presentation of our case report have been reported, DNS with severe symptoms, including quadriparesis and near-blindness, after hemorrhagic shock or prolonged respiratory arrest during complications of anesthesia [13].

The fact that hypoxic-ischemic damage to the cerebral white matter occurs in a variety of settings other than carbon monoxide intoxication supports the contention that this type of leukoencephalopathy does not depend on the unique properties of a specific intoxicant [10].

Heckmann et al. [14] hypothesize that the delay is caused by the selective necrosis of myelin-producing glia cells in the border zones of the white matter. The clinical consequences would be delayed due to the long half-life of myelin (2.5–8.7 days) as the necrosis of the myelin sheaths is known to follow the cell necrosis after 10–14 days [2]. However, the rarity of this condition seems to suggest unidentified individual susceptibilities to hypoxic neuronal injury.

There is no specific therapy or prophylaxis for DNS. Steroids, aspirin, and cerebral vasodilators were used in attempts to prevent and treat delayed neurologic sequelae, but they were reported to be ineffective [15]. Therefore, it is safer to maintain patients with acute anoxia, acute severe hypotension or both on initial prolonged bed rest, in addition to ensuring rapid restoration of their oxygenation and circulation [13].

The prognosis of post-hypoxic delayed demyelination syndrome is quite good. Choi reported 75% full recovery in one year [13], and Shillito and Drinker reported 50% full recovery within two years [16]. Wainapel et al. reported a dramatic functional recovery 3.5 months after admission for a man who developed severe spastic quadriplegia from a mixed drug overdose-induced post-hypoxic leukoencephalopathy [17].

Reported spontaneous DNS recovery was taking many months to years after the anoxic event. In our case, we noted a rapid recovery under vitamin $B_{12}$ therapy, initially

introduced for suspecting $N_2O$ toxicity and maintained for patient good response. That is suggesting that vitamin $B_{12}$ may have a place in the treatment of DNS.

Supra-therapeutic doses of cobalamin may regulate the inflammatory response and its resolution in which transcobalamins play a proven role. Such regulation may involving several mechanisms including hormone-like regulation of Tumor Necrosis Factor Alpha through reduction of excess nitric oxide, quenching of nitric oxide radicals and reactive oxygen species, the promotion of acetylcholine synthesis, central to the neuroimmune cholinergic anti-inflammatory pathway, the promotion of oxidative phosphorylation and optimal bacteriostasis and phagocytosis [18].

The proposed dose was 4/5 g intravenous of hydroxocobalamin given on up to three to five consecutive days, routinely used in the ICU as a treatment for cyanide poisoning, followed by a lower maintenance dose, dependent on patient response [18]. Hydroxocobalamin (Cyanokit) is frequently used in the smoke inhalation setting. While carbon monoxide was not our patient's mechanism of injury, that also fits the patient's time course, and the treatment was somewhat similar in that it included supratherapeutic doses of cobalamins.

Hypoxic $O_2$ pipeline condition (gas mix-up) where $N_2O$, instead of $O_2$, was inadvertently supplied to the $O_2$ pipeline occurred in The Hospital of St. Raphael in New Haven, in January 2002 and killed two patients. Even though an anesthesia machine was not involved in the New Haven cases, hypoxic "oxygen" pipeline algorithm was proposed and is applicable to anesthesia machines [19].

When $O_2$ analyzer is being used: hypoxic $O_2$ pipeline condition is suspected because of a low inhaled fraction of $O_2$ ($FiO_2$) alarm and/or reading that does not match the set $FiO_2$.

If an $O_2$ analyzer is not being used there will be no low $FiO_2$ warning. The first indication of trouble will most likely be a low $SpO_2$ alarm that is a late and non-specific warning, evocating many possible causes to be ruled out before a hypoxic $O_2$ pipeline algorithm as outlined above can be initiated with certainty [19].

In our case report, $O_2$ analyzer on the anesthesia machine was not functional because of unchanged outdated oxygen sensor capsule. The gas analyzer was very useful to suspect the pipeline mix-up when it showed 99% of inhaled fraction of $N_2O$ while anesthesia machine was set to deliver 100% oxygen. In a newly opened operation room, gas pipelines should be verified before beginning any anesthetic procedure and the anesthesia machine should be fully equipped and all its functions correctly set in order to prevent such complications and to improve security during anesthesia.

## CONCLUSION

With development of anesthesia, pipeline mix-up became a rare situation and should be present in mind in front of the diagnosis of post-hypoxic delayed demyelination syndrome should not be missed because its outcome is relatively good. Our finding suggests that early administration of supratherapeutic vitamin $B_{12}$ may have a place in the treatment of DNS, this conclusion need further investigation and more large trials.

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## Author Contributions

Jaouad Laoutid – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Nabil Jbili – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Lotfi Bibiche – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Hicham Kechna – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Moulay Ahmed Hachimi – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

## Guarantor

The corresponding author is the guarantor of submission.

## Conflict of Interest

Authors declare no conflict of interest.

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## REFERENCES

1. Ginsberg MD. Delayed neurological deterioration following hypoxia. Adv Neurol 1979;26:21–44.
2. Ginsberg MD, Hedley-Whyte ET, Richardson EP Jr. Hypoxic-ischemic leukoencephalopathy in man. Arch Neurol 1976 Jan;33(1):5–14.
3. Mizutani T, Shiozawa R, Takemori S, Tsurumaru M, Akiyama H. Delayed post-anoxic encephalopathy without relation to carbon monoxide poisoning. Intern Med 1993 May;32(5):430–3.

4. Hori A, Hirose G, Kataoka S, Tsukada K, Furui K, Tonami H. Delayed postanoxic encephalopathy after strangulation. Serial neuroradiological and neurochemical studies. Arch Neurol 1991 Aug;48(8):871–4.
5. Richardson PG. Peripheral neuropathy following nitrous oxide abuse. Emerg Med Australas 2010 Feb;22(1):88–90.
6. Alt RS, Morrissey RP, Gang MA, Hoffman RS, Schaumburg HH. Severe myeloneuropathy from acute high-dose nitrous oxide ($N_2O$) abuse. J Emerg Med 2011 Oct;41(4):378–80.
7. Ilniczky S, Jelencsik I, Kenéz J, Szirmai I. MR findings in subacute combined degeneration of the spinal cord caused by nitrous oxide anaesthesia: Two cases. Eur J Neurol 2002 Jan;9(1):101–4.
8. Beltramello A, Puppini G, Cerini R, et al. Subacute combined degeneration of the spinal cord after nitrous oxide anaesthesia: Role of magnetic resonance imaging. J Neurol Neurosurg Psychiatry 1998 Apr;64(4):563–4.
9. Hathout L, El-Saden S. Nitrous oxide-induced B12 deficiency myelopathy: Perspectives on the clinical biochemistry of vitamin B12. J Neurol Sci 2011 Feb 15;301(1–2):1–8.
10. Lee HB, Lyketsos CG. Delayed post-hypoxic leukoencephalopathy. Psychosomatics 2001 Nov–Dec;42(6):530–3.
11. Lee MS, Marsden CD. Neurological sequelae following carbon monoxide poisoning clinical course and outcome according to the clinical types and brain computed tomography scan findings. Mov Disord 1994 Sep;9(5):550–8.
12. Shprecher D, Mehta L. The syndrome of delayed post-hypoxic leukoencephalopathy. NeuroRehabilitation 2010;26(1):65–72.
13. Mizutani T, Shiozawa R, Takemori S, Tsurumaru M, Akiyama H. Delayed post-anoxic encephalopathy without relation to carbon monoxide poisoning. Intern Med 1993 May;32(5):430–3.
14. Heckmann JG, Erbguth F, Neundörfer B. Delayed postanoxic demyelination registry. Neurology 1998 Oct;51(4):1235–6.
15. Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. Arch Neurol 1983 Jul;40(7):433–5.
16. Shillito FH, Drinker CK. The problem of nervous and mental sequelae in carbon monoxide poisoning. JAMA 1936;106:669–74.
17. Wainapel SF, Gupta PC, Matz R. Post-hypoxic leukoencephalopathy with late recovery. Arch Phys Med Rehabil 1984 Apr;65(4):201–2.
18. Wheatley C. A scarlet pimpernel for the resolution of inflammation? The role of supra-therapeutic doses of cobalamin, in the treatment of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic or traumatic shock. Med Hypotheses 2006;67(1):124–42.
19. https://vam.anest.ufl.edu/Hypoxicalgorithm.pdf