NITRATES, METHEMOGLOBINEMIA, AND DRINKING WATER: A Factsheet for Clinicians

Nitrates are chemicals that occur naturally in drinking water and also result from human activities. In some areas private wells are contaminated with nitrates. Excessive nitrates can cause acquired methemoglobinemia in young infants. This severe syndrome of inadequate tissue oxygenation is potentially fatal; prompt clinical recognition and treatment is vital. Families should be counseled on nitrate safety.

Nitrate Background

- Nitrates and nitrites are naturally occurring inorganic nitrogen ions found in soil, water, and some foods. They are a natural part of the human diet. However, excessive consumption (e.g. drinking water or eating food from areas where ground water has become contaminated by excessive nitrate from fertilizers or improper manure management) can cause serious adverse health effects.

Nitrate Sources

- Drinking water
    - Nitrates occur naturally in water at low concentrations. Nitrates are also present as a result of human activities, such as the use of fertilizers and manure on irrigated farm fields that can run off and seep into wells. Nitrate-contaminated water can also be due to improper management of farm animal (i.e. cow) waste, leaky sewage pipes, and siting septic systems nearby drinking water wells.
    - Large suppliers of public water sources are required to monitor nitrate concentrations regularly, but private wells are not. In some areas private wells are contaminated with nitrates.
    - The American Academy of Pediatrics (AAP) consensus panel recommends that all prenatal and well-infant visits need to include questions about the home water supply.
    - The only way to know if the nitrate level in well water is at a safe level is to have the well water tested by a certified laboratory. <u>All private wells should be tested before use and once per year for nitrates</u>. Families should contact their state health department for assistance with selecting a certified laboratory.
    - Regulations and water testing frequency:
        - The United States Environmental Protection Agency's (EPA) Maximum Contaminant Level (MCL) for nitrates is 10 mg/L (or 10 parts per million, 10 ppm). The 10 mg/L standard was set to protect infants from nitrates. When a nitrate water test result is 10 mg/L or less, the water is considered safe for infant use.
        - Nitrates may change seasonally or randomly throughout the year. If the nitrate concentration is between 5 – 10 mg/L, monitor more closely and test the well drinking water every 3 months to confirm the water is still safe. When nitrates are present, pesticides or bacteria may also be present and additional water tests may be needed. Families should contact their local health department for guidance.
- Food
    - Nitrates can also be a problem in some vegetables, including spinach, beets, lettuce, cabbage, green beans, squash, carrots, and turnips. Because these vegetables may contain higher amounts of nitrates, recommend other foods until infants are over 6 months old.

Infant Nitrate Exposure

- Infants are exposed to nitrates when they drink contaminated well water or when contaminated well water is used to make infant formula or baby food.
- Nitrates in water are not significantly absorbed through the skin.
- Breastfeeding is safe even if a mother drinks water polluted with nitrates.

Methemoglobinemia and Other Health Effects

- Hemoglobin in blood contains iron normally found in the Fe2+ (ferrous) state. Excessive nitrates or nitrites can alter the iron in hemoglobin to the Fe3+ (ferric) state, forming methemoglobin (an abnormal form of hemoglobin

which cannot bind oxygen). Methemoglobinemia (an excess of methemoglobin) results in poor tissue oxygenation and anoxia.

- Methemoglobinemia, also known as "blue baby syndrome", can be inherited or acquired. The acquired form, such as from excessive nitrate exposure, is a serious medical emergency. Among the reported cases of acquired methemoglobinemia in US infants, most have been attributed to the use of nitrate contaminated well water for preparation of infant formula.
- Infants less than 1 year old are physiologically vulnerable to the development of methemoglobinemia due to several factors:
    - Their higher gastric pH favors nitrate-reducing bacteria that convert ingested nitrate into methemoglobin-producing nitrite.
    - Fetal hemoglobin, the predominant form in infants up to 3 months of age, is oxidized more readily to methemoglobin by nitrite than is adult hemoglobin.
    - The activity of the red blood cell enzyme systems that reduce methemoglobin back to normal hemoglobin is reduced by about half in infants compared with adults.
    - Gastroenteritis can increase the risk of developing methemoglobinemia.
- **Women who are thinking about pregnancy or who are pregnant should avoid water contaminated with nitrates. Women considering pregnancy or who are pregnant should drink water from public water supplies, water that has been tested and has safe nitrate levels, or bottled water.** While not conclusive due to study limitations, epidemiological data suggest an association between maternal ingestion of nitrate from drinking water and preeclampsia, spontaneous abortion, intrauterine growth restriction, and various birth defects. A few studies have hinted at a role for childhood nitrate intake in the risk for later developing diabetes mellitus.

METHEMOGLOBINEMIA CLINICAL MANAGEMENT

Clinical presentation

- In children and adults with acute acquired methemoglobinemia, methemoglobin levels >20% are associated with clinical symptoms.
- Early methemoglobinemia symptoms include nonspecific headache, fatigue, dyspnea, and lethargy. In infants, this may present as unusual fussiness, decreased alertness, diarrhea, vomiting, shortness of breath, and increased work of breathing.
- At higher methemoglobin levels, cyanosis becomes visible. A brownish-blue skin tone may be present due to anoxia. This condition may be harder to detect in infants with dark skin- look for a bluish color of the nasal or oral mucosa, lips, or nail beds.
- Respiratory depression, altered consciousness, shock, seizures, and death may occur. Acquired methemoglobinemia is life threatening when methemoglobin comprises more than 30% of total hemoglobin and mortality rates are high when methemoglobin levels exceed 40%.

Diagnosis

- Initial diagnosis is based on history and exam findings. In addition, the presence of methemoglobin should be suspected with 1) clinical cyanosis despite normal arterial pO2, or 2) a significant difference between the oxygen saturations measured by pulse oximetry and by arterial blood gas analysis ("saturation gap").
- A diagnosis of methemoglobinemia should be confirmed by laboratory analysis, to be done in the emergency setting (i.e. not in primary care). Hemoximetry, also called co-oximetry, is recommended way for measuring methemoglobin. Most current blood gas analyzers have incorporated the ability to do hemoximetry
- A fresh blood specimen (venous is fine) should always be obtained as methemoglobin levels tend to increase with storage.
- Note that routine pulse oximetry is inaccurate for monitoring oxygen saturation when methemoglobin is present, and should not be used for diagnosis.

Treatment

- Acute onset of acquired methemoglobinemia should be considered a medical emergency and requires immediate treatment in the ER setting.
- When the patient is symptomatic or the methemoglobin level is >20%, intravenous methylene blue (MB, dosed at 1 to 2 mg/kg over five minutes) can be life-saving and is considered the treatment of choice. Blood transfusion or

exchange transfusion may be helpful in patients who are in shock. See appropriate clinical guidelines for more detailed treatment and monitoring guidance.

Prevention and Advice for Families

- **Only use water from public water supplies, water that has been tested and confirmed as safe, or bottled water.**
- **Test well water for nitrates to ensure it is safe to drink. A nitrate test is around $50.**
- **Don't use nitrate-contaminated well water to make baby formula or to make baby food.**
- **Don't let infants drink nitrate-contaminated water.**
- **Women who are pregnant or trying to get pregnant should not drink nitrate-contaminated well water.**
- **Breastfeeding is safe even if the mother drinks water contaminated with nitrates.**
- **Because some vegetables may contain higher amounts of nitrates, choose other solid foods until infants are over 6 months old.**

Reporting

- Methemoglobinemia is not currently a mandatory notifiable condition in Washington State. However new passive surveillance has been initiated by the Yakima Health District under the supervision of Health Officer Dr. Chris Spitters. Yakima Health District requests notification of laboratory-confirmed methemoglobinemia by calling (509) 249-6541 within three days of diagnosis. Please include an exposure history and your clinical impression regarding etiology, if known.

Resources and References

For acute poisoning assistance contact your state poison center at 1-800-222-1222.
For additional non-urgent clinical and public health assistance, contact the NW PEHSU. The University of Washington based Pediatric Environmental Health Specialty Unit (PEHSU) serves medical and public health professionals in Alaska, Washington, Idaho, and Oregon. For more information contact us at 1–877–543-2436 (1-877-KID-CHEM) or pehsu@uw.edu. Visit our website http://www.depts.washington.edu/pehsu.

- ATSDR ToxFAQsTM for Nitrates and Nitrites: http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=1186&tid=258
- ATSDR Case Studies in Environmental Medicine (CSEM): Nitrate/Nitrite Toxicity (course: WB2342): http://www.atsdr.cdc.gov/csem/csem.asp?csem=28&po=0
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