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Sulfhemoglobinemia and methemoglobinemia following acetaminophen overdose

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ABSTRACT

Introduction: Though acetaminophen overdoses are common, acetaminophen induced methemoglobinemia is rare and it is thought to be due to oxidative stress from reactive metabolites. However, few prior cases of sulfhemoglobinemia in the setting of acetaminophen overdose have been reported. We report a case of mixed methemoglobinemia and sulfhemoglobinemia in the setting of a large, isolated acetaminophen ingestion.

Case report: A 30-year-old African American male presented after intentionally ingesting 50 tablets of 500 mg acetaminophen two days prior. He was cyanotic and tachypneic. Peripheral oxygen saturation was 78 % on room air and minimally improved with high-flow oxygen. He was noted to have leukocytosis, thrombocytopenia, anion gap metabolic acidosis with lactic acidemia, acute kidney injury, transaminitis, hyperbilirubinemia, and coagulopathy. Arterial partial pressure of oxygen was normal. Methemoglobin and sulfhemoglobin concentrations were 8.5 % and 5.2 %, respectively. Along with intravenous N-acetylcysteine, methylene blue was administered without clinical improvement. Hemolytic anemia was subsequently noted. Glucose-6- phosphate dehydrogenase (G6PD) deficiency was then confirmed with a quantitative assay and genetic testing. He also received one dose of intravenous metoclopramide. The patient ultimately required eight units of packed red blood cells and several weeks of hemodialysis before discharge on hospital day 43.

Discussion: Acetaminophen is structurally related to compounds known to cause methemoglobinemia and sulfhemoglobinemia. We hypothesize that these dyshemoglobinemias were triggered by acetaminophen-induced oxidative stress. The role of G6PD deficiency in the formation of sulfhemoglobinemia is unclear. Acetaminophen overdoses presenting with methemoglobinemia should prompt concern for underlying G6PD deficiency. Coincidental sulfhemoglobinemia should be considered if the clinical presentation is more severe than the methemoglobin concentration alone would suggest. Use of methylene blue in this case, despite the low measured methemoglobin percentage, which likely triggered hemolytic anemia; methylene blue use in a similar circumstance should be weighed carefully against the risk of harm

1. Introduction

Though acetaminophen overdoses are common in the United States, acetaminophen induced methemoglobinemia is rare, though the incidence and risk factors for this are unknown [1,2]. The mechanism is thought to be due to oxidative stress from reactive metabolites [2]. However, few prior cases of sulfhemoglobinemia in the setting of acetaminophen overdose have been reported [3–5].

We report a case of mixed methemoglobinemia and sulfhemoglobinemia following a large, isolated acetaminophen ingestion. Case report consent was obtained from the patient.

2. Case report

A 30-year-old African American male with a history of substance use disorder but otherwise healthy, presented after intentionally ingesting 50 tablets of 500 mg acetaminophen two days prior. He denied other significant co-ingestants, additional self-harm methods, or exposures.

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Initial vital signs were blood pressure of 111/68 mmHg, heart rate of 90 beats per minute, respirations 14 breaths per minute, oxygen saturation of 78 %, and temperature 98.2°F. He was cyanotic and tachypneic but in no acute respiratory distress. His examination was remarkable for clear lungs, scleral icterus, and upper abdominal tenderness. Oxygen was provided initially by non-rebreather mask then high flow nasal cannula with minimal change in peripheral oxygen saturation.

Initial laboratory evaluation was notable for hemoglobin 16.0 g/dL, hematocrit 47.5 %, white blood cell count 25,000/ml, platelets 46,000/ml, bicarbonate 19 mmol/L, anion gap of 27, BUN 27 mg/dL, creatinine 3.81 mg/dL (baseline 1.1 mg/dL in 2015), aspartate aminotransferase (AST) and alanine transaminase (ALT) greater than 7000 u/L, total bilirubin 10.52 mg/dl, phosphorus 4.7 mg/dL, lactic acid 8.3 mmol/L, and prothrombin time 33.0 s (INR 3.1). Ammonia was 38 μmol/L. Arterial blood gas showed pH 7.39, partial pressure of arterial carbon dioxide (PaCO2) 32 mmHg, and partial pressure of arterial oxygen (PaO2) 282 mmHg on high flow nasal cannula at maximum settings (100 % fraction of inspired oxygen, 70 liters per minute). Acetaminophen, salicylate, and ethanol concentrations were undetectable. The arterial methemoglobin concentration, obtained using spectrophotometry, was 8.5 %. Chest radiograph showed a small left lower lobe opacity, which was treated with antibiotics. Due to renal impairment, CT pulmonary angiography was deferred; bedside echocardiogram showed normal cardiac function without signs of right heart strain. Intravenous N-acetylcysteine (NAC) was started for treatment of presumed acetaminophen-induced acute liver injury.

Given no alternative cause for the patient's unresponsive abnormal pulse oximetry and dyspnea could be elucidated, we elected to trial methylene blue. A 1 mg/kg dose was given with no change in peripheral oxygen saturation or subjective dyspnea. At this point, sulfhemoglobinemia was more strongly considered and a sulfhemoglobin concentration was added onto the initial blood work. The sulfhemoglobin concentration, which was obtained from an outside reference laboratory using spectrophotometry, was found to be 5.2 %.

Two hours following methylene blue administration, repeat hemoglobin showed a decrease from 16.0 g/dL to 13.4 g/dL and within 24 h it was 9.9 g/dL. Lactate dehydrogenase exceeded 2500 u/L and haptoglobin was undetectable, consistent with hemolytic anemia. Given suspicion for methylene blue induced hemolytic anemia, a glucose-6-phosphate dehydrogenase (G6PD) qualitative assay was added onto the initial blood work and was negative. A quantitative assay was subsequently sent and found to be 7.7 U/g hemoglobin (laboratory reference range 9.9–16.6 U/g Hb). Genetic testing demonstrated G6PD variant A- (A376G/G202A), confirming moderate (class III) G6PD deficiency.

Serial methemoglobin measurements initially downtrended to 6.2 % then rose, peaking two days after presentation at 21 % and slowly decreasing to 2.3 % by hospital day 7. The sulfhemoglobin concentration rose to 6.3 % the next morning but was not checked again. Hematology recommended ascorbic acid and transfusion support as needed for likely hemolytic anemia.

Regarding the remainder of his care, continuous hemodialysis was initiated due to oliguric renal failure and he was later transitioned to intermittent hemodialysis. Hepatic function normalized by hospital day 20. The patient's hemoglobin continued to decrease, with a nadir of 6.5 g/dL. He received a total of eight units of packed red blood cells to maintain hemoglobin above 7 g/dL. The patient was discharged on hospital day 43 with residual but improving renal dysfunction and no longer required hemodialysis.

3. Discussion

Methemoglobin and sulfhemoglobin bind oxygen poorly due to the ferric (3 +) oxidation state of the heme iron. Clinical cyanosis occurs at a concentration of 0.5 g/dl of sulfhemoglobin, in contrast to 1.5 g/dl methemoglobin and 5 g/dl deoxyhemoglobin [6–8]. Based on the original hemoglobin concentration, the patient had an estimated 1.36 g/dl methemoglobin and 0.83 g/dl sulfhemoglobin.

While acetaminophen is known to cause methemoglobinemia, there are few reported cases of sulfhemoglobinemia in the setting of acetaminophen overdose. Langford and Sheikh reported a 15-year-old white female who presented after an acute acetaminophen overdose for which she was treated with NAC orally every 4 h. Intravenous metoclopramide 1 mg/kg was used prior to nearly all NAC doses due to nausea, receiving 12 doses total before developing cyanosis and peripheral pulse oximetry of 92–94 % that was refractory to supplemental oxygen and methylene blue; methemoglobin concentration obtained at that time was less than 1 %. Suspecting sulfhemoglobinemia, a sulfhemoglobin concentration was drawn and found to be 16 % [3].

Lu and colleagues reported a 17-year-old female who presented two hours after intentional ingestion of cimetidine, acetaminophen, ibuprofen, and naproxen for which she was treated with oral NAC and required several doses of intravenous ondansetron and metoclopramide due to gastrointestinal upset from the NAC. She received a total of 500 mg metoclopramide over 48 h. On hospital day 3, she developed cyanosis and pulse oximetry showed a peripheral oxygen saturation of 88 %. Methemoglobin concentration at that time was measured at 26 % and she was treated with 3 doses of methylene blue without improvement. Suspecting sulfhemoglobinemia, the concentration was retested using an alternative machine capable of distinguishing methemoglobin and sulfhemoglobin, which reported a sulfhemoglobin concentration exceeding 1.5 % and a methemoglobin concentration of 0.1 % [4].

Rodgers and colleagues reported a 16-year-old African American female who presented following an intentional acetaminophen ingestion, which was treated with oral NAC. She was given metoclopramide and diphenhydramine for nausea and vomiting due to the NAC. On hospital day 4, she developed asymptomatic cyanosis. She was given one dose of methylene blue empirically without improvement. She was later found to have a sulfhemoglobin concentration of 14.7 % and a methemoglobin concentration of 0.4 % [5].

Notably, all three prior cases postulated that the sulfhemoglobinemia may have been triggered by metoclopramide and/or NAC use. Though our patient did receive intravenous NAC as well as a single dose of intravenous metoclopramide 10 mg, his measured dyshemoglobinemias preceded any exposure to these or any other known potential causative agents aside from acetaminophen.

We suspect there are three major reasons that sulfhemoglobinemia in the setting of acetaminophen overdose is rarely reported. First, sulfhemoglobinemia is more often asymptomatic due to rightward shifting of the oxygen dissociation curve, which allows for more favorable oxygen delivery to the tissues despite sulfhemoglobin's reduced oxygen affinity [6–8]. Second, sulfhemoglobin measurements are rarely readily available; in this case, it resulted in approximately one week. Third, methemoglobin and sulfhemoglobin have similar absorption spectra (630 nm versus 620 nm), making laboratory differentiation difficult as was noted in the aforementioned case by Lu and colleagues [4,6–9].

Exploring acetaminophen as a potential cause of sulfhemoglobinemia further, acetaminophen (4-hydroxyacetanilide) is a direct metabolite of acetanilide and phenacetin (4-ethoxyacetanilide), which are known to rarely cause sulfhemoglobinemia [6,10,11]. It is unclear why acetaminophen behaves differently than its precursors; different formation rate and types of reactive metabolites may be responsible. At therapeutic doses, phenacetin is metabolized into its primary metabolite acetaminophen but can also be deacetylated to p-phenetidine (4-ethoxyaniline), an oxidizing toxic metabolite [12]. Acetaminophen does not produce p-phenetidine, and at therapeutic doses only yields a clinically insignificant amount of the oxidizing toxic metabolite n-acetyl-p-benzoquinone imine (NAPQI). Only large, untreated acetaminophen overdoses that exceed the capacity of standard detoxification pathways produce sufficient NAPQI to cause harm [10–13].

Notably, we do not suspect the rising methemoglobin concentration was due to ongoing acetaminophen toxicity, but rather oxidation from

methylene blue and oxidative stress from free, unbound hemoglobin and/or methemoglobin [6,14]. Other than a single dose of metoclopramide while hospitalized, no other potential oxidizing exposures, prior to arrival or during the hospital stay, were identified. Metoclopramide, like acetaminophen, it is an aniline derivative and exposure is a known risk factor for the development of sulfhemoglobinemia. However, our patient was not exposed to metoclopramide prior to initially developing dyshemoglobinemias. NAC is also a potential source of sulfhemoglobinemia but our patient's dyshemoglobinemias precede NAC exposure as well [3–5].

It is difficult to explain why the patient had a normal G6PD screen but low quantitative assay that was confirmed with genetic testing. It is possible that the screening test was falsely negative; qualitative assays are less sensitive to milder enzyme deficiencies [15]. Both qualitative and quantitative G6PD can also be falsely normal due to hemolysis, as G6PD concentrations are higher in surviving erythrocytes [3,9]. African American males, like our patient, are the highest risk group in the United States, where G6PD has an estimated prevalence of 2.2 % in the general population. Globally, an estimated 400 million people, or roughly 5 % of the population, are thought to be living with some form of G6PD deficiency [16–18].

In summary, we present a case of mixed methemoglobinemia and sulfhemoglobinemia in the setting of a large, untreated acetaminophen ingestion exacerbated by methylene blue administration due to occult G6PD deficiency. Though the ultimate cause of the patient's dyshemoglobinemias are unclear, we hypothesize that acetaminophen-induced oxidative stress triggered the formation of both methemoglobin and sulfhemoglobin. It is unclear what, if any, role G6PD deficiency may have played as a risk factor for forming sulfhemoglobinemia. However, we acknowledge that our report is limited by a lack of comprehensive laboratory screening and that we cannot entirely exclude an occult, alternative causative agent.

Ultimately, we conclude that acetaminophen overdoses presenting with methemoglobinemia should prompt concern for underlying G6PD deficiency. Coincidental sulfhemoglobinemia should be considered early if the pulse oximetry is lower and/or the patient appears more symptomatic than the measured methemoglobin concentration alone would suggest, though in most circumstances confirmation of sulfhemoglobinemia will be delayed. These factors prompted use of methylene blue in this case, despite the low measured methemoglobin percentage, which likely triggered hemolytic anemia. Methylene blue use in a similar circumstance, regardless of the underlying cause, should be weighed carefully against the risk of iatrogenic harm.

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Presentations

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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