METHEMOGLOBINEMIA INDUCED BY ACCIDENTAL INGESTION OF NITRITE

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Methemoglobinemia is a known complication of exposure to nitrites, and has been reported in relation to ingestion [1,2] and even inhalation [3] of some nitrite-containing compounds. It should be suspected when cyanosis fails to respond to normal therapeutic measures and a history of exposure to a potential toxic agent is present. The case of a child exposed to water contaminated with nitrites is presented. Such a case does not appear to have been reported previously in the Saudi literature.

Case Report

A male child aged 2 1/2 years was brought to the Accident and Emergency Department at King Fahad Specialist Hospital, Qassim, Saudi Arabia, by his father. The father reported that the child had become ill shortly after drinking water stored in an old discarded pharmaceutical drum. The child was conscious but agitated and appeared severely cyanosed. His temperature was 36.7° C, pulse 136 per minute, and respirations 22 per minute. Resuscitation was begun immediately with intravenous fluids, and high-flow oxygen at an FlO_2 of 40%-60% was administered via face mask. In view of the possibility of accidental poisoning, gastric lavage was also carried out. Arterial blood gases were taken and the results were essentially normal, with an oxygen saturation of 95.7%.

Despite the treatment, the child failed to improve and remained cyanosed. Blood was sent for a methemoglobin level check, and the result of 54% confirmed the clinical suspicion of methemoglobinemia. The child was given 10 mg of methylene blue intravenously over ten minutes. Within a further ten minutes, he improved dramatically and the cyanosis resolved. After an uneventful and full recovery in the inpatient unit, the child was discharged home the following day. A sample of water from the pharmaceutical drum submitted to toxicology subsequently revealed a concentration of 2.56 grams per liter of nitrite. It is considered that a dose of less than 10 mg/kg per day of nitrates (converted to nitrites by the body), and less than 0.8 mg/kg per day of nitrites will not cause methemoglobinemia in adults, but patients with reducing deficiencies and infants can tolerate much less.

The US Public Health Service recommends a maximum level of 45 parts per million (mg/L) of nitrates in drinking water.[10] It is not known how much contaminated water the patient drank, but clearly a toxic amount of nitrite was ingested.

Discussion

Methemoglobin is hemoglobin in which the iron exists in the ferric (Fe^{3+}) state, instead of the normal ferrous (Fe^{2+}) state. The level of methemoglobin is kept below 1% in the red cell by two enzyme-reducing systems. The first is a nicotinamide-adenine dinucleotide (NADH) dependent methemoglobin reductase which accounts for 95% of reduction. The second is a nicotinamide-adenine dinucleotide phosphate (NADPH) dependent methemoglobin reductase, which accounts for up to 5% of reduction under normal conditions.[4] Methemoglobin is unable to carry oxygen, and also shifts the oxygen-hemoglobin dissociation curve to the left, hindering oxygen delivery to the tissues.

Excess methemoglobin may be produced in three ways: 1) from globin chain mutations in which the hem iron is stable in the Fe^{3+} form (these are known as "M" hemoglobins); 2) from congenital deficiencies of the enzyme-reducing systems mentioned above—Hispanics, Eskimos and native Americans appear to be particularly affected by these rare enzyme deficiencies; and 3) by exposure to a wide variety of chemicals and drugs, of which the most common are nitrites, nitrates, aniline derivatives, sulphonamides and local anesthetic agents, and other causative agents such as dapsone, phenazopyridine and ingestion of naphthalene (mothballs).[4-7,10] These substances can cause oxidation of ferrous (Fe^{2+}) iron to ferric (Fe^{3+}) iron in hemoglobin.

Cyanosis due to methemoglobinemia first appears at levels of 15%, but other effects such as fatigue, headache, tachycardia and dizziness do not usually occur until levels reach 30% to 40%. Above 55% to 60%, tissue oxygenation becomes inadequate and may result in dyspnea, acidosis, arrhythmias, paralysis, coma and convulsions. Death may

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Accepted for publication 26 October 1997. Received 2 September 1997.

occur from levels in excess of 70%.[4] In hereditary methemoglobinemia, levels are rarely above 30% to 50%, and usually the only complaint is the cosmetically undesirable cyanotic appearance. It is the acquired toxic form of methemoglobinemia which produces clinically dangerous levels that may need urgent management.

Acquired methemoglobinemia may be suspected from a history of exposure to a potential causative agent and failure of the apparent cyanosis to respond to oxygen therapy. The result of oxygen saturation reported by standard arterial blood gas measurement will be normal, as this is a calculated value based on the PaO_2, which will also be normal, and assumes the presence of only normal hemoglobin, either in the oxygenated or deoxygenated state.[7] Pulse oximetry will also give inaccurate oxygen saturation readings in the presence of dyshemoglobins, including methemoglobin and carboxyhemoglobin. The pulse oximeter measures tissue light absorbance at two wavelengths, 660 nm and 940 nm. Methemoglobinemia and carboxyhemoglobinemia affect this absorbance and therefore lead to inaccurate oxygen saturation values.[7-9] Spectrophotometric analysis of arterial blood using a co-oximeter will provide an accurate value of the true level of oxygenated hemoglobin, and also the levels of methemoglobin and carboxyhemoglobin.[9] If this analysis is not available, a drop of blood from the patient can be placed on filter paper; the blood may turn a chocolate brown color compared to a normal sample. However, this test is unreliable at methemoglobin levels below 12%-14%.[10]

The emergency treatment of clinically dangerous methemoglobinemia entails oxygen, general supportive therapy, and, if practical, the removal of the etiological agent. Intravenous methylene-blue in a dose of 1-2 mg per kg as a 1 percent solution given over 5-10 minutes is the treatment of choice for acute severe methemoglobinemia. This dose may be repeated in one hour, and if necessary, at four-hour intervals subsequently, up to a maximum dose of 7 mg/kg. Methylene-blue acts as an electron carrier and facilitates the NADPH-dependent reduction of ferric iron (Fe^{3+}) to ferrous (Fe^{2+}) iron, converting methemoglobin back to hemoglobin. Failure to respond should arouse a suspicion of glucose-6-phosphate dehydrogenase (G6-PD) deficiency in the patient, where NADPH levels are low and treatment with methylene-blue will be ineffective. In high doses, however, methylene-blue itself can cause methemoglobinemia by acting as an oxidizing agent. If methylene blue is ineffective, severe methemoglobinemia may require adjunctive therapy, such as hyperbaric oxygen and exchange transfusion.[4,10] Although methemoglobinemia is an uncommon condition, it should be considered in the differential diagnosis of cyanosis not responding to oxygen therapy.

Acknowledgements

Thanks are due to Ms. Benilda Velez Bril for typing the manuscript.

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