



UPCC

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Methemoglobinemia

Methemoglobin is incapable of carrying oxygen, which results in functional anemia and tissue hypoxia. It is produced by many chemicals and drugs with oxidizing properties. It may occur in a variety of settings including occupational exposures, smoke inhalation, and therapeutic drug use. Infants are particularly susceptible.

Methemoglobin

Methemoglobin is formed when hemoglobin iron is oxidized from its normal ferrous (2+) to the ferric (3+) state. Once it has been oxidized, the iron molecule cannot bind to oxygen. Nonoxidized heme moieties in a methemoglobin molecule bind more tightly to oxygen, shifting the oxyhemoglobin dissociation curve to the left, thus making less oxygen available at the tissue level. Because red blood cells are continuously exposed to oxygen free radicals, methemoglobin is formed continuously. Endogenous reduction mechanisms keep the proportion of methemoglobin down to 1% or less in most individuals. The most important of these mechanisms is the cytochrome-*b5* methemoglobin reductase system. This is a NADH dependent mechanism and is responsible for the removal of nearly 99% of the methemoglobin that is produced under normal circumstances. If there is no unusual ongoing production, this mechanism can reduce methemoglobin to hemoglobin at a rate of nearly 15% an hour. Other reduction mechanisms include NADPH-methemoglobin reductase system, as well as sulfation enzymes, glutathione and ascorbic acid. NADPH-methemoglobin reductase plays a pivotal role in the treatment of methemoglobinemia. This enzyme will reduce dyes, such as methylene blue, which may then reduce methemoglobin to hemoglobin.

Causes of Methemoglobinemia

Exposure to an Oxidizing Agent

The most common cause of methemoglobinemia is exposure to oxidant drugs or metabolites. The list of causative agents is long (Table 1). Some of the more commonly encountered agents include benzocaine (found in many teething gels), dapson (used for prophylaxis against *Pneumocystis carinii* pneumonia), lidocaine, metoclopramide, naphthalene, nitrites and nitrates, phenazopyridine, and phenytoin. While many of the drugs listed in Table 1 may act as oxidants themselves, a number of them, such as benzocaine, dapson and analine, are metabolized by the cytochrome P-450 system into free radicals capable of forming methemoglobin. The "Blue Baby Syndrome" may occur in infants who have

been exposed to nitrates in well water. Typically, this rare phenomenon occurs in young infants living in rural areas where the nitrates from fertilizers placed on crop fields have seeped into the well water of homes nearby.

Acidosis and Food Sources in Infants

Several physiologic factors place young infants at increased risk of developing methemoglobinemia. Infants have reduced levels of cytochrome-*b5* reductase and higher percentages of fetal hemoglobin, which is more easily oxidized. Also, a higher intestinal pH facilitates the growth of certain gram-negative bacteria that may convert nitrates into more reactive nitrites. These factors, in conjunction with changes associated with metabolic acidosis, particularly those caused by diarrhea, appear to act synergistically to cause methemoglobinemia in infants. Numerous studies have demonstrated methemoglobinemia associated with foods high in nitrates. Silver beets and carrots have been implicated, as have spinach and other greens. Reports indicate that nitrites and nitrates used as preservatives may also cause methemoglobinemia.

Clinical Presentation

The clinical presentation of methemoglobinemia is dependent upon the level of methemoglobin present (Table 2). Cyanosis can become evident when 10-15% of hemoglobin has been oxidized to methemoglobin. Patients with underlying cardiac disease, respiratory dysfunction, anemia or acidosis may show symptoms at lower methemoglobin concentrations.

Diagnostic Tests

Pulse Oximetry

Pulse oximetry can be misleading. Pulse oximetry uses the ratio of light absorbance at two wavelengths to estimate the relative proportion of oxyhemoglobin. Methemoglobin absorbs both wavelengths equally, which makes pulse oximetry readings unreliable. As methemoglobin concentrations begin to rise, pulse oximetry values fall. However, they generally stay in the 80s, and at methemoglobin concentrations of 100%, pulse oximetry measurements will read approximately 85%. In cases of methemoglobinemia, pulse oximetry may provide misleading information about oxygen availability at the tissue level.

Blood Gas Analysis and Co-Oximetry

Most arterial blood gas analyzers provide *calculated* oxygen saturation. Because this calculation is dependent upon the partial pressure of oxygen (PO₂) and the pH, this value may

be falsely normal in cases of methemoglobinemia. Co-oximetry *measures* light absorbance at 4 wavelengths and is capable of giving an accurate measurement of methemoglobin concentrations. Although newer co-oximeters can differentiate between sulfhemoglobin and methemoglobin, older models cannot.

Filter Paper Test

Blood that contains high concentrations of methemoglobin appears chocolate brown. Several drops of blood placed on filter paper can help make the diagnosis. Deoxyhemoglobin will appear dark red or violet initially and will subsequently brighten with exposure to oxygen, but the chocolate-brown appearance of methemoglobin will not change with exposure to oxygen. This test is subjective and if performed, should be compared to a control blood sample.

Complete Blood Count

Whenever methemoglobinemia is suspected, a complete blood count should be obtained to check for hemolytic anemia.

Differential Diagnosis

The diagnosis of methemoglobinemia should be considered in all cyanotic patients who do not respond to oxygen therapy. In infants, the differential diagnosis of methemoglobinemia includes cyanotic congenital heart disease, which also may not respond to oxygen therapy. Infants with cyanotic heart disease who receive supplemental oxygen will demonstrate low calculated oxygen saturation and a low partial pressure of oxygen. Infants with methemoglobinemia will demonstrate normal calculated oxygen saturation and a high partial pressure of oxygen. Genetic causes of methemoglobinemia may be revealed in the family history.

Treatment

Many patients will require only supplemental oxygen, decontamination, or in the case of infants, hydration and reversal of acidosis with supplemental bicarbonate. Patients who have methemoglobinemia as a result of an acute exposure to an oxidizing agent should be treated for methemoglobin levels of $\geq 20\%$ if symptomatic, and $\geq 30\%$ regardless of symptoms. Treatment at levels less than 20% is recommended for patients who are very symptomatic or who have co-existent disease that may render the patient especially sensitive to decreased oxygen delivery (i.e., heart disease, lung disease, or anemia).

Methylene Blue

Intravenous methylene blue (1-2 mg/kg of a 1% solution given intravenously over 3-5 minutes) is the treatment of choice. Another 1 mg/kg should be given if the methemoglobinemia has not resolved after 30-60 minutes. In the presence of NADPH, methylene blue is reduced by NADPH-methemoglobin reductase to leukomethylene blue, which in turn reduces methemoglobin to hemoglobin. Methylene blue must be used with caution, especially in infants. It is contraindicated in patients with G6PD deficiency. Patients with G6PD deficiency may develop a hemolytic anemia from the oxidant stress of methylene blue and in some instances methylene blue may actually exacerbate methemoglobinemia. Non-G6PD-deficient infants also are at increased

risk of complications of methylene blue therapy and may experience hemolysis and methemoglobinemia after higher doses of methylene blue. For this reason, aggressive hydration and correction of acidosis with bicarbonate is all that is recommended for infants with mild symptoms and levels less than 20%. Failure of methylene blue therapy suggests an inadequate dose of methylene blue, inadequate decontamination, NADPH dependent methemoglobin reductase deficiency, hemoglobin M, sulfhemoglobinemia, or G-6-PD deficiency.

Relapsing Methemoglobinemia

Agents such as dapsone, analine, and benzocaine may produce a relapsing methemoglobinemia. This phenomenon is characterized by rebounding methemoglobin concentrations after initial good response to methylene blue. It is the metabolites of these agents that are the offending oxidants. When the oxidant metabolite forms methemoglobin, the parent compound is regenerated and can then be re-metabolized to the oxidant metabolite. The enterohepatic recirculation of agents such as dapsone can also contribute to this phenomenon. To counter this possibility, decontamination with activated charcoal is indicated and in some instances, continuous infusions of methylene blue have been helpful.

Alternative Treatments

Exchange transfusion may be indicated in patients with severe methemoglobinemia who don't respond to methylene blue or in which it is contraindicated. Hyperbaric oxygen therapy may also be useful but there is no data to support its efficacy.

Summary

Methemoglobinemia may be seen as a result of acidosis in young infants, but most commonly occurs after exposure to oxidizing agents. Cyanosis is usually the initial presenting symptom, and the diagnosis should be considered in any patient with cyanosis unresponsive to supplemental oxygen. For those who require treatment, methylene blue remains the treatment of choice, but must be used cautiously, especially in infants and in G-6PD-deficient individuals.

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The Utah Poison Control Center expresses its sincere thanks to
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for their generous contribution that allows us
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Table 1. Agents that may cause methemoglobinemia

Acetanilid	Hydroxyacetanilide	Nitroglycerine
Alloxan	Hydroxylamine	Nitroprusside
Ammonium nitrate	Lidocaine	Paraquat/Diquat
Aniline dyes, ink	Menadione	Phenacetin
Antipyrine	Metoclopramide	Phenazopyridine
Arsine	Methylene blue	Phenytoin
Benzene derivatives	Naphthalene	Piperazine
Benzocaine	Nitrates	Prilocaine
Chlorates	Nitric oxide	Primaquine
Chlorobenzene	Nitrites	Smoke inhalation
Chloroquine	Nitroalkanes	Sulfonamide antibiotics
Dapsone	Nitrochlorobenzene	Tolyhydroxylamine
Dinitrophenol	Nitrofurantoin	Trinitrotoluene

HIPAA and the Utah Poison Control Center

The Utah Poison Control Center (UPCC) wants to continue to provide the best service it can to patients and the health care community. The purpose of this letter is to provide clarification on why it is okay to provide information to the UPCC staff regarding patients the UPCC is following.

UPCC Mission

The mission of the Utah Poison Control Center is to prevent and minimize adverse health effects from a poison exposure through education, service, and research.

About the Utah Poison Control Center

The Utah Poison Control Center (UPCC) is a 24-hour resource for poison information, clinical toxicology consultation and poison prevention consultation. The poison center receives calls from the public, health professionals and public health officials about poisonings, overdoses, adverse reactions, bites and stings and other types of exposures. The UPCC is nationally recognized as a Certified Regional Poison Control Center by the American Association of Poison Control Centers.

The UPCC is staffed around the clock with specialists in poison information. Specialists in poison information are registered pharmacists and nurses who have additional training in clinical toxicology. The role of the specialists is to assess the situation over the telephone by taking a thorough poisoning history and to determine whether the exposure can be safely managed on-site (e.g. at home) or whether the patient needs to be seen in a health care facility. When the specialist feels that the patient needs to be evaluated in a hospital, a referral is made. The specialist contacts the charge nurse in the emergency department of the referral hospital to apprise them of the patient and to provide diagnostic and treatment recommendations.

Provision of Patient Care

The UPCC is involved in the provision of patient care through consultations over the telephone. During the initial contact, UPCC staff gathers specific details about the patient and the exposure in order to adequately assess the situation and provide appropriate triage, diagnostic and treatment recommendations.

Table 2. Symptoms associated with methemoglobin concentrations

Methemoglobin (g/dL)	Percent Total Hemoglobin	Symptoms
<1.5 g/dl	<10	None
1.5 - 3.0	10 - 20	Cyanosis
3.0 - 4.5	20 - 30	Anxiety, lightheadedness, headache, tachycardia
4.5 - 7.5	30 - 50	Fatigue, confusion, dizziness, tachypnea, tachycardia
7.5 - 10.5	50 - 70	Coma, seizures, arrhythmias, acidosis
>10.5	>70	Death

From Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999; 35(5):646-656.

Follow-up calls are performed to reassess patient status. As with any consult service, the UPCC needs patient specific information in order to assess whether the recommendations it has provided are still appropriate. Changes in patient clinical status or discovering new history that may have been obtained by the primary providers may require changes in our initial recommendations. We continue to follow the patient until the poisoning is resolved and the patient is medically cleared. Follow-up is typically with the nurse taking care of the patient, but occasionally with the resident or attending physician.

Because the UPCC is a telephone-based service, contact for follow-up is over the telephone. The UPCC staff can provide hospital staff with sufficient details to verify who is calling and their involvement with the case. The UPCC staff has information about the patient that may include reason for the exposure, substance involved, treatment provided, patient status, past medical history, circumstances surrounding the exposure, name, age, gender and weight. Not all of the above information is available in each circumstance. In rare instances, the patient name is unavailable when the patient first arrives in the hospital. This is usually when the hospital initiates contact with the UPCC rather than when the patient initiates contact with the UPCC.

Consultation of the UPCC initiated by the patient or health care provider constitutes implied consent regarding the UPCC's need to gather information necessary to adequately assess and make recommendations regarding the case as a health care provider.

Is the UPCC a Covered Entity?

The UPCC is a program of the University of Utah Health Sciences. The University of Utah HSC is a hybrid entity. The UPCC is not considered a covered entity because it does not transmit health information in electronic form in connection with a transaction for which a HIPAA standard has been adopted. However, because we provide patient care as a consultant you can provide follow-up patient specific information to us. Just because we are not a covered entity does not preclude us from working together to provide the best patient care possible.

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*CSPI denotes Certified Specialist in Poison Information.

In summary, whether or not the UPCC is a covered entity does not preclude hospitals from providing patient information to the UPCC as a provider of health care. We appreciate the opportunity to work with you to provide the best care possible to our patients. If you have any questions, please feel free to contact us at (801) 581-7504 or poison@hsc.utah.edu.

What Does Your Child See?

You Know the Difference, But They Don't.



To a child, the world is full of shapes and colors. They don't know the difference between a bottle of juice and a bottle of cleaner. Kids taste, smell and touch everything they see. The safety of your child is in your hands. Keep poisons out of theirs.

CALL US, we are here to help. Every second counts in a poison emergency.

POISON Help
1-800-222-1222
Utah Poison Control Center

WHAT DOES YOUR CHILD SEE?

The UPCC introduced a new brochure and poster targeting parents of children under age six during Poison Prevention Week, March 16-22, 2003. The "What Does Your Child See?" campaign focuses on the difficulty of distinguishing safe products from harmful products, and encourages parents to keep poisons out of reach. Please contact Renate Hulen at 801-581-7504 to order brochures or posters.

POISON Help
1-800-222-1222

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