A case of hemolysis and methemoglobinemia following amyl nitrite use in an individual with G6PD deficiency

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Received 28 August 2012; accepted 26 December 2012
Available online 5 March 2013

Abstract

A 34-year-old man presented feeling generally unwell with dark urine 3 days after inhaling amyl nitrite. His initial heart rate was 118/min, blood pressure 130/85 mmHg, O2 saturation 85% on 15 L/min oxygen, and Glasgow coma score 15. He was pale, with clear chest sounds on auscultation. His hemoglobin was 60 g/L, bilirubin 112 μM, and methemoglobin concentration 6.9% on an arterial blood gas. Amyl nitrite-induced hemolysis and methemoglobinemia were diagnosed. Methylene blue was not administered because of the relatively low methemoglobin concentration and the possibility of inducing further hemolysis. He was subsequently confirmed as having glucose-6-phosphate dehydrogenase deficiency, which had originally been diagnosed in childhood. Amyl nitrite toxicity may include concurrent methemoglobinemia and hemolysis. Administration of methylene blue for clinically significant methemoglobinemia can induce further hemolysis.

Keywords: Amyl nitrite; Glucose-6-phosphate dehydrogenase deficiency; Hematology; Toxicology

1. Introduction

Amyl nitrite is one of a number of alkyl nitrites otherwise known as “poppers”, “rush”, or “liquid gold” when utilized recreationally. Amyl nitrite produces smooth muscle relaxation leading to dizziness, euphoria, a feeling of warmth and changes in sphincter tone. This combination of effects enhances sexual experiences in some individuals.

There have been reports of hemolysis due to oxidative stress secondary to amyl nitrite.1 In patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency, optimizing effective oxygen delivery in the face of amyl nitrite-induced methemoglobinemia and hemolysis can be challenging.

2. Case report

A 34-year-old man of Greek ethnicity presented to the emergency department (ED) via his primary physician with dark urine for 3 days following his return from Vanuatu 4 weeks earlier. He had drunk 100 half-coconut shells of kava while there. He also complained of diarrhea, abdominal pain, and headaches. Four days prior to presentation he had inhaled amyl nitrite. There was no other toxic exposure, change in habit and diet or drug use. He had become increasingly dyspneic and noticed dark urine. He had a history of blood transfusions after ingesting fava beans when he was aged 2 years but could not remember his condition. On arrival in the ED he was afebrile, and had a Glasgow coma score of 15, blood pressure of 130/83 mmHg, respiratory rate of 18/min, heart rate of 118/min, and oxygen saturation of 81% on room air and 85% on 15 L/min oxygen. He was pale, with clear chest sounds, and a soft, nontender abdomen.

He had a hemoglobin (Hb) of 60 g/L [reference range (rr) 130–180 g/L], white cell count 38.2 g/L (rr 4–11 g/L) and platelets of 408 × 10^9/L (rr 150–400 × 10^9/L). A blood smear showed marked macrocytic anemia with bite cells, blister cells, spherocytes, polychromasia, left shift neutrophilia, and an appearance consistent with oxidative hemolysis. No malarial parasites were seen on thick or thin blood smears. His bilirubin was 112 μM (rr < 18 μM), haptoglobin 0.2 g/L.
(rr 0.5–3.3 g/L) and lactate dehydrogenase 2232 IU/L (rr 98–192 IU/L). The rest of his liver function tests were within normal limits. The infectious diseases service considered an infectious cause unlikely. Given the time course, his symptoms and signs did not fit those of kava toxicity. Blood gas analysis also confirmed methemoglobinemia with a peak methemoglobin (MetHb) concentration of 6.9%.

Amyl nitrite toxicity leading to methemoglobinemia and hemolysis on a background of G6PD deficiency (given the previous reaction to fava beans) was suspected. The G6PD deficiency was later confirmed by no demonstrable activity on assay and a review of his childhood records. The patient’s methemoglobinemia, which may have been higher prior to presentation, was not severe enough to warrant treatment with methylene blue during his time in the ED or during hospitalization. There was also concern about the potential adverse effects of methylene blue in the context of concurrent hemolysis and G6PD deficiency. He was admitted for observation and supportive care, and received three units of red blood cells. His oxygenation improved, hemoglobin levels remained stable post-transfusion, and MetHb levels decreased back to normal; he was discharged after 3 days.

3. Discussion

There have been reports of hemolysis due to oxidative stress secondary to amyl nitrite and in patients with G6PD deficiency. Bogart et al described methemoglobinemia and hemolysis secondary to nitrite administration in a non-G6PD deficient individual. However, documented cases of measured methemoglobinemia and hemolysis occurring concurrently following amyl nitrite exposure in G6PD deficiency are rare. This raises some interesting management issues, specifically in regard to the traditional use of methylene blue for methemoglobinemia, which could be harmful.

Maintenance of an adequate concentration of reduced glutathione enables erythrocytes to withstand a degree of oxidative stress. Glutathione reduces oxidants and maintains sulfhydryl groups that protect the integrity of the cell membrane. G6PD catalyzes the first step in the pentose-phosphate pathway of glycolysis. This pathway leads to the production of reduced glutathione and requires nicotinamide adenine dinucleotide phosphate hydrogen (NADPH). Volatile nitrite-induced hemolysis can occur without G6PD deficiency, but is more likely in patients with the condition because of decreased glutathione concentrations.

MetHb is a form of Hb that has been oxidized from the Fe$^{2+}$ (ferrous) to Fe$^{3+}$ (ferric) state. This form of Hb cannot carry oxygen. The MetHb concentration is normally maintained through reduction mechanisms at less than 1%. Methylene blue is the antidote for the treatment of significant amyl nitrite-induced methemoglobinemia. It is reduced to leuko-methylene blue by MetHb reductase, reducing MetHb to Hb. This reaction (Fig. 1) requires the presence of NADPH.

Successful treatment of methemoglobinemia with methylene blue requires adequate NADPH. Patients with G6PD deficiency have low endogenous NADPH. In addition, our patient had hemolytic anemia and required additional NADPH to produce reduced glutathione to combat amyl nitrite-induced oxidative stress. Administration of methylene blue in this case could have theoretically worsened the hemolytic anemia through two mechanisms: competitive loss of NADPH required to produce reduced glutathione because of utilization of NADPH for reduction of methylene blue; and methylene blue itself acting as a mild oxidative stressor.

Methylene blue is generally indicated for treatment of MetHb concentrations >30%, or in symptomatic patients regardless of the MetHb concentration. Anemic patients are also less likely to tolerate significantly raised MetHb concentrations. Methylene blue in high doses (>7 mg/kg) can cause paradoxical methemoglobinemia secondary to a direct oxidative effect on Hb. Common side effects of methylene blue include headache, dizziness, nausea, vomiting, dyspnea, and chest discomfort. In our patient, the measured MetHb concentration was relatively low and, despite significant anemia, it was decided not to administer antidotal treatment. Instead packed red blood cells were transfused with good effect, but not without a risk of a transfusion reaction. Administration of methylene blue to patients with G6PD deficiency has been relatively contraindicated, but remains controversial. Over 400 million people worldwide are thought to be deficient in G6PD and it is likely that many who were unaware of their G6PD status have been given methylene blue. Despite this, there are relatively few reports of related adverse effects. In addition, patients with G6PD deficiency have varying concentrations of the enzyme. Some authors suggest cautious administration of methylene blue to patients with symptomatic MetHb and G6PD deficiency.
methemoglobinemia where methylene blue has failed, exchange transfusions or hyperbaric oxygen may be beneficial. Appropriate treatment needs to be discussed with toxicologists and hematologists on a case by case basis. Chronic kava toxicity was considered early in the ED course of this patient. The roots of the kava plant are used to produce a drink with sedative and anesthetic properties that is consumed throughout the Pacific islands. Chronic toxicity effects include dermopathy, ataxia, hair loss, and liver enzyme derangement (elevated gamma-glutamyl transferase and alkaline phosphatase), with most symptoms reversible on discontinuation of use. There have been reports of hepatic failure associated with kava extract. These symptoms did not correlate with our patient’s presentation. Patients with acute toxicity may present with vomiting, sweating, dizziness, dilated pupils, blepharospasm, urinary retention, muscle weakness, acute dystonic reactions, transient liver enzyme elevation, and decreased consciousness and motor reflexes.

4. Conclusion

This case highlights the interplay between amyl nitrite, a drug that induces hemolysis and methemoglobinemia, and potential management considerations in a patient with G6PD deficiency. This is a rare occurrence, but serves to remind treating physicians of the many issues related to management of each condition and the patient as a whole.

Conflicts of interest

None declared.

References