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Significant methemoglobinemia with bovine hemoglobin infusion in a case with severe autoimmune hemolytic anemia

Bovine hemoglobin glutamer-250 (Hemopure [HP], HbO₂ Therapeutics LLC, Souderton, PA) is a chemically stabilized, polymerized bovine hemoglobin (Hb) approved for the treatment of acute anemia in surgical patients in South Africa. It is under evaluation by the Food and Drug Administration (FDA) as an acellular oxygen carrier in humans in the United States, and its use is still controver-

sial due to multiple side effects including abdominal pain, jaundice, hematuria, rash, and an increase in methemoglobin (MetHb). The increase of MetHb is proportional to the total volume of HP transfused.¹ HP has been used to treat severe anemia in multiple conditions with mixed results, including a few cases of successful treatment of severe autoimmune hemolytic anemia (AIHA).^{2,3} We report a case of severe AIHA treated with HP, resulting in a marked increase of MetHb and a poor clinical outcome.

A 24-year-old African American male with a history of refractory Evan's syndrome presented at an outside institution with active hemolysis (Hb 8.9 g/dL), hematemesis, hematuria, fatigue, weakness, and thoracoabdominal pain after receiving 2 weeks of oral amoxicillin for a urinary tract infection. He received a splenectomy 3 years earlier for refractory immune thrombocytopenia. He had no personal or family history of a hemoglobinopathy or glucose-6-phosphate dehydrogenase deficiency. He was started on methylprednisone (1000 mg daily) and given one dose of rituximab (750 mg) and cyclophosphamide (1500 mg). Over the next 48 hours, he rapidly declined, with laboratory evidence of multiorgan damage. He was intubated and ultimately transferred to our institution.

On arrival, his Hb was 2.3 g/dL with a positive direct antiglobulin test (IgG 1+, C3-negative) and a positive antibody screen due to warm autoantibodies. Additional labs included a platelet count of $112 \times 10^9/L$, absolute neutrophil count of $3 \times 10^9/L$, reticulocytes of 23.78%, haptoglobin of less than 10 mg/dL, and total and indirect bilirubin of 6.5 and 4.2 mg/dL, respectively. Peripheral smear showed spherocytes, compatible with immune-mediated extravascular hemolysis. He was continued on methylprednisone. Initial MetHb levels by arterial blood gas (ABG) were not reportable due to interference by increased bilirubin, but MetHb was eventually measured at 18.5%, believed to be elevated secondary to ongoing severe hemolysis. He received methylene blue (MB), resulting in a modest MetHb decrease (8.7%). Given the ongoing hemolysis with warm autoantibodies, red blood cell (RBC) transfusion was initially delayed. However, 6 units of Rh, K-matched RBCs were eventually transfused and Hb appropriately increased (complete blood count, 7.1 g/dL; total Hb, 6.3 g/dL by ABG). Hb by ABG remained relatively stable after the third RBC transfusion; however, he remained progressively hypoxic as evidenced by O₂Hb (fraction of oxygenated Hb) of 65% to 79% even though pO₂ was consistently greater than 150 mmHg due to FiO₂ (fraction of inspired oxygen) of 100%. He also developed significant lactic acidosis (19-26 mmol/L). By this time, he had been treated with maximal medical therapy, including rituximab, cyclophosphamide, and steroids, as well as one dose of eculizumab (900 mg) and epoetin alfa. Given his continued dire clinical status despite medical intervention, he received an initial trial of 2 units of HP, followed by 2 additional HP units, all under an FDA compassionate usage

Fig. 1. Laboratory evaluation of Hb and MetHb during hospitalization with approximate times of MB, Hemopure, and RBC administration.

waiver. Before HP infusion, MetHb was 9.4%, but increased to 18.5% after the third HP infusion. Additional MB infusion was then given with mild MetHb improvement (14.5%). As his condition continued to worsen, an additional HP unit was given, resulting in MetHb of 25.5% (Fig. 1). He ultimately went into cardiac arrest during infusion of a sixth HP unit. Postmortem examination demonstrated evidence of multiorgan ischemia, acute myocardial infarction, and cerebellar tonsillar herniation. The findings were consistent with the clinical impression of marked, prolonged tissue hypoxia.

Our patient with severe AIHA refractory to medications received in total 6 units of HP and developed significant increase of MetHb. Multiorgan failure, as a result of tissue hypoxia, as well as polypharmaceutical state, may have played roles in his inability to compensate for impaired oxygen delivery due to methemoglobinemia. Further, his ischemic status may have been so advanced that any treatment, including RBC transfusion, could not have stopped functional deterioration. This case points out the difficulties of timing of RBC transfusion and of HP use in severe AIHA.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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Dealing with anti-CD38 (daratumumab) interference in blood compatibility testing

With much interest we read the recently published letter to the editor, "An alternative method to dithiothreitol treatment for antibody screening in patients receiving daratumumab," by Schmidt and colleagues¹ Daratumumab, a novel therapy for multiple myeloma, is an IgG1κ monoclonal antibody that recognizes CD38 on myeloma cells. The use of daratumumab leads to in vitro red blood cell (RBC) agglutination and thereby to false-positive results in the indirect antiglobulin test (IAT), which is used to detect irregular antibodies. After a period of restricted