Hemolytic Anemia in a G6PD-Deficient Man after Inhalation of Amyl Nitrite ("Poppers")

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Inhaled nitrites are illegally used as aphrodisiacs or as mood-altering substances, usually by young adults. These substances are commonly known by the terms "poppers," "snappers" or "rush." Their smooth muscle-relaxant property makes them popular especially among homosexual men, and their use was found to be significantly associated with unsafe sexual habits in this population [1].

There are no data on the extent of the phenomenon in Israel, but it seems to be quite prevalent. In the United States, the use of "poppers" has been reported to be as high as 11% among occasional recreational drug users and 22% among heavy drug abusers [2]. Inhaled nitrites (most commonly the amyl derivative) have several adverse effects, some of which are hematologic. A number of cases of methemoglobinemia, Heinz body formation, and hemolytic anemia after "poppers" inhalation has been reported worldwide, and are attributed to the oxidative stress caused by nitrites [3–5]. We describe here a 19 year old man with glucose-6-phosphate dehydrogenase deficiency, who developed acute hemolysis after inhalation of amyl nitrite.

Patient Description

A 19 year old male of Jewish Sephardic origin was hospitalized in an internal medicine department complaining of severe headache and jaundice. The patient's medical history was unremarkable except for G6PD deficiency and Kawasaki disease at the age of 10. Upon questioning, the patient admitted having inhaled volatile substance he identified as "poppers" on the previous day. He claimed that it was the first time he had used this substance. After inhaling the drug he felt severe headache, and profound jaundice was noted the following day. The patient denied taking any other medications, or food that could possibly have exacerbated the hemolytic anemia of G6PD deficiency.

On physical examination the patient was hemodynamically stable, blood pressure was 130/60 mmHg and heart rate 82 beats/minute. Jaundice of the skin and sclera was prominent with no splenomegaly or hepatomegaly. The rest of the physical examination was unremarkable. The complete blood cell count on admission revealed a hemoglobin level of 13.0 g/L (normal 13.5–17.3 mg/dl), hematocrit 38.4% (normal 35–49%); and the indexes of red cell distribution width, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were normal. White blood cell count and platelet count were also normal. The noteworthy finding in blood chemistry results was high total bilirubin, 12.4 mg/dl, of which the direct component was 0.49 mg/dl. Lactate dehydrogenase was 430 U/L and all other chemistry parameters were normal. No traces of blood or bilirubin were detected in a urine sample. The following day the patient was severely icteric, but otherwise felt well. Hemoglobin level dropped to 11.9 mg/dl, hematocrit dropped to 33.9%, reticulocyte count was 5.2% (reticulocyte index = 2.6), haptoglobin level was <8.8 mg/dl

G6PD = glucose-6-phosphate dehydrogenase

(normal values are 28–284 mg/dl), bilirubin level dropped to 8.3 mg/dl with 0.5 mg/dl component of direct bilirubin, and LDH level was 382 U/L. Direct Coombs' test was negative, and qualitative G6PD assay demonstrated deficiency of the enzyme. The patient was discharged on the third day with mild jaundice.

Comment

Inhaled nitrites are commonly used as recreational drugs, usually by young adults and especially by homosexual men. Nitrites have a strong oxidant effect on red blood cells' membrane and its hemoglobin. This oxidant effect is demonstrated in several ways. A number of reports described methemoglobin formation caused by oxidative stress induced by volatile nitrite inhalation [5]. In our case, blood was drawn for methemoglobin only on the third day of hospitalization, with normal results. Since the reduction of oxidized hemoglobin occurs rapidly, an initial methemoglobinemia might have been overlooked. The oxidative damage to hemoglobin molecules caused by inhaled nitrites can induce the dissociation of heme and globin chains, consequently forming polymerized globin aggregates known as Heinz bodies. These aggregates are attached to the red blood cell's membrane, thereby altering its shape. The aggregates are removed by splenic endothelial cells, resulting in the formation of "bite-out" cells. Several cases of Heinz body formation and "bite out" cell hemolytic anemia have been described following nitrite inhalation [3,5]. G6PD deficiency, a relatively prevalent disease in Israel, probably predisposes users of inhaled nitrites to their oxidative effects, and thus to hemolysis. The inability of G6PD-deficient patients to produce reduced glutathione through the pentose-phosphate pathway of glycolysis results in red blood cells that are extremely susceptible to oxidative stress. Nitrite inhalation resulting in hemolysis in G6PD-deficient patients has been reported only twice to date [3,4].

Interestingly enough, in the present case, although the patient's indirect bilirubin level was notably high the hemoglobin level decreased only slightly. Moreover, the LDH level was in the normal range. This can be explained by an underlying Gilbert's disease. Clinicians should be aware of the potential danger of inhaled nitrites ("poppers") and particularly of their propensity to cause hemolytic anemia in G6PD-deficient patients.

LDH = lactate dehydrogenase

References

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Pearls around the neck – stones upon the heart

Yiddish proverb

From listening comes wisdom, and from speaking, repentance

Italian proverb

Capsule

More to control than class

The secretory class of immunoglobulin A (IgA) dominates in B cell immune responses at the intestinal mucosa. Switching of B cells to IgA is regulated by the enzyme activation-induced cytidine deaminase (AID), which also controls somatic hypermutation (SHM) of Ig genes. As a result, both AID-deficient mice and those lacking IgA display a predominance of mucosal IgM antibodies. However, as Fagarasan et al. report, AID-mutant mice suffer a severe outgrowth of bacterial flora in the gut, which is not seen with IgA deficiency, accompanied by a hyperproliferation of intestinal B cells, leading to hyperplasia of isolated lymphoid follicles. Somatic hypermutation, coupled with switching to the appropriate antibody class, thus appears to be essential in managing intestinal bacteria and regulating B cell immunity.

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