



Letter

Looking beyond the angiotensin receptor blocker A case of anaphylaxis to mesna

Studies have found that pulse cyclophosphamide is the treatment of choice for patients with moderate to severe systemic lupus erythematosus (SLE) nephritis.¹ Sodium 2-mercaptoethane sulfonate (mesna), is a well-known adjuvant to cyclophosphamide that is widely used for the prevention of hemorrhagic cystitis.^{2,3} Cutaneous reactions (such as rash) and angioedema have been described as drug eruptions to mesna.^{4,5} We present a case of anaphylaxis to mesna.

A 49-year-old woman with SLE complicated by severe nephritis, positive antiphospholipid antibody with prior deep venous thrombosis, asthma, seasonal allergies, and obstructive sleep apnea was receiving cyclophosphamide and mesna infusions for her SLE. Her first infusion was well tolerated without adverse effects. The second infusion was 1 month after the first. Within 2 hours of receiving her second infusion, the patient developed hypotension and was admitted to the medical intensive care unit. She was presumed to have sepsis given her immunosuppression and treated empirically with broad-spectrum intravenous antibiotics. During this admission, the patient required vasopressor support and significant fluid resuscitation. Blood and cerebrospinal fluid cultures drawn before the initiation of antibiotic treatment negative and antibiotics were subsequently discontinued. The patient recovered within 36 hours and was discharged home without antibiotics or new medications. The third infusion of cyclophosphamide and mesna was 1 month after the second. During her third infusion, the patient developed fever and rigors. The patient was admitted to the hospital for fever of unknown origin. Laboratory test results were only significant for a positive *Clostridium difficile* polymerase chain reaction test result. The patient was then discharged home with an oral course of vancomycin.

Two months later, she presented for her fourth infusion of cyclophosphamide and mesna. One hour after her infusion, the patient became hypotensive (systolic blood pressure, 80 mm Hg), tachycardic (heart rate, 110–120/min), and febrile to 102°F. She also developed rigors, nausea, and vomiting. The cyclophosphamide and mesna infusions were discontinued. Within minutes of initial symptoms, the patient reported dysphagia, oral numbness, lip swelling, and eye redness. Physical examination was notable for dry mucous membranes, bilateral conjunctival injection, mild lip swelling, and tachycardia. She was given a bolus of intravenous fluids, a histamine₁-receptor antagonist, an antiemetic, intramuscular epinephrine, an intravenous histamine₂-blocker, and intravenous steroids. Antibiotic treatment was not initiated. Laboratory testing and culture data were unremarkable. The patient's symptoms resolved within hours. Her medication list was identical

during all 3 events (atorvastatin, losartan, metformin, omeprazole, warfarin, prednisone, ondansetron, biotin, cetirizine, multivitamin, vitamin D₃, calcium, and potassium supplementation). The patient was discharged home with a new prescription for intramuscular epinephrine.

In the outpatient setting, the patient's rheumatologist continued to treat her SLE with monthly cyclophosphamide infusions but discontinued the adjuvant mesna. The patient has tolerated all subsequent infusions without similar issue or hospitalizations. Her medication list still remained the same. An interaction check between mesna and each of the patient's home medications revealed no drug-drug interactions or cross-reactivity.

This patient with a medically complex history re-presented to the hospital on multiple occasions with similar presentations after mesna infusion. In a patient who is chronically immunosuppressed, hypotension can easily be mistaken as a response to infection. Furthermore, diarrhea is a known adverse effect of multiple anti-neoplastics, and with the prevalence of asymptomatic *C difficile* infection in the community, the positive test result in the setting of fever and rigors developed during this patient's third infusion may have been a red herring. This patient's fourth infusion was associated with angioedema and severe anaphylaxis. Angioedema has become the dominant allergic disorder that results in hospitalizations in the United States.⁶ Although angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are well recognized as common offenders, it is important to highlight that it is relatively rare. A meta-analysis of 26 randomized trials with 74,857 patients in the angiotensin-converting enzyme inhibitor arm and 19 trials with 35,479 patients taking angiotensin receptor blockers revealed the weighted incidence of angioedema with angiotensin-converting enzyme inhibitors was 0.30% compared with 0.11% with angiotensin receptor blockers.⁷ In this patient's case, mesna was the clear culprit. Lastly, recognizing a mesna reaction can also further be complicated by the fact that both immediate and delayed hypersensitivity reactions have been shown.^{5,8} Caution must be exercised during and in the hours after the infusion.

In conclusion, we report a case of mesna anaphylaxis presenting as several possible yet fully plausible differentials. Physicians need to be aware that, in patients with medically complex conditions, clinical presentations and confounding factors can easily blur the clinical picture and diagnosis.

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