Digoxin toxicity after a second COVID-19 vaccination

Side effects can create drug-related complications for some patients

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Both mRNA SARS-CoV-19 vaccines now being used in the United States require two doses, separated by either 21 days (Pfizer) or 28 days (Moderna). Although there can be side effects after either dose, more have been documented with the second dose, including flu-like symptoms such as headaches, fatigue, myalgias, arthralgias and chills. The vaccine is generally well-tolerated, but the additive effects of insensible volume loss, gastrointestinal symptoms and decreased oral intake may create circumstances ripe for drug-related complications.

In the case we describe, the second dose of an mRNA SARS-CoV-19 vaccine produced a viral-like syndrome resulting in renal insufficiency from anorexia and dehydration. Exacerbated by an ACE inhibitor (lisinopril) and a P-glycoprotein inhibitor (diltiazem), the illness culminated in the development of severe digoxin toxicity with hyperkalemia. Digoxin toxicity was diagnosed by medical toxicologists at the bedside when taking into account the patient's history, presenting symptoms and visual abnormalities, renal insufficiency, hyperkalemia and slow atrial fibrillation. Hyperkalemia was likely the result of digoxin toxicity, renal insufficiency, lisinopril use and a high-potassium diet.

In the midst of an unprecedented mass vaccination campaign, clinicians must remain vigilant for the development of toxicity among patients on digoxin therapy, especially in patients experiencing influenza-like symptoms after a second dose of mRNA COVID-19 vaccine. This is particularly important in those who are on ACE inhibitors, diuretics or P-glycoprotein inhibitors, many of which are used in combination with digoxin in patients with heart failure or rapid atrial fibrillation.

The case

A 60-year-old man with a past medical history of hypertension and permanent atrial fibrillation came to the Emergency Department after two days of progressive fatigue, myalgias, lightheadedness, anorexia and blurry vision with "white flashes." He said he felt as if he had malaria. He had received the second dose of the mRNA-1273 SARS-CoV-2 vaccine four days earlier and was on medications that included digoxin, carvedilol, diltiazem, lisinopril and rivaroxaban. He had immigrated from Rwanda 10 years earlier.

The patient's initial vital signs were:

- Temperature 34.6°C
- Blood pressure 69/47 mmHg
- Pulse 39
- Respiratory rate 16
- Oxygen saturation 98 percent on room air

He was slightly diaphoretic, alert and oriented and his arms and legs were warm. An EKG showed slow atrial fibrillation, with peaked T-waves. His lab results showed potassium 8.0 mEq/dL, lactate 5.3 mEq/L, sodium 127 mEq/L, bicarbonate 21 mEq/L, creatinine 2.41 mg/dL and anion gap 8 mEq/L. His pH was 7.32 and pCO2 41 mmHg.

He was treated with 3 grams of calcium gluconate, intravenous insulin/dextrose, sodium bicarbonate and one vial of digoxin-specific Fab fragments for presumed digoxin toxicity. His serum digoxin concentration returned at 1.6 ng/mL (normal 0.8-2.0 ng/mL). He underwent emergent hemodialysis for hyperkalemia when his potassium levels failed to fall significantly despite aggressive medical measures. His heart rate and blood pressure normalized following the administration of Fab fragments and his potassium level normalized after hemodialysis.

As we talked further with the patient, we learned that he ate six bananas each day with varying amounts of beans and cassava—the nutritional staples of a common Rwandan diet.

Ultimately, no additional Fab fragments nor additional runs of hemodialysis were indicated. Digoxin and lisinopril were held at the time of discharge on hospital day three.

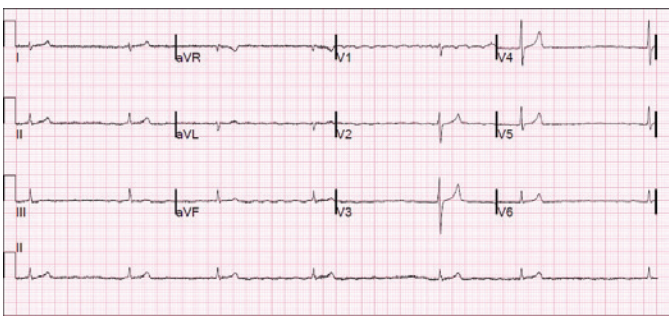
Discussion

Digoxin is a cardioactive steroid that is used to increase cardiac contractility in heart failure and slow conduction in rapid atrial fibrillation. It is eliminated primarily unchanged by the kidneys. It inhibits membrane sodium-potassium–adenosine triphosphatase pumps (Na+/K+ ATPase), which decrease membrane potentials, and leads to increased cytosolic sodium and calcium (and increased extracellular potassium). In the myocardium, this causes increased cardiac contractility and automaticity, the latter of which can result in premature beats, escape rhythms and ventricular tachycardia. In the carotid sinus, increased baroreceptor firing boosts vagal tone, which can cause bradycardia, atrioventricular blocks, hypotension or nausea and vomiting. In skeletal muscle this leads to hyperkalemia due to the sheer number of Na+/K+ ATPase pumps.

Acute toxicity manifests as nonspecific GI symptoms, neurologic symptoms (somnolence or lethargy, visual disturbances), hyperkalemia and variable bradydysrhythmias or tachydysrhythmias. Chronic toxicity has a more insidious onset and a higher mortality and is marked by variable serum potassium levels with tachydysrhythmias and other neurologic manifestations. Nearly any cardiac dysrhythmia or conduction block can be seen in toxicity, particularly unique rhythms such as slow atrial fibrillation or polymorphic and biventricular tachycardias. Serum digoxin levels, while useful in acute ingestions, often do not correlate with toxicity in chronic ingestions as digoxin has been redistributed from the serum into peripheral tissues.

Treatment relies upon supportive care and the rapid administration of digoxin-specific fragment antigen-binding (Fab) antibodies, the specific antidote for digoxin toxicity. The digoxin-Fab complexes are subsequently cleared renally. Although a number of dosing strategies exist, digoxin-specific Fab antibodies are commonly dosed based upon the patient's clinical condition and the chronicity of poisoning, with most patients needing only one vial (chronic poisoning) or two vials (acute poisoning) for adequate reversal of toxic effects. Hyperkalemia due to digoxin toxicity is also best treated with digoxin-specific Fab antibodies.

Acute-on-chronic digoxin toxicity is most frequently precipitated by renal insufficiency, often the result of acute illness, decreased oral intake and volume loss. In addition, drug-drug interactions, particularly with P-glycoprotein inhibitors, diuretics or ACE inhibitors, can lead to decreased clearance of digoxin or hypokalemia (in the case of diuretics), both of which potentiate the development of toxicity. MM



EKG showing slow atrial fibrillation

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