

TOXALERT



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Methemoglobin decreases the amount of oxygen transported and the ability to offload oxygen to tissues.

Methemoglobinemia

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The poison center is contacted by the parent of a 27-month-old male after he is found crying and holding a cup that had contained his mother's artificial nail remover. While some of the product has spilled on the child's clothing it is determined that the child may have ingested up to one ounce of the 98% nitroethane solution. Before transport to the Emergency Department, the child is given oral fluids. Upon evaluation in the ED, the child is asymptomatic with no evidence of cyanosis. He is administered activated charcoal and admitted to the pediatric intensive care unit for observation. His initial methemoglobin level is measured at 12%, however he remains asymptomatic. Seven hours after the ingestion the child develops cyanosis. He is initiated on 100% oxygen therapy and his methemoglobin level is noted to have increased to 19%. (J Tox Clin Tox 1998; 36:6)

Methemoglobinemia Defined

The primary function of hemoglobin is to transport oxygen and carbon dioxide within the body. The normal hemoglobin molecule consists of four polypeptide chains called globins that protectively wrap around four pigmented subunits called hemes. Each heme contains an iron in the ferrous (Fe^{2+}) state that can bind reversibly with a single oxygen molecule.

Methemoglobin is an abnormal form of hemoglobin that has a diminished capacity for carrying oxygen. Methemoglobin is produced when the ferrous iron within the heme molecule is oxidized to the ferric (Fe^{3+}) state. While in the oxidized state the ferric iron within the heme subunit is incapable of binding oxygen. In addition to decreasing the amount of oxygen the hemoglobin molecule

can transport, the presence of an oxidized heme unit within the molecule will decrease the ability of the reduced heme subunits to offload oxygen to the tissue.

The constant presence of endogenous and exogenous oxidizing substances results in the continuous formation of methemoglobin. In normal individuals, the methemoglobin level is maintained below 1% through two metabolic pathways. The major pathway involves the enzymatic reduction of the glycolytic product NAD to NADH (nicotinamide adenine-dinucleotide). NADH then acts as an electron donor in the reduction of the ferric (Fe^{3+}) iron of the methemoglobin to its ferrous (Fe^{2+}) state. The enzyme NADH methemoglobin reductase is required for the reduction of NAD and methemoglobin.

Within the erythrocyte, the enzymatic reduction of methemoglobin may also be accomplished through the reduction of NADP that is produced via the hexose monophosphate shunt. The NADPH then acts as a reducing agent in the enzyme dependent conversion of methemoglobin to hemoglobin. While this pathway has a very minor role in the daily reduction of methemoglobin, it can be induced through the presence of exogenous electron donors, like methylene blue. When methylene blue is administered, it is converted to a strong reducing agent called leucomethylene blue by NADPH. Leucomethylene blue can then react with methemoglobin resulting in its reduction to hemoglobin and the restoration of normal oxygen carrying capacity.

To a much lesser extent, methemoglobin can be reduced within the erythrocyte via non-enzymatic pathways that utilize en-

Methemoglobinemia (continued)

ogenous ascorbic acid or reduced glutathione as substrates.

Causes of Methemoglobinemia

There are three causes of methemoglobinemia: 1) an autosomal recessive trait that results in insufficient NADH dependent reductase enzyme production; 2) an autosomal dominant trait that manifests as structural alteration in the hemoglobin making it more

Table 1

Agents That Cause Methemoglobinemia

Acetonitrile (*nail remover*)
Anesthetics (*benzocaine, lidocaine, prilocaine*)
Aniline (*dyes*)
Chlorates (*matches, explosives, weed killers*)
Naphthalene (*mothballs*)
Volatile nitrites (*amyl, butyl, isobutyl*)
Nitroprusside
Sodium nitrite
Phenacetin
Phenazopyridine (*Pyridium[®]*)
Quinones (*chloroquine, primaquine*)
Sulfonamides (*sulfamethoxazole*)
Dapsone

susceptible to oxidation. 3) exposure to an exogenous oxidizing substance.

Methemoglobinemia most commonly results from an exposure to an oxidizing agent. Agents known to induce methemoglobinemia are shown in Table 1. The exact mechanism of toxicity varies between the agents. Some agents have direct oxidizing effects on the hemoglobin while other agents cause the formation of oxygen and peroxide free radicals, which are able to oxidize hemoglobin.

The development of methemoglobinemia following exposure to an oxidative substance is not limited to the oral route. Clinically significant methemoglobin levels have been observed in patients after dermal exposure to local anesthetics. Inhalation exposure to volatile nitrites, a common method of substance abuse, has also resulted in methemoglobinemia.

Clinical Presentation

The signs and symptoms of methemoglobinemia

are the same regardless of the etiology, however, their time of onset and duration are agent specific. For many agents, the onset of methemoglobinemia is within 1-2 hours, but is delayed for others such as dapsone and nitroethane. When methemoglobin levels are below 10% there is usually an absence of symptoms. Cyanotic skin discoloration is typically observed at levels that are greater than 15% and is often one of the earliest clinically evident features of methemoglobinemia. As methemoglobin levels rise, severity increases (see Table 2). Serious toxicity is expected with levels greater than 50%, and levels above 70% are associated with death. Patients with concomitant disease states like anemia, respiratory disease, or cardiovascular disease are at risk of developing more severe symptoms at lower methemoglobin levels than patients without these preexisting conditions. It is also important to remember that following an exposure to a methemoglobin inducing agent, patients may also exhibit additional symptoms of toxicity that are substance specific (e.g. hypotension following volatile nitrite exposure).

Laboratories

Co-oximetry is considered to be the method of choice for laboratory analysis and diagnosis of methemoglobinemia. In the setting of methemoglobinemia, pulse oximetry and arterial blood gas measurements are not consistently accurate reflections of oxygen saturation and do not directly measure serum methemoglobin levels. However, co-oximeters are capable of

Table 2

Methemoglobin Concentrations & Symptoms

15-20%	Cyanosis, chocolate brown arterial blood
20-50%	Fatigue, weakness, dizziness, anxiety, confusion, headache, dyspnea, tachycardia
50-70%	Lethargy, stupor, acidosis, coma, seizures, arrhythmias

Methemoglobinemia usually results from an exposure to an oxidizing agent.

Pulse oximetry and arterial blood gas measurements do not accurately reflect oxygen saturation.

(Continued from page 2)

directly measuring methemoglobin along with oxyhemoglobin, deoxyhemoglobin, and sulfhemoglobin.

Treatments

The use of gastrointestinal decontamination following ingestion to an oxidizing agent is substance specific and highly dependent on the time of exposure. In most cases, GI decontamination is reserved for early presenters that have no clinical or laboratory signs of methemoglobinemia. The use of methods to enhance elimination like hemodialysis and hemoperfusion are not well supported in the literature. However, in the case of dapsone, multiple dose activated charcoal may be efficacious.

Methylene blue is the current treatment of choice for toxin-induced methemoglobinemia. In patients with elevated methemoglobin levels the decision to treat with methylene blue is based on the methemoglobin level as well as the clinical presentation. Typically, methylene blue therapy is initiated at methemoglobin levels between 10-30% in symptomatic patients or patients with concomitant disease states. In asymptomatic patients therapy with methylene blue is not usually initiated until levels are above 30%.

Methylene blue is supplied as a 1% intravenous solution. The usual dose of methylene blue, 1-2 mg/kg, is administered slowly over 3-5 minutes. Resolution of symptoms along with a decrease in the methemoglobin level is ex-

pected to occur within 30 to 60 minutes. If necessary, 1 mg/kg doses maybe repeated as needed. As with any drug, certain adverse effects may be seen with the therapeutic use of

methylene blue. Following administration of methylene blue, patients may complain of feelings of restlessness or apprehension, dyspnea, or chest pain.

Caution: G6PD deficiency

With large doses, methylene blue is an oxidative agent that is capable of inducing methemoglobinemia. In patients with normal G6PD enzyme levels, the exacerbation of methemoglobinemia following methylene blue therapy is rarely seen and is typically a result of the administration of suprathreshold doses. However, G6PD deficient patients have a relative lack of the enzyme necessary for the conversion of methylene blue to the reductive substrate leukomethylene blue, putting them at greater risk for the paradoxical development of increased methemoglobin levels. Additionally, these patients are at risk for the development of hemolytic anemia following the administration of methylene blue. Therefore, in G6PD deficient patients, methylene blue must be administered with caution and at a lower dose.

In conclusion, exposure to an oxidizing substance is the most common cause of methemoglobinemia. The early recognition of the clinical signs and symptoms of methemoglobinemia along with the use of accurate laboratory tests will assist in the provision of adequate therapy. While the use of cytochrome P-450 enzyme inhibitors, n-acetylcysteine, and

Methylene blue increases the conversion of methemoglobin to hemoglobin and restores normal oxygen carrying capacity.

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TOXALERT



TOXNOTES: Sunscreens



“I just applied sunscreen to my 2 year old, and he rubbed some in his eye and in his mouth. Will he be OK?”.

The Maryland Poison Center receives numerous calls each year concerning ocular exposures to sunscreens and ingestions of small amounts. Most sunscreens contain approximately 5% PABA (para-aminobenzoic acid) or PABA esters (e.g. octyl dimethyl PABA). All of these compounds can produce eye irritation but no permanent damage to the eyes. Eye irrigation is recommended, even for waterproof sunscreens. Accidental ingestions by children will possibly cause nausea and vomiting but are considered to be non-toxic unless massive amounts are swallowed. Studies have shown that ingestions of >10 grams/day (200 ml of sunscreen/day) for days is necessary to induce symptoms other than GI irritation. However, occasionally sunscreens will contain other more toxic compounds such as ethanol. The Maryland Poison Center can help identify the ingredients of the sunscreen as well as recommend any necessary treatment.

Most sunscreens contain PABA or PABA esters and result in only minor symptoms.