Kaplan USMLE Step 1 prep: Overseas traveler experiences weakness

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If you're preparing for the United States Medical Licensing Examination® (USMLE®) Step 1 exam, you might want to know which questions are most often missed by test-prep takers. Check out this example from Kaplan Medical, and read an expert explanation of the answer. Also check out all posts in this series.

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This month's stumper

A 31-year-old man comes to the physician because of a 3-day history of generalized weakness and nausea. He returned from a trip to Africa a day ago. During his trip, he took an unknown antimalarial medication that was leftover from a friend who had visited Africa the previous year. Weakness and nausea developed after taking these pills. Vital signs are within normal limits, and physical examination shows mild jaundice. Laboratory studies show:

- Leukocyte count: 8,000/mm^3.
- Hemoglobin: 10.5 g/dL.
- Hematocrit: 32%.
- Platelet count: 195,000/mm^3.
- Total bilirubin: 3.0 mg/dL.
- Direct bilirubin: 0.5 mg/dL.
- Alanine aminotransferase (ALT): 19 U/L.
- Aspartate aminotransferase (AST): 17 U/L.
- Alkaline phosphatase: 50 U/L.

Peripheral blood smear shows bite cells. Which of the following is most likely decreased as a result of this patient's diagnosis?

A. NADH.

B. Oxidized glutathione.

C. Oxidized ubiquinone.

D. Reduced glutathione.

E. Reduced ubiquinone.

The correct answer is D. The patient has glucose 6-phosphate dehydrogenase (G6PDH) deficiency, usually a silent disorder unless the patient is challenged with a strong oxidizing agent. The pills the

patient acquired from a friend were most likely primaquine, which, in addition to being an antimalarial agent, is a strong oxidizing agent. The red blood cell (RBC) membrane contains glutathione to protect against oxidative damage. When oxidized glutathione is generated, the RBC enzyme glutathione reductase regenerates the protective form of glutathione (reduced glutathione).

Glutathione reductase requires the cofactor NADPH, which is produced in the RBC by G6PDH. In individuals with a defective G6PDH, reduced glutathione cannot be regenerated and proteins and lipids in the RBC membrane may be susceptible to oxidizing agents. This then causes the RBC membrane to become leaky and the cell lyses, leading to hemolytic anemia.

Why the other answers are wrong

Choice A: G6PDH converts $NADP^+$ to NADPH (along with glucose 6-phosphate being oxidized to 6-phosphogluconate), and cannot use NAD^+ or NADH as a substrate. NADH can also not be used by glutathione reductase to regenerate the protective form of glutathione.

Choice B: Oxidized glutathione forms through the action of oxidizing agents on reduced glutathione. The patient has a decreased ability to generate reduced glutathione, not oxidized glutathione.

Choices C and E: Ubiquinone, which is also known as coenzyme Q, is required for the proper functioning of the mitochondrial electron transfer chain. RBCs lack mitochondria, therefore alterations in ubiquinone oxidation state do not lead to hemolytic anemia.

Tips to remember

- G6PDH deficiency is usually asymptomatic unless a strong oxidizing agent is introduced into the body—for example, via foods or drugs.
- Red blood cells protect their membranes from oxidative damage with reduced glutathione, which is preferentially oxidized by the oxidizing agents instead of membrane lipids and proteins.
- NADPH, a product of the G6PDH reaction, is used to regenerate reduced glutathione, the protective form of glutathione.

For more prep questions on USMLE Steps 1, 2 and 3, view other posts in this series.