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Severe Neurologic Deficit after Nitrous Oxide Anesthesia

Admir Hadzic, M.D., Krzysztof Glab, M.D.,† Kevin V. Sanborn, M.D.,‡ Daniel M. Thys, M.D.§*

THE interaction of nitrous oxide and vitamin B_{12} is well known from experimental studies in animals and anecdotal clinical reports.[1–4] Nitrous oxide oxidizes cobalamin in vitamin B_{12} and disrupts several pathways involved in one-carbon chemistry. The result is an irreversible inactivation of the enzyme methionine synthase, which requires vitamin B_{12} in the +1 oxidation state to act as its coenzyme. The clinical syndrome associated with oxidation of vitamin B_{12} develops after prolonged exposure to nitrous oxide and consists of megaloblastic erythropoiesis and subacute combined degeneration of the spinal cord.[2–4] We present the case of a patient who developed a severe neurologic deficit 6 weeks after anesthesia with nitrous oxide.

Case Report

A 47-yr-old previously healthy former ballet dancer underwent elective cosmetic surgery of the face and scalp. Her preanesthesia assessment disclosed a history of thyroidectomy at age 16 and a remote history of anemia. The patient did not remember the exact indications for the operation or the type of anesthesia that she received in her home country (Russia) but denied any difficulties perioperatively. She denied smoking or alcoholism and claimed to be an occasional vegetarian. There was no history of intake of vitamins or other medications. Her hematocrit was 41% with a mean corpuscular volume of 99 femtoliters (fl; normal 81–99 fl). The surgical procedure lasted 8 h, during which the patient was anesthetized with fentanyl (200 μg) and isoflurane (0.27–0.7%) in a mixture of oxygen and 70% N_2O. Intraoperative blood loss was less than 100 ml. Her intraoperative and immediate postoperative course was uneventful, and she was discharged home in good condition. Six weeks later, the patient was readmitted to the hospital with complaints of paresthesia in the extremities and unsteady gait. On admission, she gave a history of loss of balance, frequent falling, and worsening numbness and weak-

* Chief Resident in Anesthesiology.

† CA-2 Resident in Anesthesiology.

‡ Associate Director of Anesthesia; Associate Clinical Professor of Anesthesiology.

§ Director of Anesthesia; Professor of Clinical Anesthesiology.

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Department of Anesthesiology, St. Luke's–Roosevelt Hospital Center, Amsterdam Avenue at 114th Street, New York, New York 10025.

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ness in her lower back, suprapubic region, and lower extremities. A neurologic examination disclosed weakness and decreased muscle tone in both lower extremities. The patient walked with a broad base. The complete blood count on admission included hematocrit of 34% and mean corpuscular volume of 105 fl. Results of magnetic resonance imaging of her head and spine were normal. Analysis results of her cerebrospinal fluid were normal except for slightly increased proteins. The serum vitamin B_{12} concentration was 8.0 pg/ml (normal 130–770 pg/ml) and folate concentration 19.5 ng/ml (normal 1.5–20.6 ng/ml). An electrophysiologic study was suggestive of a generalized demyelinating polyneuropathy, whereas a Schilling test was diagnostic of pernicious anemia. Her neurologic condition gradually improved with monthly injections of cobalamin. Sixteen weeks after the initiation of therapy, her only complaint was mild fatigue.

Discussion

A case of severe neurologic deficit after nitrous oxide anesthesia in a patient with unsuspected pernicious anemia is described. To date, there are three reports of the development of subacute combined degeneration of the spinal cord after routine nitrous oxide anesthesia in five patients.[5–7] All of these patients, including the one in our report, had unrecognized subclinical vitamin B_{12} deficiency and underwent routine surgery under nitrous oxide anesthesia in duration of at least 90 min. After an uneventful immediate perioperative period, several weeks later they presented with severe neurologic deficits. They all had hematologic features of megaloblastic anemia at some time, decreased vitamin B_{12} concentrations, and a favorable but slow response to B_{12} therapy (table 1).

In our patient, the diagnosis of subacute combined degeneration of the spinal cord was made on the basis of the following criteria: (1) recent exposure to nitrous oxide, (2) typical clinical presentation, (3) postoperative anemia unexplained by intraoperative blood loss, (4) increase in mean corpuscular volume, (5) low serum vitamin B_{12} concentration, (6) normal values for folate, (7) slightly increased protein concentration in her cerebrospinal fluid, and (8) the results of the electrophysiologic study. Underlying pernicious anemia is the most likely explanation for our patient's failure to restore her levels of B_{12} postoperatively. Other neurologic diseases that can be confused with vitamin B_{12} deficiency include multiple sclerosis, cervical spondylosis, spinal cord tumors, and syphilitic meningomyelitis. These were excluded by her clinical course and by the results of the diagnostic tests. However, a coincidental administration of nitrous oxide to a patient who was in the midst of developing neurologic manifestations associated with pernicious anemia cannot be excluded.

The interaction of cobalamin and nitrous oxide was first reported by Lassen *et al.*[2] in 1956. Patients undergoing treatment for tetany with prolonged sedation with nitrous oxide experienced hematologic changes identical to those produced by vitamin B_{12} deficiency. The neurologic effects of chronic exposure to nitrous oxide were reported in 1978 in several individuals who used nitrous oxide for recreational purposes.[3,4] They presented with a neurologic syndrome consisting of weakness and spasticity of the legs, ataxia, paresthesias of the hands and legs, and mental status changes.

To date, cobalamin is known to be required in two biochemical reactions in humans: the conversion of L-methylmalonyl coenzyme A into succinyl coenzyme A and the formation of methionine by methylation of homocysteine. The transmethylation reaction is essential to DNA synthesis and to the maintenance of the myelin sheath by the methylation of myelin basic protein. Active vitamin B_{12} contains cobalt in its reduced form (Co+). Nitrous oxide irreversibly oxidizes active reduced cob(I)alamin to inactive cob(III)alamin.[1] The inactive cobalamin is excreted so that repetitive exposure to nitrous oxide results in depletion of cobalamin body stores.

The most common causes of vitamin B_{12} deficiency are pernicious anemia, postgastrectomy, intestinal organisms ("blind loops"), and ileal abnormalities. Certain clinical features of vitamin B_{12} deficiency are common to all etiologies. The hematologic manifestations are almost entirely the result of anemia. The gastrointestinal manifestations reflect the effect of cobalamin deficiency on the rapidly proliferating gastrointestinal epithelium. The neurologic complications are the most worrisome, because infrequently, patients may fail to revert to normal with treatment.[8] The most prominent findings are in the peripheral nerves and dorsal and lateral columns of the spinal cord. Fragmentation and spongy degeneration of myelin usually begin in the lower cervical and upper thoracic regions.[9] Patients first complain of paresthesias in the hands or legs. Neurologic symptoms progress if untreated; ataxia and stiffness eventually are followed by paraplegia and dysfunction of bowel and bladder. Occasionally, the neurologic disease occurs in a patient with a normal hematocrit and normal erythrocyte indexes.[8]

The shortest duration of exposure to nitrous oxide required to produce megaloblastic hematopoiesis varies among patients and may depend on their general

Table 1. Neurologic Sequelae Associated with Nitrous Oxide Anesthesia in Patients with Unrecognized Vitamin B12 Deficiency

Table 1. Neurologic Sequelae Associated with Nitrous Oxide Anesthesia in Patients with Unrecognized Vitamin B12 Deficiency

Reference	Age (yr)	Gender	Operation	Duration of Anesthesia (h)	Onset of Symptoms (wk)	Symptoms and Signs	Vitamin B12 Blood Concentration*	Mean Corpuscular Volume (fl) (normal = 81–99 fl)	Hematocrit (%)	Results of B12 Therapy
Schilling[5] (1986)	36	F	Abdominal hysterectomy	1.5	5	Numbness, paresthesias, weakness, Lhermitte's sign	100 ng/L (normal > 170 ng/L)	92,† 108‡	38,† 41‡	Dramatic improvement
	58	F	Laparotomy	1.5	6	Paresthesias, weakness	NA	76,† NA‡	29.5,† NA‡	Dramatic improvement
			Laparotomy 2 mo later		4	Weakness, loss of position and vibration sense	180, 169 ng/L (normal > 325 ng/L)	92,† 99‡	29,† 37‡	Dramatic improvement
Holloway and Alberico[7] (1990)	54	F	Cervical decompression and fusion	2.3		Weakness, spasticity, inability to walk	<50 pg/ml (normal 200–950 pg/ml)	122,† 127‡	NA	Incomplete recovery
	46	F	L5–S1 discectomy	2.0	NA	Numbness in legs, difficulty walking, blurred vision	106 pg/ml (normal 200–1,000 pg/ml)	NA,† 104‡	NA,† 42‡	Complete resolution
Flippo *et al.*[6] (1993)	59	M	Excision of scalp melanoma, neck dissection	3.5	2.5	Weakness, dizziness, paresthesias, gait disturbance confusion	<75 pM (normal > 150 pM)	110,† 113‡	NA,† 37‡	Complete resolution
Present report	47	F	Face and scalp cosmetic surgery	8.0	6	Paresthesias, unsteady gate, decreased muscle tone, weakness	8 pg/ml (normal 130–770 pg/ml)	99,† 105‡	41,† 34‡	Complete resolution

NA = not applicable.

* Units and normal values vary from laboratory to laboratory. Each value for vitamin B12 blood concentration is shown as published with units and normal values as presented in the original publication. Note that ng/L = pg/ml and that 200 pg/ml = 150 pM.

† Laboratory values measured at the time patients underwent surgery.

‡ Laboratory values measured at the time patients presented with neurological symptoms.

health. In healthy patients undergoing general surgery, mild megaloblastic bone marrow changes can be seen after 12 h of exposure to 50% N_2O. These changes become marked after 24 h of exposure.[10] Seriously ill patients could be at increased risk of nitrous oxide-related bone marrow changes.[11] Experimental data suggest that the threshold concentration of nitrous oxide below which nitrous oxide has no biochemical effect is 1,000 ppm (0.1%).[12] In one study, 3 of 20 dentists exposed to mean concentrations of nitrous oxide of up to 4,600 ppm had abnormal bone marrow.[13] It has been found that methionine synthase activity is low after several hours of routine anesthesia with nitrous oxide.[14] Recovery of the enzyme activity takes 3–4 days, because the oxidation of cobalamin is irreversible and new enzyme must be synthesized to restore the activity. The incidence of nitrous oxide-related neurologic complications and the minimum duration of exposure to nitrous oxide required to produce neurologic complications are not known. It is possible that nitrous oxide-related neurologic manifestations are mostly mild or transient and thus underreported, because most anesthesiologists are not aware of the progress of their patients several weeks after anesthesia and surgery. We learned about our case after the patient was admitted to the hospital and an anesthesiology consultation was requested by the surgeon.

We conclude that the use of nitrous oxide should be reconsidered in patients who have an increased mean corpuscular volume on their routine preoperative hematology screen, history of unexplained anemia, or vitamin B_{12} deficiency. In a patient who presents with a complex neurologic defect several weeks after anesthesia with nitrous oxide, cobalamin deficiency should be suspected.

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Hiroshi Ishimura, M.D.,*

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* Staff Anesthesiologist, De
Corporation Yawata Works
higashiku, Kitakyushu, 805,
† Instructor, Department
pational and Environmental
gaoka, Yahatanishiku, Kitaky
‡ Associate Professor, Depa
Occupational and Environm
Iseigaoka, Yahatanishiku, Kit
§ Professor, Department
pational and Environmental
gaoka, Yahatanishiku, Kitaky
‖ Chief Anesthesiologist, D
Corporation Yawata Works
higashiku, Kitakyushu, 805,

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