Pseudomethemoglobinemia

A Case Report and Review of Sulfhemoglobinemia

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Objectives: To see if methemoglobin could potentially be misdiagnosed and the limitation of present co-oximeters.

Patient: A 17-year-old girl who overingested a combination of cimetidine, acetaminophen, ibuprofen, and naproxen in a suicide attempt.

Method: Use of pulse co-oximeters to aid in the diagnosis of suspected sulfhemoglobinemia.

Results: Diagnosis of sulfhemoglobinemia achieved with final confirmation made with gas chromatography. Patient steadily improved with supportive care.

Conclusions: There is a potential for the diagnosis of methemoglobin with some of the limitations of present co-oximeters. The laboratory diagnosis of sulfhemoglobinemia can be difficult to make.


SULFHEMOGLOBIN (SulfHb) is a green-pigmented molecule with a greatly reduced oxygen affinity. This particular cause of “cyanosis” has been associated with many drugs, exposure to sulfur compounds, and constipation. However, it is not completely understood why sulfhemoglobinemia develops. Moreover, it can be a readily missed diagnosis due to the similarity clinically and spectrophotometrically of SulfHb and to methemoglobin (MetHb).

REPORT OF A CASE

A 17 year-old girl presented to the emergency department complaining of nausea, vomiting, and abdominal pain 2 hours after an intentional overdose of cimetidine, acetaminophen, ibuprofen, and naproxen. Her medical history was noteworthy for depression, suicide attempts, and use of tobacco, but she denied the use of alcohol or other drugs. On presentation, she was alert and oriented. Her vital signs were as follows: temperature, 37.2°C; arterial blood pressure, 138/84 mm Hg; heart rate, 112/min; respirations, 16/min; and pulse oxygen, 99%. Findings from her physical examination revealed tachycardia and frequent vomiting but otherwise were unremarkable. Laboratory test values were noteworthy for acetaminophen (4 hours after ingestion), 1959 µmol/L, and potassium, 3.4 mEq/L. Results of her other tests for electrolyte levels, liver function, coagulation studies, and salicylate and alcohol levels were all within normal limits. The electrocardiogram was unremarkable. She was admitted with the initial impression of acetaminophen toxicity.

The patient received a “loading dose” of oral N-acetylcysteine, 140 mg/kg, but the dose was promptly vomited. During the next 24 hours, she had repeated episodes of emesis associated with administration of N-acetylcysteine (70 mg/kg every 4 hours). In an attempt to alleviate her gastrointestinal tract symptoms, the patient was administered metoclopramide (100 mg intravenously [IV]). Because of continued nausea and vomiting, she received ondansetron (16 mg IV) and metoclopramide (100 mg IV per dose; total dose, 300 mg) over 48 hours. By hospital day 2, the patient’s gastrointestinal tract symptoms resolved and the N-acetylcysteine was administered without any problems. She completed a total of 18 doses of N-acetylcysteine by the next day.
On hospital day 3, the patient experienced several dystonic reactions, developed discoloration of her lips, face, and nailbeds, and complained of severe headaches. Her vital signs at this time were as follows: blood pressure, 130/90 mm Hg; heart rate, 90/min; respirations, 20/min; and pulse oxygen, 88%. Findings from physical examination were unremarkable except for a blue-gray general appearance. Results of her liver function tests and coagulation studies remained within normal limits. An arterial blood gas test was performed using a Dow Corning 2500 Co-oximeter (Dow Corning, Ambridge, Pa) that revealed a MetHb level of 0.26 (normal, 0.01-0.02). The patient was treated with a total of 3 doses of methylene blue (1 mg/kg IV) without improvement of her cyanosis. Suspecting sulfhemoglobinemia, another arterial blood gas test was performed using a co-oximeter capable of evaluating SulfHb levels, the Dow Corning 270 Co-oximeter. A SulfHb level of greater than 0.015 and a MetHb level of 0.001 were found. Final confirmation of sulfhemoglobinemia was achieved with gas chromatography.

**RESULTS**

After a definitive diagnosis was made, the patient steadily improved with supportive care. Complete recovery occurred over the next several months with no adverse sequelae.

**COMMENT**

Most presentations of cyanosis are secondary to difficulties with the respiratory or the cardiac system. However, hemoglobinopathies, such as methemoglobinemia and sulfhemoglobinemia, can present in this manner and are often not considered.

This case of sulfhemoglobinemia presents several issues that have been poorly delineated in the medical literature: (1) differentiating SulfHb from MetHb and (2) difficulties in diagnosing sulfhemoglobinemia.

Methemoglobin is hemoglobin where the heme has been oxidized from the normal ferrous (Fe²⁺) to the ferric state (Fe³⁺) making it incapable of oxygen transport. This leads to a decreased oxygen-carrying capacity and a leftward shift of the oxy-deoxygenated dissociation curve. Oxygen unloading in the tissues is diminished, predisposing to tissue hypoxia. Treatment with methylene blue is successful in most cases.

Sulfhemoglobin, also in the ferric state, additionally has a sulfur atom incorporated in the hemoglobin. This abnormal hemoglobin is also rendered incapable of oxygen transport. However, counteracting this, tissue oxygen delivery is somewhat protected by a rightward shift of the oxygen dissociation curve by decreasing the oxygen affinity of the unaffected hemoglobin. The rightward shift allows for easier oxygen unloading in tissues. Although patients may have a similar percentage of hemoglobin effected as patients with methemoglobinemia, patients with sulfhemoglobinemia have less severe clinical symptoms because of the difference in their effects on the oxygen dissociation curve. Sulfhemoglobin cannot be reconverted to normal hemoglobin, as MetHb is, with methylene blue, and has no effective antidote. Although transfusions may be useful in some cases, SulfHb is only eliminated after the red blood cells’ life span is naturally concluded (after ≈ 120 days).

The production of SulfHb requires a compound with oxidative properties and a source of sulfur. This has been demonstrated in the laboratory where an oxidant, phenacetin, given with precipitated sulfur produced SulfHb, whereas the oxidative agent given alone caused MetHb. However, in the human model, the origin of sulfhemoglobinemia is less clear because in some cases the sulfur source is not clearly evident. A number of drugs have been associated with sulfhemoglobinemia. These include acetanilid, phenacetin, nitrates, trinitrooluene, and sulfur compounds. However, theoretically, any oxidative agent that causes methemoglobinemia can be a possible precipitant of sulfhemoglobinemia. The origin of sulfur, in cases where it is not overtly apparent, has been theorized to come from hydrogen sulfide released by intestinal organisms (particularly in patients with constipation) and/or glutathione.

Specifically, our case is perplexing because of the drugs that were associated with the sulfhemoglobinemia. Metoclopramide is a drug with mild oxidant activity that has been associated with rare reports of sulfhemoglobinemia after long-term use. It is structurally related to the aniline dyes and to prilocaine which are known to produce methemoglobinemia. N-acetylcysteine is a biochemical precursor of glutathione and a source of hydrogen sulfide. These two drugs may have acted together in this patient to produce the sulfhemoglobinemia. Curiously, N-acetylcysteine is a commonly prescribed therapy for acetaminophen overdose and is frequently used along with metoclopramide, yet few documented cases of sulfhemoglobinemia exist. Perhaps, the very large dose of metoclopramide in this case was essential for the production of sulfhemoglobinemia.

Many commonly used co-oximeters are not capable of detecting SulfHb. Co-oximeters use spectrophotometric techniques to measure different types of hemoglobins. Typically, the most commonly used machines differentiate only 4 types of hemoglobin: oxygenated-hemoglobin, deoxygenated-hemoglobin, MetHb, and carboxyhemoglobin. Therefore, when other types of hemoglobin are present, such as SulfHb and fetal hemoglobin, these hemoglobins are either undetected or falsely measured as one of the other types of hemoglobin. Fetal hemoglobin is the most studied interfering hemoglobin and has been shown to have a positive linear correlation with carboxyhemoglobin. Little data, however, are available regarding the effects of interfering substances on MetHb measurements. Moreover, different co-oximeters vary among each other and can be quite different from gas chromatography, which is considered the “criterion” standard. The disadvantage with gas chromatography is the need for specialized equipment, time, and expertise. Presently, co-oximeters are the most commonly used instruments for assessing MetHb, with SulfHb known as a possible cause for erroneously elevated levels of methemoglobin, a phenomenon that can be pseudo-methemoglobinemia.

The cause for this interference has long been known. Sulfhemoglobin has an absorption band very similar to
Several techniques have been used to differentiate SulHb from MetHb spectrophotometrically. One method uses the addition of cyanide to eliminate the MetHb absorption band peak (cyanide does not affect the SulHb absorption band). Carbon monoxide can also be used for its ability to bind to SulHb and not to MetHb. Finally, newer generation co-oximeters that are designed to assess SulHb and other additional types of hemoglobin (increased number of spectrophotometric wavelength readings are assessed) can differentiate between these 2 types of hemoglobin.

Present clinical practice does not routinely incorporate these tests in the evaluation of a patient with cyanosis. The diagnosis of sulfhemoglobinemia requires a high index of suspicion, especially when there is a poor response to methylene blue treatment, and confirmation with special laboratory techniques.

**CONCLUSIONS**

A case of sulfhemoglobinemia presenting like methemoglobinemia, pseudomethemoglobinemia, is presented. The cause for the sulfhemoglobinemia has been proposed as the combination of N-acetylcysteine and high doses of metoclopramide. Difficulties with present-day diagnosis of methemoglobinemia are described. Diagnosis of sulfhemoglobinemia requires a high index of suspicion and confirmation with special laboratory techniques.

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REFERENCES