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Megaloblastic hematopoiesis in a 20 year old pregnant female

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Summary

Background: Nitrous oxide can cause disordered blood cell proliferation and lead to pancytopenia and altered immune function.

Case Report: A young pregnant female patient presented after binge nitrous oxide abuse with altered mental status and abnormal vital signs. From her initial assessment she was noted to have pancytopenia and was found to have megaloblastic, hyper-cellular changes in a subsequent bone marrow biopsy. This presentation was determined to be secondary to toxic effects after heavy use of nitrous oxide.

Conclusions: Nitrous oxide exposure, including use as an inhalant, over 12 hours can lead to bone marrow abnormalities such as megaloblastic hematopoiesis.

key words: **megaloblastic hematopoiesis • nitrous oxide • pregnancy**

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BACKGROUND

Megaloblastic hematopoiesis is a hypercellular bone marrow failure syndrome intimately linked with abnormal cobalamin (B12) and folate metabolism or deficiency. These nutrients have a critical role in the synthesis of DNA. Nitrous oxide inhibits the enzyme methionine synthase, a critical enzyme in nucleic acid synthesis, by inhibiting cobalamin from acting as a coenzyme [1,2]. As a result patients develop disordered blood cell proliferation, which subsequently can cause pancytopenia and altered immune function. In contrast to aplastic anemia or other marrow failure syndromes, the marrow of these patients will be hypercellular and dysfunctional.

CASE REPORT

A 20 year old pregnant active duty white female (Gravida 3 Para 2 at 18 weeks estimated gestational age) presented to the emergency department (ED) in the custody of the local police for altered mental status. The patient was suspected of polysubstance abuse and had a history of substance abuse.

In the ED, the patient was afebrile, tachycardic to 110, tachypneic to 22 and hypotensive to 91/52. While the patient, had a cachectic appearance, she was alert and oriented toward person, place and year. Otherwise her thought processes were confused and questions were answered inappropriately and she became combative to the point of pulling out her intravenous therapy lines and her Foley catheter. Her physical exam was otherwise unremarkable. The patient was anemic with a hematocrit of 19.4% and an absolute neutrophil count of 120 and 122 on repeat (Table 1).

The patient stated that her drug use increased when her mother, also an active duty soldier, was killed in Afghanistan 5 months previously. Using the monies awarded from her mother's life insurance policy, the patient began purchasing prescription oral narcotics hydroxymorphone (Palladone, Dilaudid) and oxymorphone (Opana) on the street. After several months of oral use, she then began to crush and snort oxymorphone. Eventually, the patient added nitrous oxide from aerosol containers to her drug use regimen.

The patient had been absent without leave (AWOL) for 2 months before presenting to the ED and was being followed by the Army Substance Abuse Program for a history of marijuana abuse. As a result of her AWOL status, the

authorities were notified and the local police (she did not live on the post) were sent to her residence, where she was found locked in her house and surrounded by hundreds of empty aerosol containers.

She was admitted to the hospital for observation and management. She was retrained due to risk of self-injury; she made continued attempts to ambulate in her altered state; attempted to remove her Foley catheter using her feet and continued to be combative with the medical staff.

On hospital day 2, the patient was started on methadone 25mg daily. The patient was transfused 1 unit of irradiated packed red blood cells for anemia. On hospital day 3, due to continued decreased cell counts in her complete blood count (CBC), a bone marrow biopsy was performed showing possible viral inclusions and 7% myeloblasts noted on flow cytometry. Hematology/oncology and pathology consultants both agreed that the patient's significant response of her CBC suggested marrow failure due to substance abuse and subsequent B12 deficiency rather than a viral etiology or primary bone marrow process.

The patient was transferred to the mother baby unit where an ultrasound showed a singleton pregnancy of 18 week 2 days gestation. The patient remained stable with asymptomatic transition to methadone maintenance. She was then transferred to a 28 day inpatient rehabilitation program. Although she successfully completed the rehabilitation program, she continued on methadone maintenance and failed a random drug screen. She subsequently was separated from the Army.

The patient delivered at 38 weeks gestation via repeat cesarean section complicated by pre-eclampsia. At time of delivery, the patient was transitioned off of the methadone one month previously and on acetaminophen and oxycodone (Percocet) throughout the day.

DISCUSSION

Nitrous oxide as an anesthetic in dental offices has been linked to decreased fertility and spontaneous abortions in female dental office employees. Scavenged nitrous oxide, administered to the patient via a mask and tube, can help reduce the amount of nitrous oxide exposed to dental office employees by up to 90% or more [3].

Table 1. Complete blood count values during admission.

	White blood count	Hematocrit	Platelets	Absolute neutrophil count
Emergency Department	1,000	19.4%	35,000	109
Admission	800	21.3%	38,000	122
Day 1	1,100	19.7%	43,000	151
Day 2	1,900	25.2%	41,000	281
Day 3	4,800	25.6%	43,000	1,804
Day 4	9,000	27.4%	114,000	8,172
Discharge	15,400	27.1%	274,000	11,504

Nitrous oxide as an anesthetic agent was discovered by Joseph Priestley in 1786, upon finding that the gas relieved his toothache [4]. Nitrous oxide results in opioid receptor agonism through the mitigation of the release of corticotrophin releasing factor from the hypothalamus. It is also known to stimulate NMDA subtype glutamate receptors, which may contribute to its hypnotic effects [5]. The nitrous oxide, which can be found in household items such as whip cream containers, is also used as an inhalant to stimulate euphoria. A survey of teenagers aged 12–17 years old in the United States conducted by the National Household Survey on Drug Abuse found that 9% of this group used inhalants. Among the teenagers that reported inhalant use, 21.7% reported a lifetime use of nitrous oxide [6]. Inhalants are often used by teenagers that are homeless, incarcerated, have dropped out of school, or have suffered physical or sexual abuse or neglect. Nitrous oxide, as well as other inhalants, can be directly inhaled, inhaled from a plastic bag containing the gas, from a cloth soaked in the chemical, from aerosols, or from aerosols sprayed directly into nose or mouth.

In extremes of age the use of nitrous oxide results in neurotoxicity that is implicated in long lasting cognitive defects. Nitrous oxide is known to readily cross the placenta [5].

Our patient presented with a history, exam findings, and labs that all supported the diagnosis of megaloblastic hematopoiesis. The constellation of symptoms she presented with was rapidly and immediately recognized to be intimately related to her binge usage of inhalant nitrous oxide, along with the possibility of alternate and contributing toxic exposures. On review of her bone marrow aspirate, it was determined that her more appropriate diagnosis was megaloblastic hematopoiesis with possibility of viral coinfection. With the possibility of viral coinfection, the consideration of the patient as having acquired aplastic anemia was felt to be warranted.

CONCLUSIONS

Use of nitrous oxide for more than 2 hours can result in megaloblastic bone marrow changes. In a study of 18 intensive therapy unit patients with nitrous oxide administration followed by megaloblastic bone marrow changes there was an 89% mortality rate [2,7]. While short term exposure to nitrous oxide does not affect bone marrow function, nitrous oxide exposure longer than 12 hours does produce temporary bone marrow abnormalities, including megaloblastic hematopoiesis. After a 12 hour exposure, megaloblastic changes are milder than in patient who receive 24 hour exposure, however, patients who receive folic acid prior to nitrous oxide do not have these abnormalities [1].

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