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TOXICOLOGY OBSERVATION

If Vitamins Could Kill: Massive Hemolysis Following Naturopathic Vitamin Infusion

Zhanna Livshits · Robert S. Hoffman · Kenneth B. Hymes · Lewis S. Nelson

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Abstract
Introduction Hemolysis from naturopathic remedies remains poorly reported in the medical literature, although it is most commonly noted in the patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. We report a case of massive intravascular hemolysis following the infusion of a naturopathic preparation that contains vitamins.

Case Report A 47-year-old African-American man presented to the hospital with 3 days of fever, dyspnea, emesis, dark urine, and progressive confusion. His symptoms began 1 day following an infusion of a vitamin complex. His physical examination was significant for lethargy and scleral icterus. Initial laboratory studies were notable for anemia (hemoglobin, 3.3 g/dL and hematocrit, 11%), brisk reticulocytosis (33%), acute renal insufficiency (creatinine, 2.8 mg/dL), and indirect hyperbilirubinemia (total bilirubin, 4.4 mg/dL). His peripheral smear demonstrated "blister cells," erythrocytes that have been left devoid of precipitated hemoglobin by the spleen, which are commonly seen in patients with G6PD deficiency. His physician revealed that the infusion contained vitamins B and D complex, free amino acids, magnesium, and taurine. The patient clinically improved and was discharged to home. G6PD concentration was significantly reduced to 4.7 U/g Hb upon recovery.
Discussion Life-threatening intravascular hemolysis may occur following a naturopathic vitamin infusion and may identify previously unknown G6PD deficiency. Since most properly formulated naturopathic treatments have few toxic ingredients, the possibilities of improper formulation, toxic diluents, or contaminants should be considered. Inadequate regulatory oversight of naturopathic remedies has the potential to allow serious toxicity especially in genetically predisposed individuals.

Keywords Hemolysis · G6PD deficiency · Naturopathic · Vitamin

Previous Presentation of Data None.

Z. Livshits (✉) · L. S. Nelson
The New York City Poison Control Center,
455 First Avenue, Room 123,
New York, NY 10016, USA
e-mail: doczhanna@gmail.com

L. S. Nelson
e-mail: lnelsonmd@gmail.com

R. S. Hoffman · L. S. Nelson
Department of Emergency Medicine, New York University School of Medicine,
New York, NY, USA

R. S. Hoffman
e-mail: bobhoffmd@gmail.com

R. S. Hoffman
Department of Medicine (Clinical Pharmacology), New York University School of Medicine,
New York, NY, USA

R. S. Hoffman
The New York City Poison Control Center,
455 First Avenue, Room 123,
New York, NY 10016, USA

K. B. Hymes
New York University Cancer Institute,
160 East 34th Street,
New York, NY 10016, USA
e-mail: Kenneth.Hymes@nyumc.org

Introduction

Although hemolysis is a well-recognized adverse effect of various medications, it remains a rather poorly described

complication of alternative therapy. There are several reports in the literature of hemolysis associated with naturopathic remedies in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. For example, acute hemolysis following high-dose ascorbic acid [1] and the homeopathic remedy *Acalypha indica* (Indian copperleaf, "acal") are well described [2]. Similarly, four cases of hemolytic crisis after topical application of henna were reported in G6PD-deficient children ranging in age from 20 days to 4 years [3]. The shift towards the wider use of alternative medicine warrants further evaluation of the efficacy of these xenobiotic preparations and vigilance for their adverse effects. We report a middle-aged man who developed a life-threatening hemolytic response following administration of a "vitamin infusion" by a practitioner of alternative medicine.

Case Report

A 47-year-old African-American man presented to the hospital with a 3-day history of fever, shortness of breath, nausea, emesis, dark urine, and progressive confusion. These symptoms began 1 day after he had received an infusion of a "vitamin complex" at his physician's office to "boost his immune system." The patient was asymptomatic at the time of infusion. His medical history was significant for retroperitoneal fibrosis and multiple urologic procedures, for which he was taking oxybutynin and tamsulosin.

His initial vital signs were: blood pressure, 133/76 mmHg; heart rate, 120 beats/min; respiratory rate, 16 breaths/min; temperature, 37.2°C; and oxygen saturation by pulse oximetry, 100% on room air. His physical examination revealed lethargy with the ability to provide a complete history, mild scleral icterus, and jaundiced skin. He had unremarkable cardiac, respiratory, and abdominal examinations. His cranial nerves, sensation, and motor examinations were grossly symmetrical and intact, and the patient did not exhibit meningeal signs. Laboratory study results were notable for the following values: hemoglobin, 3.3 g/dL; hematocrit, 11.1%; MCV, 90.6; MCH, 26.2; platelets, 647,000/μL; reticulocyte count, 33%; haptoglobin, <10 mg/dL; BUN, 68 mg/dL; creatinine, 2.8 mg/dL (baseline, 1.4 mg/dL); and total bilirubin, 4.4 mg/dL (direct bilirubin undetectable). The patient was admitted with the diagnosis of hemolytic anemia. He underwent transfusion of 2 units of packed red blood cells; this was followed by an appropriate rise in his hemoglobin concentration to 7.0 g/dL. His platelet count normalized to 272,000/μL. Since the diagnosis of thrombotic thrombocytopenic purpura (TTP) could not be excluded initially, the patient also underwent plasmapheresis. TTP was eventually excluded by lack of red blood cell fragmentation on peripheral blood smear and a lack of thrombocytopenia.

When the patient became ill, his wife contacted the physician to inquire about the contents of the vitamin infusion. The physician, who practices both alternative and conventional medicine, revealed that he had administered an infusion containing vitamins B and D complex, free amino acids, magnesium, and taurine. He did not comment on the preparation method.

An extensive diagnostic panel including direct Coombs antiglobulin test to test for antibodies present directly on the erythrocytes' membrane, a peripheral blood smear, and a G6PD activity was unrevealing. A direct Coombs antiglobulin test was negative. His peripheral smear demonstrated "blister cells," i.e., erythrocytes whose precipitated hemoglobin was removed during passage through the spleen (Fig. 1). His initial G6PD activity was normal during the acute phase of illness.

Over the course of the week, the patient improved dramatically following withdrawal of the presumed offending xenobiotic, close observation, and active management. He was discharged from the hospital in stable condition. At 2-week follow-up, his hemoglobin concentration was 11.4 g/dL. His G6PD activity 3 months following the event was significantly reduced at 4.7 U/g Hb (reference range, 7.0–20.5 U/g Hb).

Discussion

The growing popularity of alternative medical treatments warrants intense vigilance. Herbal and vitamin preparations are neither standardized nor closely monitored by a governmental organization. There are patients with the potential to suffer from significant toxicity. G6PD deficien-

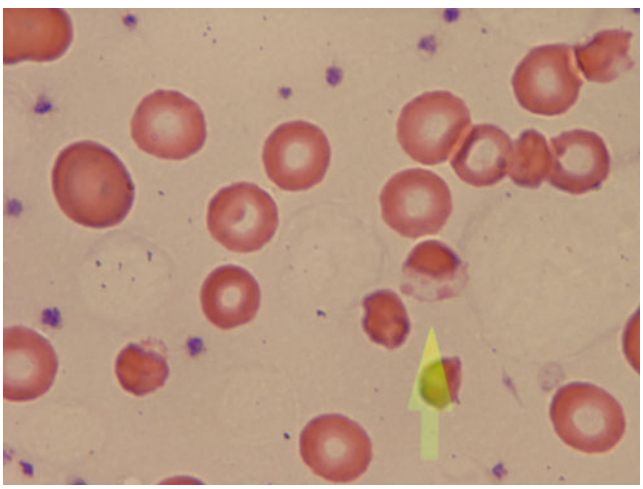

Fig. 1 Peripheral blood smear, with the *arrow* pointing to "blister cell"

cy, distinguished by severity of reduction of G6PD half-life, commonly predisposes individuals to hemolysis. There are several G6PD deficiency variants, classified according to the magnitude of G6PD enzyme deficiency, decreasing in severity with increasing class number. Class I variant implies severe G6PD deficiency, and patients with this disorder suffer from chronic hemolytic anemia. Class II, also known as the Mediterranean variant, commonly found in the Caucasian population, demonstrates an intermediate severity of G6PD deficiency with a markedly reduced enzymatic half-life in both immature and mature red blood cells. Hemolysis is intermittent and may be severe. Class III variant affects approximately 11% of African-Americans, including the case patient, with a moderate (10–60%) deficiency of G6PD [4]. Enzymatic activity is commonly normal in immature erythrocytes (reticulocytes) and diminished in mature erythrocytes. The age at presentation is variable, and the first presentation of G6PD deficiency often involves a hemolytic crisis [5, 6]. In contrast to patients with the class II G6PD deficiency, who may demonstrate reduced G6PD activity during acute hemolysis, patients with class III G6PD deficiency may have a falsely normal G6PD activity in the acute phase due to the presence of functional G6PD in reticulocytes. Therefore, diagnosis can only be made several weeks following resolution of the hemolytic crisis in this latter patient population.

The following xenobiotics have been associated with hemolysis in patients with G6PD deficiency [6]. The list is not comprehensive.

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

One of the major limitations of this report is the inability to confirm the exact ingredients, concentrations, and preparation method of the infusion since the practitioner was not willing to participate in the investigation. Although it is unknown which xenobiotics were included in the infusion received by the patient, copper and many other transition metals are highly associated with hemolysis when administered parenterally.

Properly formulated naturopathic products are generally not problematic. Life-threatening reactions associated with these products may be attributed to improper dilution, incorrect diluents, and/or contaminants or adulterants. Vitamins, which fall under a broad category of dietary supplements, are not monitored by the Food and Drug Administration. The word “vitamin” implies a safe product to the consumers. When taken out of the context of dietary supplements, and into the realm of alternative medicine, there is lack of quality data collection and regulatory oversight by a governing body. Inadequate regulation of naturopathic remedies has the potential to overlook the risk for serious toxicity, especially in genetically predisposed individuals.

Conclusion

Infusion of naturopathic preparations, including vitamins, may result in hemolysis in individuals with undiagnosed G6PD deficiency. Lack of quality assurance and inadequate regulation of their ingredients and preparation may allow the introduction of xenobiotics that can cause life-threatening toxicity in susceptible individuals.

Conflict of Interest The authors have no conflicts to report.

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