Cetirizine as a Causative Agent for Drug Induced Methemoglobinemia: A Case Report and Review

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A case of methemoglobinemia (MHb) in a teenage woman, triggered by an acute ingestion of approximately 120 to 180 mg of cetirizine, allegedly, with no suicidal intent is described. The patient presented with anxiety and tremors and rapidly developed central cyanosis unresponsive to oxygen supplementation. There was a history of recurrent, spontaneously remitting, unprovoked “blue discoloration of hands.” Investigations confirmed the diagnosis of MHb, and the patient responded to ascorbic acid and methylene blue, although the baseline methemoglobin level remained slightly high. The exact enzymatic deficiency could not be ascertained as the patient refused to undergo complete testing. To the best of our knowledge, this is the first documentation of cetirizine as a causative agent for drug induced MHb. Cetirizine, a selective histamine H1 receptor antagonist is eliminated via oxidation and conjugation processes, which use pathways other than cytochrome P450 enzyme system. The metabolism could potentially create by-products, like superoxide or hydrogen peroxide, which could act as strong reducing agents and oxidize hemoglobin into ferric containing methemoglobin. In this case, an unusually high systemic load of the drug speculatively saturated and overwhelmed the protective enzyme systems, which resulted in clinical manifestation of MHb.

ABBREVIATIONS Cr, creatinine; Fe, iron; Fe^{+3} , ferric iron; Fe^{+2} , ferrous iron; MHb, methemoglobinemia; NADPH, nicotinamide adenine dinucleotide phosphate; PICU, pediatric intensive care unit; SaO_2 , arterial blood oxygen saturation

KEYWORDS cetirizine; hypoxia; methemoglobin; methemoglobinemia; toxicity

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Introduction

Methemoglobinemia is defined by the presence of elevated levels of oxidized heme groups that contain iron (Fe) in ferric form (Fe^{+3}) as opposed to the physiological ferrous form (Fe^{+2}).¹ Fe^{+3} has an increased affinity for oxygen, which makes it ineffective to release and deliver oxygen at tissue sites. This results in tissue hypoxia and a shift of oxygen-hemoglobin dissociation curve to left. In normal circumstances, methemoglobin is spontaneously formed within the red blood cells from imperfect intracellular reactions through the process of auto-oxidation and electron dissociation, which leads to release of free superoxide radicals and production of Fe^{+3} in heme groups.^{1–3} Physiologically, the protective enzymes, namely cytochrome-b5 reductase (nicotinamide adenine dinucleotide methemoglobin reductase) via the major and nicotinamide adenine dinucleotide phosphate (NADPH) reductase via the minor pathway, reduce methemoglobin and maintain it at an insignificant homeostatic level of approximately 1%.^{1–3}

Cetirizine, commonly used to treat allergic symptoms is a selective antagonist of the histamine H1 receptor. Unique from older antihistaminic receptor agents, it less readily crosses the blood-brain barrier and causes minimal sedation or amnesic effects. Having greater

affinity for H1 receptors than other muscarinic acetylcholine receptors, its anticholinergic side effects are insignificant. The reported adverse effects of cetirizine are headache, somnolence, tremor, anxiety, nausea, abdominal pain, cough, hyperventilation, and hematuria among others.⁴ Cetirizine does not undergo metabolism via the cytochrome P450 enzyme system. It is reduced and eliminated through other oxidation and conjugation pathways,⁴ which can potentially release by-products that act as powerful reducing agents like free radicals, such as superoxide or hydrogen peroxide, and can oxidize hemoglobin into Fe^{+3} containing methemoglobin. We describe the first report documenting cetirizine as a causative agent for drug induced MHb.

Case Report

An 18-year-old African American female with a past history of anxiety and depression developed abdominal pain while moving into her dormitory room. She took 2 tablets (20 mg) of cetirizine, reportedly for alleviation of pain, which she had bought over the counter for seasonal allergies. She took an additional 10 to 16 tablets of 10 mg each within the next hour as the pain persisted. Shortly afterwards, she started experiencing nausea and worsening abdominal pain. She was brought to

Figure 1. Showing cyanosis of hands upon admission. **Figure 2.** Showing resolution of cyanosis after treatment.

the emergency department by her father. She denied any suicidal thoughts, ideation, or intention behind the ingestion. In the past, she had received counseling and behavioral therapy for anxiety and depression but no medication. She attributed those symptoms to her traumatic childhood. There was no past history of surgical procedures, illnesses, or any other drug intake. She admitted to 1 episode of attempted self-harm with a knife approximately 6 years ago. She denied ingestion of medications other than cetirizine during or before this episode or any recent intake of green beans, carrots, beets, or spinach. She was shown a bottle of cetirizine and confirmed the ingestion of the particular drug. She was taking her regular diet and drinking city water. She had 1 younger sibling with autism spectrum disorder.

In the emergency department, on arrival her vital signs were normal and the arterial blood oxygen saturation (SaO_2) was 94% on room air. She weighed 42.18 kg, was anxious and tremulous but in no respiratory distress. The rest of the examination, as well as the results of serum electrolyte and liver and renal function tests were normal, except for low bicarbonate (19 mmol/L), high total bilirubin (1.9 mg/dL), and high normal creatinine (Cr, 1.2 mg/dL) values. The hematological profile was unremarkable. The results of urine tests for illicit drugs and pregnancy were negative, and the serum levels of acetaminophen, salicylate, and lactate were normal. The patient was admitted to the PICU and placed on a suicide watch pending psychiatry evaluation. In the PICU, the SaO_2 was found to be consistently low on continuous monitoring following an initial recording of 85% on forehead and 75% on left hand. There was no respiratory distress, but cyanosis was noted on fingers, toes, and tongue, which did not alleviate with provision of 100% oxygen via nasal cannula (Figure 1). An echocardiogram ruled out cardiac causes of cyanosis. The arterial blood gas test showed methemoglobin level of 38%, pH of 7.45, pCO_2 of 21.1 mm Hg, bicarbonate at 14.6 mmol/L, and pO_2 of 82.4 mm Hg. The arterial blood was noted to have a dark

red-brown appearance to it. The patient was started on oral supplementation of vitamin C and intravenous infusion of methylene blue with a diagnosis of methemoglobinemia (MHb). Within 1 hour of the first dose of methylene blue, blood methemoglobin level dropped to 22% and SaO_2 improved to low 90% (Figure 2). The second and last dose of methylene blue was given 4 hours later while the oral supplementation of vitamin C was continued. The blood level of methemoglobin trended down consistently and dropped to 3.3% by the day of discharge. A workup for congenital MHb revealed normal activity of methemoglobin reductase and absence of hemoglobin M on electrophoresis. Cytochrome b 5 reductase could not be evaluated due to patient's refusal for further testing. The blood sulfhemoglobin level was normal. Hemoglobin electrophoresis and glucose-6-phosphate-dehydrogenase enzyme evaluation were normal. The initial urine analysis showed high urobilinogen with trace protein and moderate bilirubin, which subsequently normalized. Serum Cr level rose to 1.4 mg/dL and then decreased to 0.9 mg/dL before discharge. Total serum bilirubin level trended to a maximum of 3.7 mg/dL and then decreased to 3.1 mg/dL on the day of discharge. On further query, the patient admitted to having episodes of blue discoloration of hands, for "as long as I can remember," and which remitted spontaneously. Her psychiatric evaluation was reported as normal. She was discharged on ascorbic acid in oral daily dose of 1000 mg. She did not return for follow up after a single visit to the hematology clinic despite several requests. The patient and her father gave their consent for this case report.

Discussion

This is the first report documenting cetirizine as a causative agent for drug induced MHb. After extensive literature search using search engines PubMed and Google Scholar and using key words, such as, MHb, methemoglobin, cetirizine, antihistamine, and drug toxicity, we did not find any prior documentation or

reference to such a case.

Our patient had used cetirizine in normal doses in the past for seasonal allergies with no apparent adverse reactions. In very high doses this time she displayed nausea, abdominal pain, tremors, and anxiety, as well as MHb. It is plausible that the defense mechanisms exercised by the above mentioned protective enzymes in red blood cells were exhausted by the excessively high concentration of the drug, leading to oxidation of Fe^{2+} of hemoglobin molecules into ferric state (Fe^{3+}) and causing methemoglobin in this case. Most of the cases of acquired MHb are reported to be due to the toxicity and drug interactions of sulfonamides, dapsone, trimethoprim, benzocaine, prilocaine, and nitrates, all of which can either directly or indirectly oxidize hemoglobin.^{1,2} Ash-Bernal et al⁵ accounted for 42% of acquired MHb to be due to dapsone. Yildirim et al⁶ recently described a 20-year-old female with prilocaine-induced MHb. Exposure to these drugs overwhelms the protective enzyme systems and causes a multifold increase in the formation of methemoglobin, thus leading to clinical MHb. Cetirizine might have the same effects with abnormally high serum concentrations.

Methemoglobin is physiologically increased in infants under 6 months of age who produce only approximately 50% to 60% of the normal adult level of cytochrome-b5 reductase.² Among the congenital forms of MHb, cytochrome-b5 reductase deficiency is the most common defect.^{1,2} Most cases of this autosomal recessive mutation are categorized as type I, in which the production of this protective enzyme is absent only in mature erythroid cells.^{1,2} In type II, which is less common, cytochrome-b5 reductase synthesis is lacking in all cells.^{1,2} Such patients fail to thrive and exhibit serious neurologic morbidities, such as, developmental delay, microcephaly, and seizures. Hemoglobin M disease is another type of MHb in which mutations in the molecular globin result in a diminished ability to reduce ferric iron to ferrous states.¹ Methemoglobinemia can also be caused by impaired production of NADH and NADPH in pyruvate kinase deficiency, and glucose-6-phosphate dehydrogenase deficiency.^{2,7,8} We believe that our case fell in the category of type 1 cytochrome-b5 reductase deficiency, although this diagnosis could not be confirmed as the specific enzyme was not assayed. The occurrence and severity of clinical manifestation of MHb correlate with methemoglobin concentrations in blood. Central cyanosis and discoloration of the skin are observed with methemoglobin level of 10% to 30%,^{1,2} while, at levels between 25% and 50%, dyspnea, cyanosis, changes in mental status, headache, confusion, fatigue, exercise intolerance, and dizziness may occur. Patients with methemoglobin level above 50% suffer from seizures, coma, and even death if the

level exceeds 70%.⁵ Those having other abnormal hemoglobin species, such as carboxyhemoglobin, sulfhemoglobin, and sickle hemoglobin; or suffering from anemia, sepsis, and significant cardio-respiratory disorders may experience variably severe symptoms at levels as low as 5% to 8%.³⁻⁵

The standard treatment of acute MHb is intravenous or oral methylene blue, in addition to supplemental oxygen. Methylene blue provides an artificial electron acceptor for NADPH methemoglobin reductase in red blood cells allowing the enzyme to function at an expedited pace.^{3,5} Vitamins C and B12 can activate a reductive pathway to decrease methemoglobin, and the former is generally used as treatment for chronic MHb.^{3,5} In our case, the exact enzymatic defect could not be established as the patients refused for some of the testing. However, the increased MHb and serum bilirubin levels suggested chronic mild MHb and hemolysis. The patient was discharged on vitamin C considering such a possibility. The transient mild elevation of serum Cr was possibly due to either cetirizine toxicity, acute episode of MHb, or a combination of both. The history of depression and anxiety could be attributed to an ongoing mild chronic MHb so far undiagnosed, although a traumatic early childhood experience of being homeless might have played a role. Changes in mental status and anxiety have been described with MHb, most likely secondary to associated hypoxia.^{2,3,5} It is conceivable that chronic intermittent mild hypoxemia contributed to her symptoms of anxiety and depression. Over 45 toxic agents and drugs have been described to induce MHb, but there was no history of any such exposure, and environmental toxins were unlikely as the patient was in a college students' dormitory with strict safety standards.⁸

Summary

We have described a novel case of MHb in a teenage woman, triggered by an acute ingestion of approximately 120 to 180 mg of cetirizine, allegedly with no suicidal intent. The patient responded to the standard treatment with methylene blue and vitamin C. The past history of recurrent self remitting "blue discoloration of hands," mild psychiatric symptoms, and the presence of low grade hyperbilirubinemia suggested a chronic process. The exact enzymatic deficiency could not be established as the patient declined for the specific investigations. Sequential follow up could not be accomplished as she did not return for outpatient visits despite multiple requests. In the absence of any other triggering factor, we believe that MHb in this case was caused by an excessively high blood concentration of cetirizine, which exhausted the protective enzyme system of the body against the disease.

ARTICLE INFORMATION

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