

Vitamin-Induced Hemolysis

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Case Summary

A 47 year-old African American man presented to the hospital with three a day history of fever, shortness of breath, nausea, emesis, dark urine, and progressive confusion. The symptoms began one day following an infusion of a “vitamin complex” at his physician’s office. The patient’s medical history was significant for retroperitoneal fibrosis with multiple urological procedures, for which he was taking oxybutinin and tamsulosin.

His initial vital signs were: BP, 133/76 mm Hg; HR, 120/min; RR, 16/min; T, 98.9°F; SpO₂, 100%RA. His physical examination was significant for lethargy, mild scleral icterus, and jaundice. Laboratory studies were notable for a hemoglobin, 3.3 g/dL; hematocrit, 11.1%; reticulocytes, 33%; creatinine, 2.8 mg/dL (baseline 1.4 mg/dL); total bilirubin, 4.4 mg/dL. He was admitted with the diagnosis of hemolytic anemia and transfused 2 units of packed red blood cells, which was followed by an appropriate rise in his hemoglobin. Since the diagnosis of xenobiotic-induced hemolytic anemia could not be excluded, the patient received plasmapheresis. His outpatient physician, who practices both homeopathic and western medicine, revealed that he administered an infusion containing vitamin B and D complex, free amino acids, magnesium, and taurine. He did not comment on the preparation method.

What are the mechanisms by which xenobiotic-induced hemolysis occurs?

Hemolysis refers to premature destruction of red blood cells in the circulation, usually before the completion of their typical 120 day life span. Hemolysis is commonly xenobiotic-induced and occurs for via either immune or non-immune-mediated mechanisms.

Immune-mediated hemolysis refers to an antigen-antibody reaction following drug exposure, and is often divided into three types.

- In Type I immune mediated reaction the xenobiotic acts as a hapten, and binds tightly to the erythrocyte cell membrane glycoprotein with subsequent IgG formation directed against the drug. The antigen-antibody complex is removed by the splenic macrophages. Large doses of penicillin are needed to induce hemolysis via this mechanism.
- A Type II reaction differs in that the xenobiotic binds the red blood cell membrane glycoprotein with low affinity, attracts IgM, and the antigen-antibody complex is targeted by the innate complement system. In contrast to Type I reaction, small doses of xenobiotics, such as quinidine, may trigger hemolysis.
- The Type III reaction is an autoimmune process, where the xenobiotic is thought to alter the natural suppressor system, resulting in antibody formation against the cellular components of red blood cell membrane. α -Methyldopa classically induces hemolysis via this mechanism.

Non-immune mediated hemolysis is induced by oxidants, non-oxidizing xenobiotics, microangiopathic processes, spider and snake venom, and osmotically active xenobiotics.

Patients with glucose-6-phosphate dehydrogenase (G6PD) are specifically prone to oxidant-induced hemolysis. This enzyme indirectly restores the cell's antioxidant agent glutathione and provides erythrocyte with defense against oxidant damage. In G6PD-deficient cells, sulfhydryl groups on globin protein become oxidatively crosslinked, unfolding the protein chain, resulting in the hemoglobin molecules precipitation as Heinz bodies within the erythrocytes. Non-oxidants such as arsine, copper and lead may directly damage hemoglobin or the red blood cell membrane or may deplete the erythrocyte's intrinsic reducing system spearheaded by glutathione.

Microangiopathic-inducing xenobiotics include ticlopidine, clopidogrel, cyclosporine and tacrolimus. Platelet aggregates form throughout the vasculature, likely due to inactivation of ADAMTS 13 (metalloprotein that breaks down large multimers of vWF), resulting in trauma to the erythrocyte. Venom of *Loxosceles reclusa* (brown recluse spider) leads to hemolysis via interaction of sphingomyelinase-D with the erythrocyte membrane. Crotalinae snake venom produces hemolysis via hemostatically active components that interfere with the coagulation cascade. Hypophosphatemia reduces phosphorylation of intracellular molecules including ATP and 2,3-diphosphoglycerate resulting in reduced membrane deformability. Water may osmotically swell the erythrocyte causing it to lyse.

Table 1: Oxidant drugs that cause hemolysis in patients with G6PD deficiency

Doxorubicin	Phenylhydrazine
Furazolidone	Primaquine
Isobutyl nitrite	Sulfacetamide
Methylene blue	Sulfamethoxazole
Nalidixic acid	Sulfanilamide
Naphthalene	Sulfapyridine
Nitrofurantoin	Toluidine blue
Phenazopyridine	Trinitrotoluene

From: Goldfrank's Toxicology Emergencies: Eighth Edition

What are the clinical implications of G6PD Deficiency?

G6PD is an enzyme that generates NADPH via the hexose monophosphate shunt, a pathway that converts glucose to an energy source in erythrocytes. (Figure 1) NADPH is needed to regenerate glutathione, and G6PD deficiency leaves the erythrocyte susceptible to oxidant-induced damage.

G6PD deficiency is an X-linked inherited disorder with variable phenotype, and produces a defect in the G6PD enzyme that reduces its half-life. Approximately 7.5% of the world population is affected, although the magnitude of the enzyme dysfunction varies widely. Classification of G6PD deficiency according to the degree of enzyme deficiency allows prediction of the severity of hemolysis. Class I and II individuals, mostly from the Mediterranean region, have less than 10% of G6PD activity under normal conditions and suffer from fulminant hemolysis, classically with exposure to fava beans and other oxidant stressors. Class III patients (type A) have a moderate (10-60%) G6PD deficiency and often present with limited hemolysis in response to certain drugs or infections. Class III G6PD deficiency affects approximately 11% of the African American population. The age of presentation is variable, and the first presentation of G6PD deficiency involves a hemolytic crisis.

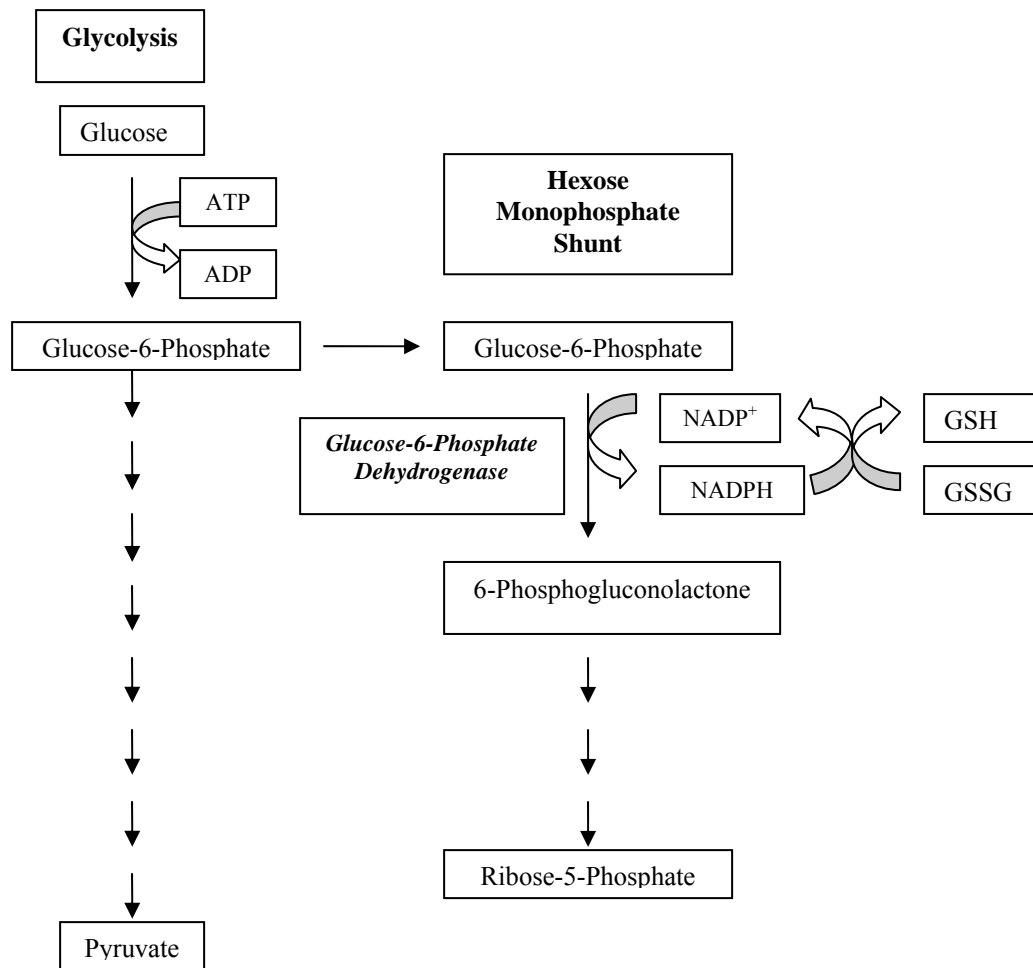


Figure 1: Hexose Monophosphate Shunt in Erythrocytes

Case continuation

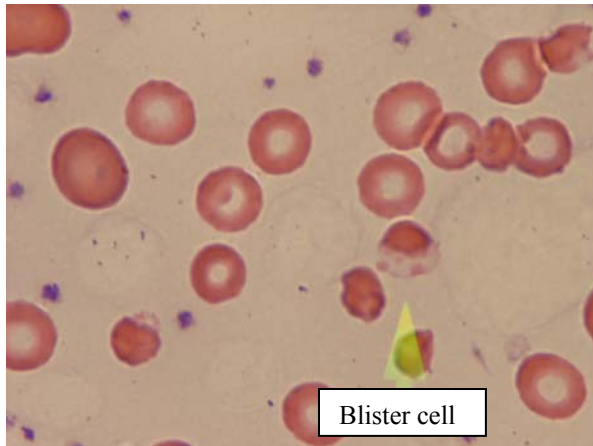
The patient continued to improve clinically. A direct Coombs antiglobulin test was negative. His peripheral smear demonstrated “blister cells,” erythrocytes that have been left devoid of precipitated hemoglobin by the spleen. These are commonly noted in patients with G6PD deficiency. The patient was discharged from the hospital in stable condition. Follow up hemoglobin in 2 weeks was 11.4 g/dL. His G6PD status will be confirmed upon complete recovery.

How can diagnostics point to G6PD deficiency in a patient with acute hemolytic anemia?

Patients with G6PD deficiency will have anemia with unaffected platelet and leukocyte count (these are all reduced in patients with aplastic anemia, for example), elevated total bilirubin with normal direct bilirubin (suggesting an elevated indirect bilirubin), elevated lactate dehydrogenase, increased reticulocyte count, and a negative Coombs test. The Coombs reagent is an antiglobulin that detects presence of antibodies and/or complement coating the erythrocytes in a direct test. The Indirect Coombs test identifies autoantibodies in the patient’s serum and may

be falsely negative if there is only a small concentration of immunoglobulin present. Direct Coombs test is used to evaluate for presence of xenobiotic or autoimmune condition-induced erythrocyte antibodies, whereas Indirect Coombs test is typically used to screen for serum antibodies during blood crossmatch procedures.

The peripheral blood smear may demonstrate Heinz bodies, or precipitated hemoglobin, in the erythrocyte. Alternatively, there may be blister cells present, the erythrocyte whose precipitated hemoglobin was removed during passage through the spleen. (See peripheral blood smear below). Blister cells are commonly seen in glucose 6-phosphate dehydrogenase deficiency.



Courtesy of Kenneth Hymes, M.D.

Measuring serum G6PD concentration should **not** be done for approximately 3 months after acute hemolytic event. Since the remaining erythrocytes will have adequate G6PD activity and will have survived the oxidant stressor, the G6PD activity measurement will be falsely elevated. That is, the older cells, with dysfunctional G6PD, will have hemolyzed, leaving only the younger cells, which still have adequate enzyme activity.

Can a patient have a G6PD deficiency-associated hemolytic crisis following a vitamin infusion?

G6PD-deficient erythrocytes hemolyze when faced with oxidants. Unfortunately, the literature on vitamin-induced acute hemolysis is sparse. There is a reported case of acute hemolysis in a 32 year-old man of Nigerian descent diagnosed with HIV and treated with high dose of ascorbic acid. Another report of G6PD deficiency-induced hemolysis was described in a patient treated with a homeopathic remedy *Acalypha indica* (Indian copperleaf, "acal"). Four cases of hemolytic crisis were described in G6PD deficient children ranging from 20 days to four years of age after topical application of henna. It is unknown what minerals were included in this infusion, but copper and many other transition metals are highly associated with hemolysis when administered parenterally.

Properly formulated naturopathic products have little active ingredient, and are generally not poisonous, since the nature of the preparations are highly diluted. The life-threatening reactions may be attributed to improper dilution, incorrect diluents, and/or contaminants or adulterants.

References:

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