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Ascorbic Acid for the Treatment of Rasburicase induced Methemoglobinemia in the Setting of Acute Renal Failure

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I.V. ascorbic acid for treatment of apparent rasburicase-induced methemoglobinemia in a patient with acute kidney injury and assumed glucose-6-phosphate dehydrogenase deficiency

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Abstract

Purpose A case of apparent rasburicase-induced methemoglobinemia and acute kidney injury treated with i.v. ascorbic acid because of suspected glucose-6-phosphate dehydrogenase (G6PD) deficiency is reported.

Summary A 46-year-old African-American man with a recent diagnosis of multiple myeloma and renal insufficiency was admitted to the hospital with a cough, hemoptysis, and fatigue. His medical history included hypertrophic cardiomyopathy, ventricular tachycardia, attention deficit/hyperactivity disorder, and pleural effusion. No treatments for multiple myeloma were started before hospital admission. Levofloxacin 750 mg orally daily for possible pneumonia, lenalidomide 10 mg orally daily, and dexamethasone 20 mg orally weekly were administered. Plasmapheresis was also initiated. Laboratory test results revealed sustained hyperuricemia, which was believed to be due in part to tumor lysis, and a single dose of rasburicase 6 mg i.v. was administered. Subsequently, the patient experienced a decrease in oxygen saturation. Methemoglobinemia was suspected, and the patient's methemoglobin fraction was found to be 14.5%. The patient developed worsening shortness of breath and a drop in hemoglobin concentration, consistent with methemoglobinemia and hemolysis. Ascorbic acid 5 g i.v. every 6 hours was initiated for a total of six doses. Because the patient was assumed to have G6PD deficiency, which was later confirmed, methylene blue was avoided. Within 24 hours, the patient's oxygen saturation values and symptoms improved.

Conclusion A patient with apparent rasburicase-induced methemoglobinemia and acute kidney injury was treated with i.v. ascorbic acid (5 g every six hours for six doses) because of the possibility, later proved, that he had G6PD deficiency. The methemoglobinemia resolved without worsening of renal function.

Methemoglobins are characterized by the presence of oxidized heme iron (ferrous iron) and are formed spontaneously at low concentrations under normal physiological conditions due to the usual oxidative stressors present in the body.[1] Metabolic pathways reduce the heme iron to the ferric state and thus help maintain the functionality of hemoglobin in oxygen transport. The most active reducing enzyme in red blood cells is cytochrome b_5 reductase, which requires cytochrome b_5 and nicotinamide adenine dinucleotide for activity. Additional reducing mechanisms include the nonenzymatic substances ascorbic acid and glutathione, as well as nicotinamide adenine dinucleotide phosphate (NADPH) flavin reductase. Drugs such as rasburicase and dapsone are known to cause an elevation in methemoglobin—methemoglobinemia—susceptible patients.[2,3] Patients with a deficiency of glucose-6-phosphate dehydrogenase (G6PD) are at risk for methemoglobinemia.

G6PD deficiency occurs most frequently in individuals of African, Asian, Mediterranean, or Middle Eastern descent.[4] Moreover, the mutation responsible for the deficiency is located on the X chromosome and, therefore, more common in men. In the United States, 1 in 10 African-American males have G6PD deficiency.[4] G6PD plays an integral role in the hexose monophosphate shunt, which is the only source of reduced NADPH, a cofactor in the metabolism of glutathione.[5] Oxidants produced by drugs in the presence of G6PD deficiency cannot be reduced due to the deficiency in glutathione production, and the result is methemoglobinemia. In addition, the presence of oxidative stress depletes glutathione, which leads to further oxidation and the formation of Heinz bodies (insoluble hemoglobin cross-links).[5,6] Subsequently, red blood cells become stiff and susceptible to destruction, resulting in hemolysis. In patients without G6PD deficiency, methylene blue remains the standard of care for the treatment of methemoglobinemia; however, patients with G6PD deficiency are unable to reduce methylene blue to its active antioxidant metabolite, leukomethylene blue.[7] Moreover, methylene blue in this population can worsen oxidative stress and potentially worsen hemolysis.[4] Although tests for G6PD deficiency are available, such testing is not feasible for all patients receiving drugs that put them at risk for methemoglobinemia due to a long delay for test results at some institutions and the urgent nature of some of the treatments. We report a case of a patient with presumed G6PD deficiency who developed methemoglobinemia after receiving rasburicase for the treatment of tumor lysis syndrome.

Case report

A 46-year-old African-American man (weight, 98 kg) with a recent diagnosis of multiple myeloma and renal insufficiency was admitted to the hospital with a cough, hemoptysis, and fatigue. His medical history included hypertrophic cardiomyopathy, ventricular tachycardia, attention deficit/hyperactivity disorder, and pleural effusion for which he had undergone thoracentesis four days before admission. His outpatient medications included methylphenidate, zolpidem, and naproxen sodium. No treatments for multiple myeloma were started before hospital admission. His laboratory test values at hospital admission appear in Table 1. Therapy initiated in the hospital included levofloxacin 750 mg orally daily for possible pneumonia, lenalidomide 10 mg orally daily, and dexamethasone 20 mg orally weekly starting on the day of admission. Antimyeloma treatment was started on admission because multiple presenting symptoms were thought likely due

to the myeloma. In addition, the patient was scheduled for plasmapheresis every other day for four to six sessions.

Table 1

Patient's Laboratory and Other Values[a]

Value	Institution's Normal Range	Hospital Day							
		1	2	3	4	5	6	7	8
Serum potassium conc., meq/L	3.5–5.1	5.5	4.6	4.2	5.0	4.5	3.6	3.9	3.9
Blood urea nitrogen conc., mg/dL	8–26	56	68	74	95	123	68	46	61
Serum creatinine conc., mg/dL	0.8–1.5	4.86	3.89	4.05	4.38	5.36	3.69	3.29	4.0
Uric acid conc., mg/dL	<8	14.1	12.3	NM	1.5	1.7	3.0	3.2	6.2
Urine output, mL/24 hr	NA	1300	1150	350	2775	5830	3840	2350	1650
Serum calcium conc., mg/dL	8.4–10.5	10.0	9.1	9.2	9.2	9.4	9.1	9.0	9.1
Serum phosphate conc., mg/dL	2.5–4.7	5.7	5.8	4.4	4.5	5.9	3.5	3.8	NM
Serum total bilirubin conc., mg/dL	0.2–1.2	NM	NM	NM	11.4	7.7	NM	3.3	NM
Oxygen saturation, %	NA	97–100[b]	NM	75–80[c]	83–98[d]	95–100[d]	95–98[b]	98–100[b]	NM
Hemoglobin conc., g/dL	11.6–15.2	8.4	7.6	8.3	5.7	7.2	7.5	9.5	9.8
Serum free light chains, κ/λ ratio	0.26–1.65	5948.09	NM	NM	NM	NM	NM	NM	NM
Methemoglobin fraction, %	<1.2	NM	NM	14.5	8.1	1.2	0.5	NM	0.5

- a Day 1 was the day of admission. Rasburicase was given on day 2, and ascorbic acid was started on day 4. NM = not measured, NA = not available.
- b On room air.
- c On oxygen 15 L/min via nonrebreather mask.
- d On oxygen 6 L/min via nasal cannula.

KEY POINTS

- Methemoglobinemia and hemolysis can occur after rasburicase administration, particularly in patients with G6PD deficiency.
- Patients with G6PD deficiency should not receive methylene blue to treat methemoglobinemia.
- Ascorbic acid may be effective in the treatment of methemoglobinemia and appears safe in the setting of renal dysfunction at a dose of 5 g i.v. every six hours.

On hospital day 2, laboratory test results revealed sustained hyperuricemia, which was believed to be due in part to tumor lysis, given the patient's myeloma burden, and worsened by renal failure; therefore, a single dose of rasburicase 6 mg i.v. was administered. At this time, the benefits of treating this oncological emergency outweighed the risks of administering rasburicase in a patient whose G6PD status was unknown. In addition, the turnaround time for G6PD test results was three to four days. During the morning of hospital day 3, the patient developed a decrease in oxygen saturation and was placed on a nonrebreather mask with 15 L/min of supplemental oxygen, despite being asymptomatic. Methemoglobinemia was suspected, and the patient's methemoglobin fraction was found to be 14.5% (normal range, 0.0–1.2%).

On day 4, the patient developed worsening shortness of breath and a drop in hemoglobin concentration, consistent with methemoglobinemia and hemolysis. At this time, the patient received three units of blood, and treatment was started with ascorbic acid 5 g i.v. every 6 hours for a total of six doses. The patient was assumed to have G6PD deficiency based on the development of methemoglobinemia after rasburicase and his race; consequently, methylene blue was avoided. Within 24 hours of initiating ascorbic acid, the patient's oxygen saturation values and symptoms improved. The patient received two sessions of hemodialysis for volume overload on hospital days 5 and 6 and was given a unit of blood on each of those two days; reticulocyte counts were not performed during that time. Moreover, his serum creatinine concentration remained relatively stable, and his urine output was satisfactory throughout the majority of the hospital stay. Follow-up serum creatinine values after discharge ranged from 2.86 to 7.11 mg/dL.

A blood sample collected on hospital day 7 for measurement of G6PD yielded a result in the low normal range, 6.0 units per gram of hemoglobin (normal range, 4.6–13.5 units/g hemoglobin). A recheck one month later yielded a G6PD result of 5.3 units/g hemoglobin, but results may be unreliable in the setting of recent blood transfusions or elevated reticulocyte counts, which were likely a factor in this case.

Discussion

In patients with G6PD deficiency and methemoglobinemia, the risk of hemolysis after methylene blue administration points to the need for additional treatment options. Non-pharmacologic

management with hyperbaric oxygen and exchange transfusions have been used for patients with methemoglobinemia who were refractory to methylene blue but not as first-line therapy.[8] This leaves a significant gap in therapy for a select patient population.

Case reports of rasburicase-induced methemoglobinemia have been published, but the majority of those patients receiving treatment, besides transfusion, received methylene blue.[9–14] As previously mentioned, methylene blue is not the ideal option in a patient with suspected G6PD deficiency. To date, there is only one published report of using ascorbic acid in rasburicase-induced methemoglobinemia.[9] The patient was a 52-year-old African-American man with refractory multiple myeloma. The patient met the criteria for tumor lysis syndrome and acute kidney injury before therapy initiation and received rasburicase 6 mg i.v. on the first day of therapy with cyclophosphamide and methylprednisolone. Starting on the second day of therapy, the patient showed signs of hypoxemia (oxygen saturation as measured by pulse oximetry [Spo_2], 75%) without clinical symptoms of respiratory distress, and his methemoglobin fraction was subsequently found to be 12.9%. Ascorbic acid 1 g orally once daily was initiated instead of methylene blue due to the unknown nature of the patient's G6PD status. By day 4 of therapy, the patient's methemoglobinemia had resolved, with a normal Spo_2 (>95%) and a much lower methemoglobin fraction (<2%). On day 3 of therapy, he developed hemolytic anemia thought to be due to G6PD deficiency, a recently discovered condition, and required a total of 8 units of packed red blood cells.

The proposed mechanism of ascorbic acid in the treatment of methemoglobinemia is the reduction of the oxidative stress common with this condition.[15] Efficacy in reducing oxidative stress was found in patients with hemodialysis-induced methemoglobinemia who received ascorbic acid 1 g i.v. before each hemodialysis session for two months.[16] A peak serum ascorbic acid concentration of at least 10 mmol/L must be achieved to prevent further formation of methemoglobin.[17] An oral ascorbic acid dose of 1.25 g achieves a mean serum concentration of 0.134 mmol/L, and extrapolation to a maximally tolerated oral dosage of 3 g every four hours would result in a peak concentration of 2.2 mmol/L.[18] Peak serum ascorbic acid concentrations are estimated to reach 13.4 mmol/L after 50 g of ascorbic acid is given i.v. The concern with administering high doses of ascorbic acid to achieve these concentrations is the increased risk of hyperoxalate-induced nephrotoxicity.[19] One of the metabolites of ascorbic acid is oxalate. The high doses of ascorbic acid may lead to increased calcium oxalate crystallization in the renal tubules and epithelium, causing acute tubular injury.

There are limited published data regarding the successful treatment of methemoglobinemia with high-dose ascorbic acid. One case report described the use of high-dose ascorbic acid for dapsone-induced methemoglobinemia.[15] The patient was an 85-year-old Korean woman who ingested seven tablets of dapsone and arrived at the emergency room with decreased mental status and cyanosis. The patient's mental status, cyanosis, and methemoglobin concentration continued to worsen 7 hours after her arrival at the hospital, with a peak methemoglobin fraction of 64.4%. Methylene blue was unavailable at the time of treatment, so ascorbic acid 10 g i.v. was administered. The patient's methemoglobin fraction improved over 15 hours to 38%; however, after a second dose of ascorbic acid 10 g i.v., the patient's methemoglobin fraction increased to

46.9%. An additional dose of ascorbic acid 10 g i.v. was administered, with slow improvement in both her symptoms and laboratory test values (methemoglobin fraction, 21.5%). After the first 30 g of ascorbic acid was administered, an additional five doses of ascorbic acid 10 g i.v. every 6 hours was administered, for a total of 80 g. Fifty-four hours into the patient's care, the last dose of ascorbic acid was given, and the patient's methemoglobin fraction was 12.2% and continued to decline to normal limits within 130 hours after her arrival at the hospital. The patient's renal function remained stable throughout the duration of ascorbic acid treatment and hospitalization.

Compared with the patient with dapsone-induced methemoglobinemia, our patient received a total of 30 g of ascorbic acid over a 36-hour period—a more conservative dosage due to the patient's baseline renal dysfunction. While our patient's peak methemoglobin fraction (14.5%) was not as high as that in the dapsone patient case (64.4%), normalization of laboratory values was achieved within a shorter time frame (2 days versus 5.5 days). Ascorbic acid therapy in our patient was safe, as demonstrated by stability in the serum creatinine and blood urea nitrogen concentrations and urine output.

Conclusion

A patient with apparent rasburicase-induced methemoglobinemia and acute kidney injury was treated with i.v. ascorbic acid (5 g every six hours for six doses) because of the possibility, later proved, that he had G6PD deficiency. The methemoglobinemia resolved without worsening of renal function.

References

1. Quigley JG, Means RT, Glader B. The birth, life, and death of red blood cells: erythropoiesis, the mature red blood cell, and cell destruction. In: Greer JP, Arber DA, Glader B, et al., eds. *Wintrobe's clinical hematology*. Philadelphia: Lippincott Williams and Wilkins; 2014:83–124.
2. *Elitek (rasburicase) prescribing information*. Bridgewater, NJ: sanofiaventis U.S.; 2015 Mar.
3. *Dapsone prescribing information*. Princeton, NJ: Jacobus Pharmaceutical; 2000 Mar.
4. Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician*. 2005; 72:1277–82.
5. Glader B. Hereditary hemolytic anemias due to red blood cell enzyme disorders. In: Greer JP, Arber DA, Glader B, et al., eds. *Wintrobe's clinical hematology*. Philadelphia: Lippincott Williams and Wilkins; 2014:728–45.
6. Dhaliwal G, Cornett PA, Tierney LM. Hemolytic anemia. *Am Fam Physician*. 2004; 69:2599–606.
7. Sikka P, Bindra VK, Kapoor S, et al. *Blue cures blue but be cautious. J Pharm Bioallied Sci. 2011; 3:543–5*.
8. Do Nascimento TS, Pereira RO, de Mello HL, Costa J. Methemoglobinemia: from diagnosis to treatment. *Rev Bras Anestesiol*. 2008; 58:651–64.
9. Sonbol MB, Yadav H, Vaidya R, et al. Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. *Am J Hematol*. 2013; 88:152–4.
10. Bauters T, Mondelaers V, Robays H, et al. Methemoglobinemia and hemolytic anemia after rasburicase administration in a child with leukemia. *Int J Clin Pharm*. 2011; 33:58–60.
11. Bhat P, Sisler I, Collier AB 3rd. Exchange transfusion as treatment for rasburicase induced methemoglobinemia in a glucose-6-phosphate dehydrogenase deficient patient. *Pediatr Blood Cancer*. 2008; 51:568.
12. Borinstein SC, Xu M, Hawkins DS. Methemoglobinemia and hemolytic anemia caused by rasburicase administration in a newly diagnosed child with Burkitt lymphoma/leukemia. *Pediatr Blood Cancer*. 2008; 50:189.

13. Browning LA, Kruse JA. Hemolysis and methemoglobinemia secondary to rasburicase administration. *Ann Pharmacother*. 2005; 39:1932–5.
14. Kizer N, Martinez E, Powell M. Report of two cases of rasburicase-induced methemoglobinemia. *Leuk Lymphoma*. 2006; 47:2648–50
15. Park SY, Lee KW. High-dose vitamin C management in dapsone-induced methemoglobinemia. *Am J Emerg Med*. 2014; 32:684.e1–3.
16. Yang C, Hsu S, Wu M, Chien C. Effects of vitamin C infusion and vitamin E coated membrane on hemodialysis-induced oxidative stress. *Kidney Int*. 2006; 69:706–14.
17. Dotsch J, Demirakca S, Cryer A, et al. Reduction of NO-induced methemoglobinemia requires extremely high doses of ascorbic acid in vitro. *Intensive Care Med*. 1998; 24:612–5.
18. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med*. 2004; 140:533–7.
19. Cossey LN, Rahim F, Larsen CP. Oxalate nephropathy and intravenous vitamin C. *Am J Kidney Dis*. 2013; 61:1032–5.