A 29 year old female with acetaminophen overdose, anemia, and hypoxemia

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A 29 year old African American woman presented to the emergency room complaining of several days of nausea, vomiting and fatigue. She underwent a dental procedure one week prior and had been taking an estimated acetaminophen dose of 5-6 grams/day for pain. Her last dose was 24 hours prior to presentation. She denied abdominal pain, diarrhea, constipation, shortness of breath or change in abdominal girth. She had no significant past medical history or family medical history. She used no other medications. She did not drink, smoke or take illicit drugs.

On admission, her temperature was 97.9, heart rate 90, blood pressure 120/85 mmHg and respiratory rate 20. Head and neck: scleral icterus. Chest: clear. Cardiac: tachycardia without murmur or rub. Abdomen: right upper quadrant tenderness, normal bowel sounds, no distention, no organomegaly and no rebound or guarding. Skin: warm, dry and without jaundice.

Admission labs revealed: WBC 15,400 cells/µL with 95% neutrophils, hemoglobin 14.3, platelets 232,000, INR 2.7. The comprehensive metabolic panel was normal except for a total carbon dioxide of 26 meq/L (anion gap of 10), AST 13078, ALT 13382, alkaline phosphatase 91, total bilirubin 6.7 mg/dL. Acetaminophen level was 39.6.

Hospital Course

The patient was treated with intravenous fluids, antiemetics and N-acetylcysteine for accidental acetaminophen overdose. Her admitting symptoms improved and her transaminases quickly trended downward. On day 4 of admission, she became acutely short of breath with a room air oxygen saturation of 85% (SpO2) that did not improve with 1.00 FIO2 administered via a nonrebreather mask. Her exam was unchanged with the exception of a respiratory rate of 22. She had no other complaints.

Laboratory values at that time revealed a WBC count of 24,800 cells/µL with 80% neutrophils, hemoglobin 8.7, and platelets 195,000. The INR was 1.4. A repeat hemoglobin (done 3.5 hours later) was 7.1. There were Pappenheimer inclusions. The total bilirubin was 17.4 mg/dL with direct bilirubin level of 4.1 mg/dL. The bicarbonate level was 24 with an anion gap of 15. The haptoglobin was <6 mg/dL, reticulocyte count was 4.0% (index of 2.1), and the indirect antibody screen was negative. The lactate dehydrogenase (LDH) was 4565 UNITS/L. Arterial blood gas evaluation revealed a pH of 7.57, paCO2 of 35 mmHg, paO2 of 296 mmHg on 1.00 FIO2 with a corresponding oxygen saturation (SpO2) of 85%. A chest x-ray revealed no infiltrate, pneumothorax, mass, cardiomegaly or effusion.

What test is most appropriate at this time, and what is the likely diagnosis?
Most appropriate test: Methemoglobin level via co-oximetry

Diagnosis: Methemoglobinemia and hemolytic anemia associated with acetaminophen overdose and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Discussion

A discussion of acetaminophen overdose and the resultant oxidative sequelae requires a brief review of acetaminophen metabolism. Approximately 90% of ingested acetaminophen is metabolized in the liver via glucuronide or sulfide conjugation for urinary excretion. The remaining 10% is metabolized via the cytochrome P450 system to N-acetyl-p-benzoquinone imine (NAPQI), which is a potent oxidizing agent. Under normal conditions, NAPQI is reduced via conjugation with glutathione to a nontoxic substance and excreted. In the setting of toxic acetaminophen levels, hepatic glutathione stores are exhausted, and NAPQI causes oxidative damage to the liver. This can result in fulminant hepatic failure if prompt measures are not taken to regenerate glutathione.

Oxidative stress from acetaminophen overdose can cause other untoward effects such as methemoglobinemia. Methemoglobin is the oxidized form of hemoglobin where the red blood cell ferrous iron (Fe^{2+}) is converted to the ferric state (Fe^{3+}). Ferric iron is unable to bind oxygen and the presence of methemoglobin increases oxygen affinity in unaffected heme molecules. This effect shifts the oxyhemoglobin curve to the left and decreases oxygen delivery to the tissues. This shift leads to significant tissue hypoxia in the setting of high methemoglobin levels and can cause shock at levels higher than 50%. Methemoglobinemia can be congenital (associated with cytochrome b5 reductase deficiency), although most cases are acquired. Many drugs have been implicated in methemoglobinemia (Table 1), and the most common offending agents are dapsone and topical benzocaine spray. Patients with methemoglobinemia generally exhibit cyanosis after exposure to a commonly implicated drug and can present with headache, fatigue, confusion, or seizures depending on the methemoglobin level.

Treatment of methemoglobinemia primarily involves removal of the offending agent. Methylene blue can be given to reduce iron to the ferrous state via formation of leukomethylene blue and regeneration of glutathione. If a symptomatic patient has a methemoglobin level of 20% or if the level exceeds 30% (regardless of symptomatology), administration of methylene blue should be considered. However, this treatment is not effective and is potentially toxic in certain settings such as G6PD deficiency. Specifically, methylene blue (an oxidant) consumes erythrocyte nicotinamide adenine dinucleotide phosphate (NADPH) as it is reduced to leukomethylene blue (Figure 1). The G6PD deficient red blood cell has abnormally small stores of NADPH that are rapidly consumed. G6PD deficient patients cannot continue to reduce methylene blue and thus the accumulation of this oxidant exacerbates hemolysis.

Our patient had evidence of hemolysis: decreased hemoglobin level, elevated LDH, Pappenheimer bodies, and an elevated unconjugated bilirubin. Hemolytic anemia and methemoglobinemia following acetaminophen overdose have been described and are usually
associated with G6PD deficiency. G6PD deficiency is the most common enzymatic disorder of red blood cells in humans. This is an X-linked disorder, and as a result is usually manifest in males. Most female carriers (heterozygous) are asymptomatic but can exhibit hemolysis similar to affected males due to variable Lyonization (random deactivation of x chromosomes during embryonic female development).

Our patient suffered hepatic and hematologic oxidative sequelae of acetaminophen toxicity. Her methemoglobin level measured by co-oximetry was 14.1% 12 hours after her crisis began. Her G6PD status was unknown at the time of this episode but deficiency was considered due to her hemolysis. Given the mild symptomatology of her methemoglobinemia, she was treated conservatively with supplemental oxygen therapy and blood transfusion. Her methemoglobin level, hypoxia and anemia improved over the next 24 hours, and she was discharged home 48 hours later. Her G6PD level was measured during her crisis and was found to be 8 (7.0-20.4). G6PD levels may be normal in the setting of active hemolysis due to preferential destruction of the most severely deficient erythrocytes. A follow up level is required to confirm the diagnosis. Several months after this episode, her G6PD level was 5.0.

Clinical Pearls:

1) Co-oximetric measurement of methemoglobin levels is the test of choice for suspected methemoglobinemia.

2) Acetaminophen overdose can cause multiple sequelae related to oxidant stress such as hepatic necrosis, methemoglobinemia, and hemolytic anemia.

3) If non-immune hemolytic anemia coincides with methemoglobinemia, consider G6PD deficiency and withhold treatment with methylene blue.

4) If methylene blue is ineffective or causes hemolysis in the setting of methemoglobinemia, consider G6PD deficiency.

5) Blood transfusion during acute hemolytic crisis can replete G6PD as donor RBCs are generally not deficient.
Table 1- Commonly used drugs implicated in methemoglobinemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Dapsone</td>
<td>methylene blue</td>
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<tr>
<td>local anesthetic agents</td>
<td>nitrate compounds</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>phenacetin</td>
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<tr>
<td>Sulfonamides</td>
<td>primaquine</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>rasburicase</td>
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Suggested readings:


Sklar GE. Hemolysis as a potential complication of acetaminophen overdose in a patient with glucose-6-phosphate deficiency. Pharmacotherapy 2002; 22(5):656-8