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Case Studies in Environmental Medicine

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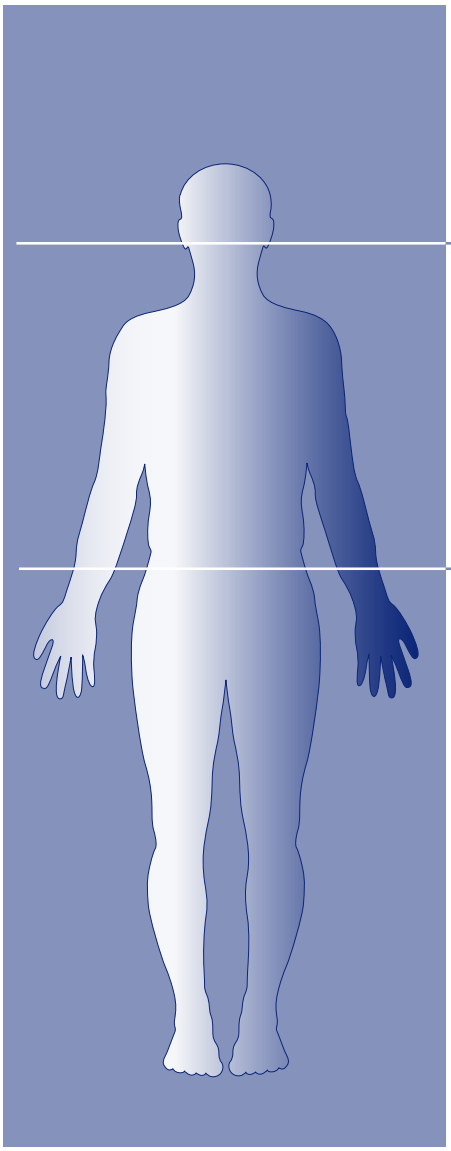

NITRATE/NITRITE TOXICITY

Environmental Alert

- Nitrate toxicity causes methemoglobinemia, which is a wholly preventable disease.
- Infants younger than 4 months of age are at particular risk of nitrate toxicity from contaminated water.
- The widespread use of nitrate fertilizers increases the risk of well-water contamination in rural areas.

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. This course is also available on the ATSDR Web site, www.atsdr.cdc.gov/HEC/CSEM/. See page 3 for more information about continuing medical education credits, continuing nursing education units, and continuing education units.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Disclaimer

The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this monograph, ATSDR has made diligent effort to ensure the accuracy and currency of the information presented, but makes no claim that the document comprehensively addresses all possible situations related to this substance. This monograph is intended as an additional resource for physicians and other health professionals in assessing the condition and managing the treatment of patients potentially exposed to hazardous substances. It is not, however, a substitute for the professional judgment of a health care provider. The document must be interpreted in light of specific information regarding the patient and in conjunction with other sources of authority.

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Each content expert for this case study indicated no conflict of interest to disclose with the case study subject matter.

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Case Studies in Environmental Medicine (CSEM): Nitrate/Nitrite Toxicity

Goals and Objectives

The goal of the CSEM is to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients.

After completion of this educational activity, the reader should be able to discuss the major exposure route for nitrates/nitrites, describe two potential environmental and occupational sources of nitrate/nitrate exposure, give two reasons nitrates/nitrites is a health hazard, describe three factors contributing to nitrate/nitrite toxicity, identify evaluation and treatment protocols for persons exposed to nitrates/nitrites, and list two sources of information on nitrate/nitrite.

Accreditation

Continuing Medical Education (CME)

The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1.0 hour in category 1 credit toward the American Medical Association (AMA) Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Nursing Education (CNE)

This activity for 1.2 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

Continuing Education Units (CEU)

CDC has been approved as an Authorized Provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.1 continuing education units (CEUs).

Instructions

See page 4

The questionnaire and posttest must be completed and returned electronically, by fax, or by mail for eligibility to receive continuing education credit.

Instructions for Completing CSEM Online

1. Read this CSEM, *Nitrate/Nitrite Toxicity*; all answers are in the text.
2. Link to the MMWR/ATSDR Continuing Education General Information page (www.cdc.gov/atsdr/index.html).
3. Once you access this page, select the Continuing Education Opportunities link.
4. Once you access the MMWR/ATSDR site online system, select the electronic file and/or register and test for a particular ATSDR course.
   a. Under the heading "Register and Take Exam," click on the test type desired.
   b. If you have registered in this system before, please use the same login and password. This will ensure an accurate transcript.
   c. If you have not previously registered in this system, please provide the registration information requested. This allows accurate tracking for credit purposes. Please review the CDC Privacy Notice (www.cdc.gov/privacy.htm).
   d. Once you have logged in/registered, select the test and take the posttest.
5. Answer the questions presented. To receive continuing education credit, you must answer all of the questions. Some questions have more than one answer. Questions with more than one answer will instruct you to "indicate all that are true."
6. Complete the course evaluation and posttest no later than **January 4, 2007**.
7. You will be able to immediately print your continuing education certificate from your personal transcript.

Instructions for Completing CSEM on Paper

1. Read this CSEM, *Nitrate/Nitrite Toxicity*; all answers are in the text.
2. Complete the evaluation questionnaire and posttest, including your name, mailing address, phone number, and e-mail address, if available.
3. Circle your answers to the questions. To receive your continuing education credit, you must answer all of the questions.
4. Sign and date the posttest.
5. Return the evaluation questionnaire and posttest, no later than **December 4, 2006**, to CDC by mail or fax:

Mail
Continuing Education Coordinator
Division of Health Education and Promotion, ATSDR
1600 Clifton Road, NE (MS E-33)
Atlanta, GA 30333

or

Fax
404-498-0061
ATTN: Continuing Education Coordinator

6. You will receive an award certificate within 90 days of submitting your credit forms. No fees are charged for participating in this continuing education activity.

Case Study

A 2-month-old infant is vomiting and has diarrhea, tachypnea, and cyanosis

A 2-month-old female infant is brought to your clinic in a rural area for a routine well-baby checkup. According to the child's chart, she was delivered 2 weeks early because of maternal toxemia. There was no neonatal distress; her birth weight was 7 pounds and 11 ounces.

Today, the mother states that she has noticed an intermittent bluish discoloration of the baby's lips, tip of the nose, and ears. Physical examination of the infant is negative for both cardiac murmurs and abnormalities on lung auscultation. A below-average weight gain is noted. Feedings consist of 4 ounces of diluted formula every 2 hours. The infant has occasional loose stools. You instruct the parents to increase caloric feedings with vitamin and mineral supplements and to call you immediately if any further episodes of the bluish discoloration occur.

Approximately 3 weeks later, the baby's frantic parents call your office; the infant is crying incessantly and has vomiting and profuse diarrhea. When the baby is brought to your clinic a few minutes later, she is afebrile but has tachypnea, cyanosis, and drowsiness. Her blood pressure is 78/30 mm Hg (normal 50th percentile for her age is 80/46 mm Hg), heart rate is 140/min, and respiration rate is 40/min. An ambulance is summoned and 100% oxygen by face mask is administered; however, no improvement in the cyanosis is noted on her arrival at the hospital emergency department.

The examining emergency physician now notes a grade II/VI systolic murmur and central cyanosis, which has not improved despite administration of 100% oxygen for nearly 1 hour. There is no evidence of cardiac failure, atelectasis, pneumonitis, or pneumothorax. Therapy is started, which results in a dramatic resolution of the cyanosis. The infant is discharged on the second hospital day with no evidence of central nervous system hypoxic damage.

Pretest

(a) What is the most likely cause of this infant's cyanosis?

(b) What laboratory tests, either obtained during the hospitalization or ordered subsequently, would assist in confirming the diagnosis?

(c) What steps, if any, can be taken to prevent a recurrence of cyanosis and distress in this infant?

Exposure Pathways

Nitrate (NO_3^-) and nitrite (NO_2^-) are naturally occurring inorganic ions, which are part of the nitrogen cycle. Microbial action in soil or water decomposes wastes containing organic nitrogen first into ammonia, which is then oxidized to nitrite and nitrate. Because nitrite is easily oxidized to nitrate, nitrate is the compound predominantly found in groundwater and surface waters. Contamination with nitrogen-containing fertilizers, including anhydrous ammonia as well as animal or human natural organic wastes, can raise the concentration of nitrate in water.

Nitrate-containing compounds in the soil are generally soluble and readily migrate with groundwater.

- Shallow, rural domestic wells are most likely to be contaminated with nitrates, especially in areas where nitrogen-based fertilizers are in widespread use.

Approximately 14 million households in the United States use private wells to supply their drinking water (Bureau of the Census 1993). In agricultural areas, nitrogen-based fertilizers are a major source of contamination for shallow groundwater aquifers that provide drinking water. A recent United States Geological Survey study showed that >8,200 wells nationwide were contaminated with nitrate levels above the U.S. Environmental Protection Agency (EPA) drinking water standard of 10 parts per million (ppm) (US Geological Survey 1995).

- Other nitrate sources in well water include seepage from septic sewer systems.

Because of the risks for potential adverse health effects, persons who use drinking water that contains nitrate levels >10 milligrams per liter (mg/L) should have alternative sources of water or appropriate treatment of existing supplies. Information regarding testing of well water can be obtained from city or county health departments. Other sources of nitrate contamination are organic animal wastes and contamination from septic sewer systems, especially in wells <100 feet deep. During spring melt or drought conditions, both domestic wells and public water systems using surface water can show increased nitrate levels.

- Foodstuffs contaminated with nitrites and sausage preserved with nitrates and nitrites have caused symptomatic methemoglobinemia in children.

Although vegetables are seldom a source of acute toxicity, they account for >70% of the nitrates in a typical human diet. Cauliflower, spinach, collard greens, broccoli, and root vegetables have a naturally greater nitrate content than other plant foods do. The remainder of the nitrate in a typical diet comes from drinking water (about 21%) and from meat and meat products (about 6%) in which sodium nitrate is used as a preservative and color-enhancing agent.

Symptomatic methemoglobinemia has occurred in children who have eaten sausage heavily treated with nitrates and nitrites. For infants, the major source of nitrate exposure is drinking water used to dilute formula.

- Deliberate abuse of volatile nitrite inhalants can cause severe methemoglobinemia and death.

Accidental exposure to nitrites in chemical laboratories and ingestion in suicide attempts have been described. Deliberate abuse of volatile nitrites (amyl, butyl, and isobutyl nitrites) as psychedelics or aphrodisiacs frequently occurs. These agents are known by street names such as “snappers,” “poppers,” “Locker Room,” and “Rush.”

Nitrate or nitrite exposure also can occur from certain medications. Infants and children are especially susceptible to nitrate exposure through topical silver nitrate used in burn therapy. Other medications implicated in cases of nitrate or nitrite toxicity are quinone derivatives

(antimalarials), nitroglycerine, bismuth subnitrite (antidiarrheal), ammonium nitrate (diuretic), amyl and sodium nitrites (antidotes for cyanide and hydrogen sulfide poisoning), and isosorbide dinitrate/tetranitrates (vasodilators used in coronary artery disease therapy) (Table 1).

Sodium nitrite used as an anticorrosive agent in cooling fluids, ammonium nitrate found in cold packs, and nitrous gases used in arc welding are other possible sources of exposure. An ethyl nitrite folk remedy called "sweet spirits of nitre" has caused fatalities. Serious poisoning and death have occurred when sodium nitrate was mistaken for table salt and ingested with food.

Table 1. Reported Inducers of Methemoglobinemia

Agent	Source/Use
Inorganic nitrates/nitrites	Contaminated well water Meat preservatives Vegetables: carrot juice, spinach Silver nitrate burn therapy Industrial salts Contaminants of nitrous oxide canisters for anesthesia
Organic nitrites	
Butyl/isobutyl nitrite	Resorcinol
Amyl/sodium nitrite	Inhalant in cyanide antidote kit
Nitroglycerine	Oral, sublingual, or transdermal pharmaceuticals for treatment of angina
Others	
Aniline/aminophenols	Laundry ink
Nitrobenzene	Industrial solvents, gun-cleaning products
Local anesthetics	Benzocaine, lidocaine, Propitocaine, prilocaine
Sulfonamides	Antibacterial drugs
Phenazopyridine	Pyridium
Antimalarials	Chloroquine, primaquine
Sulfones	Dapsone
p-Aminosalicylic acid	Bactericide (tuberculostatic)
Naphthalene	Mothballs
Copper sulfate	Fungicide for plants, seed treatments
Resorcinol	Antiseborrheic, antipruritic, antiseptic
Chlorates	Matches, explosives, pyrotechnics
Combustion products	Fires

Adapted from Dabney et al. (1990).

Challenge

(1) What questions will you ask the parents of the infant in the case study to help determine the cause of the cyanosis?

(2) If well water used to dilute formula is implicated in the cyanosis, what are some possible causes of its nitrate contamination?

Who's At Risk

- Infants younger than 4 months of age are at the greatest risk for nitrate toxicity.

Infants younger than 4 months of age who are fed formula diluted with water from rural domestic wells are especially prone to developing acute acquired methemoglobinemia from nitrate exposure. The pH of the gut is normally higher in infants than in older children and adults. Higher gut pH enhances the conversion of ingested nitrate to more potent nitrite; gastroenteritis with vomiting and diarrhea can exacerbate nitrite formation.

A large proportion of hemoglobin in infants is in the fetal hemoglobin form, which is more readily oxidized by nitrites to methemoglobin than adult hemoglobin is. At approximately 24 weeks gestation, hemoglobin F accounts for 90% of the hemoglobin in the body; the production of adult hemoglobin increases after 32 weeks gestation (Canadian Paediatric Society 1992). Additionally, premature or newborn infants might be more susceptible because they can have two to five times the level of fetal hemoglobin (American Academy of Pediatrics 1970).

In infants, reduced nicotinamide-adenine dinucleotide (NADH)-dependent methemoglobin reductase (reduced form of nicotinimide adenine dinucleotide), the enzyme responsible for reduction of methemoglobin back to normal hemoglobin, has only about half the activity present in adults. These factors combine to place young infants who are fed formula diluted with nitrate-contaminated well water at the greatest risk for toxicity. Little evidence exists showing that breast-fed infants develop methemoglobinemia from exposure to nitrates ingested by the nursing mother.

The first reported case of fatal acquired methemoglobinemia in an infant due to ingestion of nitrate-contaminated well water occurred in 1945. Since then, about 2,000 similar cases of acquired methemoglobinemia in young infants have been reported worldwide; about 10% of such cases result in fatality. The most recently reported U.S. case of infant mortality due to this source was in 1987.

In pregnant women, the level of methemoglobin increases from the normal (0.5% to 2.5% of total hemoglobin) to a maximum of 10.5% at the 30th week of pregnancy and subsequently declines to normal after delivery. Thus, pregnant women might be more sensitive to the induction of clinical methemoglobinemia by nitrites or nitrates at or near the 30th week of pregnancy.

An estimated 1% to 2% of the U.S. population using drinking water from public water systems might be consuming nitrates in excess of the EPA-recommended maximum concentration. It is also estimated that residents in as many as 603,000 homes consume drinking water from nitrate-contaminated domestic wells. Although suppliers of public water sources are required to monitor regularly nitrate concentrations, in general, rural wells are not routinely tested for nitrates.

- About 1% to 2% of the U.S. population that uses drinking water from public water systems might be exposed to nitrates in excess of the EPA-recommended maximum concentration.

Challenge

(3) What recommendations can you make to the infant's family in the case study to prevent further cyanotic episodes?

Biologic Fate

In humans, ingested nitrate is rapidly absorbed from the proximal small bowel and distributed throughout the body. Nitrate then enters the large bowel from the blood, where it is rapidly converted to highly reactive nitrite, in part by fecal microorganisms. The formed nitrite is reabsorbed into the blood, where it reacts with the ferrous (Fe^{2+}) iron of deoxyhemoglobin, forming methemoglobin with iron in the ferric (Fe^{3+}) valence state. Ferric iron is unable to transport oxygen.

- In vivo conversion of nitrates to nitrites significantly enhances nitrates' methemoglobin-inducing potency.

Nitrates are rapidly converted in the liver to denitrated metabolites and inorganic nitrites, which are then excreted in urine. Approximately 60% to 70% of an ingested nitrate dose is excreted in urine within the first 24 hours. About 25% is excreted in saliva through an active blood nitrate transport system and potentially is reabsorbed. Half-lives of parent nitrate compounds are usually <1 hour; half-lives of metabolites range from 1 to 8 hours.

- Nitrates are excreted rapidly in the urine.

Challenge

(4) What factors make infants younger than 4 months of age more susceptible to developing methemoglobinemia when exposed to nitrates?

Physiologic Effects

Unless favorable conditions exist for reducing nitrate to nitrite in the gut (i.e., high pH, proper intestinal microbial flora), ingested nitrate (NO^{3-}) is metabolized and excreted without producing apparent adverse effects. The effects of nitrite (NO^{2-}) are the same whether nitrite-containing compounds are ingested or inhaled, or nitrite is produced in vivo from nitrate.

Hematologic Effects

- Acute acquired methemoglobinemia is the most important adverse health effect caused by excessive nitrate exposure.

The principal mechanism of nitrite toxicity is the oxidation of the ferrous iron (Fe^{2+}) in deoxyhemoglobin to the ferric (Fe^{3+}) valence state, producing methemoglobin. Methemoglobin cannot reversibly bind or transport circulating oxygen. Depending on the percentage of total methemoglobin in oxidized form, the clinical picture is one of oxygen deprivation with cyanosis, cardiac dysrhythmias and circulatory failure, and progressive central nervous system (CNS) effects. CNS effects can range from mild dizziness and lethargy to coma and convulsions.

- Some methemoglobin-inducing agents can also cause Heinz body hemolytic anemia or sulfhemoglobinemia.

Hemoglobin protein can also be oxidized, causing denaturation and erythrocyte hemolysis and resulting in hemolytic anemia. The denatured protein is visible on special peripheral blood stains as Heinz bodies (minute bodies sometimes seen in erythrocytes by the dark illumination method). Many agents that induce methemoglobin can also induce a sulfhemoglobinemia, which is usually benign but might confound the diagnosis. Sulfhemoglobin might produce a cyanosis apparent at concentrations as low as 3% to 5% total hemoglobin.

Two normally present enzymes (one NADH dependent, the other reduced nicotinamide adenine dinucleotide phosphate [NADPH] dependent) reduce methemoglobin back to hemoglobin. A physiologic methemoglobinemia (1% to 2% of total hemoglobin) is typical in humans as a result of exposure to oxidizing substances and diet. A rare congenital methemoglobinemia (10% to 50% of total hemoglobin) can be found in persons with either hemoglobin M disease (a disease caused by a group of abnormal hemoglobins in which a single amino acid substitution favors the formation of methemoglobin, in spite of normal quantities of methemoglobin reductase) or a deficiency of NADH-dependent methemoglobin reductase. Acquired methemoglobinemia is caused by exposure to oxidizing substances including nitrates and

nitrites. Persons with an NADH-dependent reductase deficiency might be more susceptible to developing symptomatic methemoglobinemia after exposure to nitrates and nitrites.

Cardiovascular Effects

In large doses, nitrite is an excellent vasodilator because of its relaxing action on vascular smooth muscle; hypotension and shock can result. Systolic flow murmurs can be heard on auscultation in persons with severe methemoglobinemia, which can develop with too-rapid intravenous administration of sodium nitrite (used as an antidote for cyanide and hydrogen sulfide poisoning) or sodium nitroprusside (used in hypertensive crisis therapy). In patients who have inhaled volatile nitrites, transient electrocardiographic changes (T-wave inversions and ST-segment depression) might be noted.

- Hypotension, shock, and cardiac arrhythmias can occur in cases of severe methemoglobinemia.

Respiratory Effects

Metabolic acidosis develops in cases of severe methemoglobinemia, especially in young infants or when hypotension and shock are present. Dyspnea and tachypnea are common findings in patients with significant methemoglobinemia. Respiratory tract irritation can occur in patients who abuse volatile nitrites.

- Severe methemoglobinemia might lead to metabolic acidosis.

Other Effects

A chocolate-brown or slate-gray central cyanosis (involving the trunk and proximal portions of the limbs, as well as the distal extremities, mucous membranes, and lips) is one of the hallmarks of methemoglobinemia. This cyanosis is due to the dark chocolate-brown color of methemoglobin itself and can become noticeable at a concentration of 10%–15% of total hemoglobin.

- Chocolate-brown cyanosis is an indicator of methemoglobinemia.

Concern has been expressed about the cancer-causing potential of nitrates and nitrites used as preservatives and color-enhancing agents in meats. Nitrates can react with amino acids to form nitrosamines, which have been reported to cause cancer in animals.

A slight increase in stomach cancer incidence was seen in a group of 1,756 male workers at a nitrate fertilizer plant. An increased incidence of stomach cancer has been observed in one group of workers with occupational exposures to nitrate fertilizer (Zandjani et al. 1994).

Clinical Evaluation

History and Physical Examination

- Cyanosis that fails to improve with administration of 100% oxygen is a sentinel finding in cases of methemoglobinemia.

Evaluation of a patient with suspected nitrate/nitrite exposure includes a complete medical history and physical examination. Clues to potential exposure are often obtained by reviewing the following items with the patient or family:

- location of home (urban, suburban, or rural);
- drinking water source and supply (if well water: depth, location, type of well construction, and frequency of microbiologic and nitrate testing);
- surrounding activities (agricultural or industrial) and proximity to drinking-water source;
- type of sewer system (municipal or septic) and proximity to drinking-water source;
- recent flooding;
- occupations, avocations, and hobbies of family members;
- nutritional status (for infants: type of formula, feeding regimen, and source of dilution water);
- family history, including recent use of medications by infant and mother; and
- history of recent gastroenteritis with vomiting or diarrhea.

Physical examination should include special attention to the color of the skin and mucous membranes. If there is a history of gastroenteritis (especially in infants), evaluate the patient for the possible presence of dehydration (poor skin turgor, sunken fontanelle, dry mucous membranes). All cyanotic patients should be assessed for possible cardiac and lung disease (cardiac murmurs, gallops, arrhythmias; rales, rhonchi, wheezes, dullness or hyperresonance in the chest). A central chocolate-brown or slate-gray cyanosis that does not respond to administration of 100% oxygen is indicative of methemoglobinemia. Cyanosis due to cardiorespiratory compromise most often improves with administration of 100% oxygen.

In young infants, look for labored breathing, respiratory exhaustion, hypotension, below-average weight gain, and failure to meet developmental markers. Gastroenteritis can increase the rates of production and absorption of nitrites in young infants and aggravate methemoglobinemia.

Signs and Symptoms

Signs and symptoms of methemoglobinemia can be directly correlated with the percentage of total hemoglobin in the oxidized form (Table 2).

- Signs and symptoms of methemoglobinemia are related to the percentage of oxidized hemoglobin in the blood.

The lips and mucous membranes of patients with nitrate/nitrite toxicity usually have more of a brownish than a bluish cast. Dyspnea, especially on exertion, is common. Varying degrees of central nervous system depression might be present. The cardiac and pulmonary examinations are usually normal, but systolic flow murmurs might be detected. Cardiac arrhythmias and hypotension can occur in patients with severe poisoning, although death from methemoglobinemia alone is uncommon, except in infants.

Laboratory Evaluation

Most commonly, a drop of the patient's blood is placed on a piece of filter paper next to a drop of blood from person who does not have methemoglobinemia; when dry, the blood with methemoglobin will turn a deep chocolate-brown or slate-gray color. A tube of methemoglobin-containing blood will not turn red when shaken in air or when oxygen is bubbled through it, whereas blood that is dark because of normal deoxyhemoglobin will turn red.

- Methemoglobinemia results in distinct changes in blood color and oxygen-carrying capacity.

Screening Tests

- Examination of blood color.
- Determination of the calculated versus measured arterial saturation gap.
- Hemoglobin and hematocrit.
- Serum-free hemoglobin (for hemolysis detection).
- Serum haptoglobin (for hemolysis detection).

Table 2. Signs and Symptoms of Methemoglobinemia

Methemoglobin Concentration (%)	Clinical Findings
10–20	Central cyanosis of limbs/trunk; usually asymptomatic
20–45	Central nervous system depression (headache, dizziness, fatigue, lethargy, syncope), dyspnea
45–55	Coma, arrhythmias, shock, convulsions
>70	High risk for mortality

From Dabney et al. (1990).

- Heinz bodies on peripheral blood smear.
- Urinalysis.

Specialized Tests

- Determination of methemoglobin level.
- Tests for causes of congenital methemoglobinemia.
- Hemoglobin electrophoresis.
- Activity of NADH-dependent methemoglobin reductase.

Tests for Causes of Failure of Methylene Blue Therapy (see Treatment and Management section)

- Activity of glucose-6-phosphate dehydrogenase (G-6-PD).
- Activity of NADPH-dependent methemoglobin reductase.
- Sulfhemoglobin blood level (not readily available for clinical use).

Direct Biologic Indicators

- Measurements of nitrates or nitrites in blood, urine, or saliva are not clinically useful.

Although 80% to 90% of the body's excretion of nitrate is through urine and saliva, biologic nitrate or nitrite levels are generally not useful for diagnostic purposes. However, urinary and salivary nitrate concentrations can be important indicators of exposure requiring remedial action. The correlation between blood nitrite and methemoglobin is not usually linear at lower nitrite concentrations because a certain minimum amount of nitrite must enter the bloodstream before a measurable increase in methemoglobin concentration can be detected.

Indirect Biologic Indicators

- The most useful diagnostic test for nitrate toxicity is a blood methemoglobin level.

The methemoglobin level in blood is the most useful screening, as well as diagnostic, test for nitrate toxicity. Methemoglobin can be measured in whole blood using a visible spectrophotometer (or co-oximeter) at 635 nanometers. To express the methemoglobin level as a percentage, total hemoglobin content of the blood sample also must be determined. Oximeters used to measure methemoglobin levels can falsely report sulfhemoglobin as methemoglobin. Although sulfhemoglobinemia is seldom severe enough to be life-threatening, its presence can explain some methylene blue treatment (see Treatment and Management section) failures. For the evaluation of suspected congenital methemoglobinemia, hemoglobin electrophoresis is helpful.

- Percent oxygen (O_2) saturation is an important but nonspecific finding in patients with methemoglobinemia.

In patients with methemoglobinemia, the partial pressure of oxygen (PO_2) is usually normal despite the presence of an abnormal hemoglobin that cannot bind or transport oxygen. The percent O_2 saturation calculated by some blood-gas instruments from the PO_2, or calculated manually with a nomogram, will be normal. However, the percent O_2 saturation actually measured with a co-oximeter will be decreased,

resulting in a calculated versus measured arterial "percent O_2 saturation gap." This finding is not specific for methemoglobinemia, however, because carboxyhemoglobinemia and sulfhemoglobinemia produce the same findings.

Percent O_2 saturation determined with a pulse oximeter might be unreliable in patients with methemoglobinemia, especially after administration of methylene blue (see Treatment and Management section). Arterial blood gases should be used to monitor oxygenation in such patients.

Environmental Indicators

In young infants, drinking water is the most common source of nitrate exposure. Water tests for nitrate can be obtained from any public health laboratory that uses approved EPA procedures. Results should be carefully compared to the reference units provided by the laboratory. Some laboratories report nitrate levels as milligrams per liter nitrate; others report nitrate levels as milligrams-per-liter nitrate-nitrogen (NO_3-N).

- Because drinking water is the most common source of nitrates, testing the water supply of patients with a suspected exposure is prudent.

Challenge

(5) In addition to methemoglobinemia, what other clinical conditions might occur from exposure to methemoglobin-inducing substances?

(6) What laboratory tests are useful for evaluating a patient with suspected methemoglobinemia?

Treatment and Management

In cases of mild nitrate toxicity (blood methemoglobin levels <20%), asymptomatic patients do not require treatment other than avoiding ingestion or inhalation of substances that cause methemoglobinemia. In symptomatic patients with moderate or severe toxicity and hypoxia or dyspnea, 100% oxygen should be administered immediately to saturate fully all remaining normal hemoglobin.

- Methylene blue is an effective antidote for most patients with methemoglobinemia.

Specific therapy for methemoglobinemia consists of intravenous administration of methylene blue at a dose of 1 to 2 milligrams/kilograms (mg/kg) body weight (0.1 to 0.2 milliliters [mL]/kg body weight of a 1% solution in saline) over a 5- to 10-minute period. Within 15 minutes of methylene blue administration, cyanosis will usually begin obviously to improve. If no response to the initial injection occurs within 15 minutes in seriously ill patients, or within 30 to 60 minutes in moderately ill patients,

a second methylene blue dose of 0.1 mL/kg body weight can be given. Caution is advised because methylene blue can slightly worsen methemoglobinemia when given in excessive amounts. In general, the total dose administered during the first 2 to 3 hours should not be >0.5 to 0.7 mL/kg of body weight.

Methylene blue should not be administered to a patient with known G-6-PD deficiency because severe hemolytic anemia can develop. For severe, life-threatening methemoglobinemia, especially when the patient responds poorly to methylene blue therapy or when the patient has G-6-PD deficiency, treatment options include exchange transfusion and hyperbaric oxygen therapy. During treatment in the hyperbaric chamber, sufficient oxygen can be dissolved directly in the blood to support life; reversible binding to hemoglobin is not required.

Blood transfusion might be required if massive hemolysis develops. In persons with severe hemolysis, maintaining a brisk urine flow and alkalinizing the urine by administration of sodium bicarbonate might help protect against renal injury from erythrocyte breakdown products.

Patients with severe poisoning who are experiencing seizures or cardiac arrhythmias might require anticonvulsant or antiarrhythmic therapy. If a local anesthetic is suspected of being the etiologic agent for the methemoglobinemia, however, lidocaine probably should be avoided.

- Treatment alone is insufficient; the nitrate source must be identified and eliminated from the patient's environment.

Treatment alone is not adequate for nitrate poisoning. The patient and the nitrate source must be permanently separated. In the case of infantile acquired methemoglobinemia, well water used in preparing formula is a primary etiologic suspect. Physicians and community health personnel should be aware that high nitrate levels in water supplies might suggest the presence of bacterial contamination or agricultural chemicals. Such chemicals might have serious consequences, especially for infants and pregnant women (increased methemoglobin sensitivity), as well as potential fetal risk. The conventional approach of boiling water to destroy microorganisms is not a safe practice when nitrate contamination is suspected. Evaporation increases the nitrate concentration.

Alternative sources of uncontaminated water might include water from a well that has been tested and found to have an acceptable nitrate content, bottled water, water from a new and deeper well, or water from a regularly monitored public water supply. Water treatment technologies (ion exchange resins or reverse osmosis) to remove nitrate from water are not adequate to remove other associated contaminants, especially coliform bacteria. Private wells should be tested annually for nitrate concentration.

Challenge

(7) Why might some patients with methemoglobinemia not respond to treatment with methylene blue?

(8) What options are available to treat significant methemoglobinemia in a patient who has G-6-PG deficiency?

Standards and Regulations

The nitrate limit in drinking water was established as a safeguard against infantile acquired methemoglobinemia. EPA's maximum contaminant level (MCL) for nitrates is 10 ppm. The MCL for nitrites is 1 ppm.

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Answers to Pretest and Challenge Questions

Pretest

(a) In an infant, cyanosis that is unresponsive to oxygen therapy is most likely due to methemoglobinemia.

(b) The clinical laboratory tests that will confirm the diagnosis of methemoglobinemia are blood color and arterial blood gases. When a drop of methemoglobin-containing blood is placed on filter paper, it dries a deep chocolate-brown or slate-gray color. The level of methemoglobin in the blood can be measured using a co-oximeter. Analysis of arterial blood gases will reveal normal oxygen pressure.

(c) The initial step in preventing a recurrence of the infant's cyanosis and distress is to identify the cause of the infant's cyanosis. The next step is to correct or eliminate the cause. If the infant is suffering from acquired methemoglobinemia, the agent must be identified and removed from the infant's environment. In the case of infantile acquired methemoglobinemia, well water used to prepare formula should be tested for the presence of nitrates. Ingestion of nitrate-containing water is not an uncommon cause of methemoglobinemia in infants, especially those living in rural areas.

Challenge

(1) Questions that may help define the cause of the cyanosis include location of the home; activities around the home; type of sewer system at the home; occupations, avocations, and hobbies of family members; drinking water source and supply. Questions to ask of families with infants include the type of formula, feeding regimen, and source of dilution water; the infant's history of recent gastroenteritis; and family history, including recent use of all medications by both infant and mother. For information on taking a complete exposure history, see *Case Studies in Environmental Medicine: Taking an Exposure History* (ATSDR 2001).

(2) Causes of high nitrate concentrations in well water include runoff from the use of nitrogen-containing agricultural fertilizers (including anhydrous ammonia) and seepage of organic nitrogen-containing material from animal wastes or septic sewer systems.

(3) The well water should be tested for nitrate concentration and presence of coliform bacteria. The family can contact the local health department to perform the test on the well. It is most important to identify the source of the methemoglobin-inducing agent and to preclude any further exposure. If nitrate-contaminated well water is the source, you should recommend using bottled water or an alternative water source other than the contaminated well to dilute formula.

You could also recommend frequent testing of the well for nitrate concentration and bacterial contamination, or drilling a new and deeper well, taking into consideration the proximity of septic sewer systems, location of animal wastes, and proximity to agricultural land that might be regularly treated with nitrogen-based fertilizers.

(4) Infants younger than 4 months of age are more susceptible to developing methemoglobinemia because the pH of the gut is normally higher than in older children and adults, which enhances the conversion of ingested nitrate to the more potent nitrite. The bacterial flora of the young infant's gut is also different from that found in older children and adults and might be more likely to convert ingested nitrate to nitrite. Gastroenteritis can increase both the in vivo transformation of nitrate to nitrite and the systemic absorption of nitrite from the large intestine.

A large proportion of hemoglobin in young infants is in the form of fetal hemoglobin. Fetal hemoglobin is more readily oxidized to methemoglobin by nitrites than is adult hemoglobin. Also, in infants, NADH-dependent methemoglobin reductase, the enzyme responsible for reduction of induced methemoglobin back to normal hemoglobin, has only about half the activity it has in adults.

(5) Hemolytic anemia or sulfhemoglobinemia can be caused by many substances that induce methemoglobinemia.

(6) The level of methemoglobinemia can be measured with a co-oximeter. Although biologic nitrate and nitrite levels can be determined, these tests are not routinely performed; it is more expedient to identify and measure nitrate at its source (e.g., contaminated well water).

If congenital methemoglobinemia is suspected or if the patient responds poorly to treatment with methylene blue, the following tests should be performed: hemoglobin electrophoresis, G-6-PD activity, and the activities of NADH-dependent and NADPH-dependent methemoglobin reductases.

(7) Some patients may not respond to methylene blue treatment because they have a G-6-PD deficiency, sulfhemoglobinemia, or hemoglobin M disease.

(8) Treatment options for patients with G-6-PD deficiency include exchange transfusion and hyperbaric oxygen therapy.

Sources of Information

More information on the adverse effects of nitrates and nitrites and treating and managing cases of exposure to nitrates and nitrites can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Nitrate/Nitrite Toxicity* is one monograph in a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education and Promotion, Office of the Director, at 404-498-0101.

Notes

Case Studies in Environmental Medicine:

Nitrate/Nitrite Toxicity

Evaluation Questionnaire and Posttest, Course Number SS3054

Course Goal: To increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients.

Objectives

- Explain why nitrates/nitrites may be an acute and chronic health hazard.
- Describe the known factors contributing to nitrate/nitrite toxicity.
- Assess a patient's environmental or occupational exposure to nitrates/nitrites.
- Evaluate and treat nitrate/nitrite exposure.
- List sources of information on nitrate/nitrite.

Tell Us About Yourself

Please carefully read the questions. Provide answers on the answer sheet (page 29). Your credit will be awarded based on the type of credit you select.

1. **What type of continuing education credit do you wish to receive?**
   ****Nurses should request CNE, not CEU. See note on page 28.**
   A. CME (for physicians)
   B. CME (for non-attending)
   C. CNE (continuing nursing education)
   D. CEU (continuing education units)
   E. [Not used]
   F. [Not used]
   G. [Not used]
   H. None of the above

2. **Are you a...**
   A. Nurse
   B. Pharmacist
   C. Physician
   D. Veterinarian
   E. None of the above

3. **What is your highest level of education?**
   A. High school or equivalent
   B. Associate, 2-year degree
   C. Bachelor's degree
   D. Master's degree
   E. Doctorate
   F. Other

4. Each year, approximately how many patients with nitrate/nitrite exposure do you see?
A. None
B. 1–5
C. 6–10
D. 11–15
E. More than 15

5. Which of the following best describes your current occupation?
A. Environmental Health Professional
B. Epidemiologist
C. Health Educator
D. Laboratorian
E. Physician Assistant
F. Industrial Hygienist
G. Sanitarian
H. Toxicologist
I. Other patient care provider
J. Student
K. None of the above

6. Which of the following best describes your current work setting?
A. Academic (public and private)
B. Private health care organization
C. Public health organization
D. Environmental health organization
E. Non-profit organization
F. Other work setting

7. Which of the following best describes the organization in which you work?
A. Federal government
B. State government
C. County government
D. Local government
E. Non-governmental agency
F. Other type of organization

Tell Us About the Course

8. How did you obtain this course?
A. Downloaded or printed from Web site
B. Shared materials with colleague(s)
C. By mail from ATSDR
D. Not applicable

9. How did you first learn about this course?

A. State publication (or other state-sponsored communication)
B. *MMWR*
C. ATSDR Internet site or homepage
D. PHTN source (PHTN Web site, e-mail announcement)
E. Colleague
F. Other

10. What was the most important factor in your decision to obtain this course?

A. Content
B. Continuing education credit
C. Supervisor recommended
D. Previous participation in ATSDR training
E. Previous participation in CDC and PHTN training
F. Ability to take the course at my convenience
G. Other

11. How much time did you spend completing the course, and the evaluation and posttest?

A. 1 to 1.5 hours
B. More than 1.5 hours but less than 2 hours
C. 2 to 2.5 hours
D. More than 2.5 hours but less than 3 hours
E. 3 hours or more

12. Please rate your level of knowledge before completing this course.

A. Great deal of knowledge about the content
B. Fair amount of knowledge about the content
C. Limited knowledge about the content
D. No prior knowledge about the content
E. No opinion

13. Please estimate your knowledge gain after completing this course.

A. Gained a great deal of knowledge about the content
B. Gained a fair amount of knowledge about the content
C. Gained a limited amount of knowledge about the content
D. Did not gain any knowledge about the content
E. No opinion

Please use the scale below to rate your level of agreement with the following statements (questions 14–24) about this course.

A. Agree
B. No opinion
C. Disagree
D. Not applicable

14. The objectives are relevant to the goal.

15. The tables and figures are an effective learning resource.

16. The content in this course was appropriate for my training needs.

17. Participation in this course enhanced my professional effectiveness.

18. I will recommend this course to my colleagues.

19. Overall, this course enhanced my ability to understand the content.

20. I am confident I can explain why nitrates/nitrites may be an acute and chronic health hazard.

21. I am confident I can describe the known factors contributing to nitrate/nitrite toxicity.

22. I am confident I can assess a patient's environmental or occupational exposure to nitrates/nitrites.

23. I am confident I can evaluate and treat nitrate/nitrite exposure.

24. I am confident I can list sources of information on nitrate/nitrite.

Posttest

If you wish to receive continuing education credit for this program, you must complete this posttest. Each question below contains four suggested answers, of which one or more is correct. **Circle all answers.**

25. Which of the following subpopulations are most at risk of adverse effects from nitrate exposure?

A. Pregnant women.
B. Telephone line workers.
C. Newborn infants.
D. Infants younger than 4 months of age.
E. Fetuses.

26. Which of the following are possible sources of nitrate exposure?

A. Certain topical burn medications.
B. Shallow domestic wells in rural areas.
C. Meat preservatives.
D. Seepage from septic tanks.
E. All of the above.

27. Which of the following statements about nitrates are true?

A. Nitrates can be converted to nitrites in the gut.
B. The higher alkalinity of an infant's gut protects it from nitrate toxicity.
C. Vomiting and diarrhea can affect the absorption of nitrites.
D. No case of nitrate poisoning has been reported since 1950.
E. Adults are immune from nitrate toxicity if they drink water from public water systems.

28. Methemoglobinemia can be induced by which of the following?

A. Chloroquine.
B. Lidocaine.
C. Nitroglycerine.
D. Chlorates.
E. All of the above.

29. Which of the following statements are true regarding nitrates?

A. Fecal organisms convert nitrites back to nitrates.
B. Nitrites react with deoxyhemoglobin to form Fe^{3+}.
C. Most of an ingested dose is excreted in the urine and saliva.
D. In humans, ingested nitrates is rapidly absorbed from the proximal small bowel.
E. All of the above.

30. Which of the following might be adversely affected by nitrates?

A. Cardiovascular system.
B. Pulmonary system.
C. Hematologic system.
D. Fetal development.
E. All of the above.

31. Which of the following statements are true?

A. Signs and symptoms of methemoglobinemia are roughly correlated with percent total oxidized hemoglobin.
B. Fetal hemoglobin is more readily oxidized by nitrites to methemoglobin than is adult hemoglobin.
C. Methemoglobin causes arterial blood to be brown in color.
D. Blood methemoglobin level is the most useful diagnostic test for nitrate toxicity.
E. All of the above.

32. Which of the following treatments can be used for patients with nitrate toxicity?

A. One hundred percent oxygen.
B. Methylene blue.
C. Hyperbaric oxygen therapy.
D. Exchange transfusion.
E. All of the above.

Note to Nurses

CDC is accredited by the American Nurses Credentialing Center's (ANCC) Commission on Accreditation. ANCC credit is accepted by most State Boards of Nursing.

California nurses should write in "ANCC - Self-Study" for this course when applying for relicensure. A provider number is **not** needed.

Iowa nurses must be granted special approval from the Iowa Board of Nursing. Call 515-281-4823 or e-mail marmago@bon.state.ia.us to obtain the necessary application.

Case Studies in Environmental Medicine:

Nitrate/Nitrite Toxicity

Answer Sheet, Course Number SS3054

Instructions for submitting hard-copy answer sheet: Circle your answers. To receive your certificate, you must answer **all** questions. Mail or fax your completed answer sheet to

Fax: 404-498-0061, ATTN: Continuing Education Coordinator

Mail: Agency for Toxic Substances and Disease Registry
ATTN: Continuing Education Coordinator
Division of Health Education and Promotion
1600 Clifton Road, NE (MS E-33)
Atlanta, GA 30333

Remember, you can access the case studies online at www.atsdr.cdc.gov/HEC/CSEM/ and complete the evaluation questionnaire and posttest online at www2.cdc.gov/atsdrce/.

Online access allows you to receive your certificate as soon as you complete the posttest.

Be sure to fill in your name and address on the back of this form.

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Name: E-mail (not required):

Address:

Zip code:

○ Check here to be placed on the list to pilot test new case studies

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Access the case studies online at www.atsdr.cdc.gov/HEC/CSEM/ and complete the evaluation questionnaire and posttest online at www2.cdc.gov/atsdrce/.

Online access allows you to receive your certificate as soon as you complete the posttest.

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