Digoxin Toxicity Caused by an Interaction with the Novel Hepatitis C Medication Ledipasvir/Sofosbuvir

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ABSTRACT. Digoxin is commonly used for the management of patients with heart failure and atrial fibrillation. However, digoxin has a narrow therapeutic index and is susceptible to drug–drug interactions that may induce digoxin toxicity. Here, we report the first published case of digoxin toxicity caused by an interaction with the new hepatitis C medication, ledipasvir/sofosbuvir. A 69-year-old male with heart failure and atrial fibrillation being managed with digoxin developed typical symptoms of digoxin toxicity after starting ledipasvir/sofosbuvir. He then had a cardiac arrest due to ventricular tachycardia/fibrillation for which he received an implantable cardioverter-defibrillator shock. Serum digoxin level was found to be elevated, and the patient’s symptoms resolved after treatment with digoxin immune Fab. This case highlights the need for careful monitoring of digoxin levels, particularly when initiating a medication that may affect the absorption or clearance of digoxin.

KEYWORDS. Digoxin toxicity, drug–drug interaction, ventricular fibrillation, ventricular tachycardia.

Introduction

Digoxin, a cardiac glycoside initially used by Sir William Withering in 1785 for heart failure, is one of the oldest drugs used today in cardiovascular medicine. It is an inotropic agent primarily used to treat patients with persistent symptoms of heart failure (HF) and atrial fibrillation (AF), despite optimal medical therapy.1,2 The bioavailability of digoxin is, in part, dependent on the function of the permeability glycoprotein (P-gp). P-gp is a 170-kilodalton plasma membrane protein that belongs to the ATP-binding cassette superfamily3 and is considered to be the most relevant ATP-binding cassette transporter in cardiovascular medicine. P-gp works as an efflux transporter which is mainly expressed in epithelial and endothelial barrier-forming tissues such as enterocytes and the blood–brain barrier.3–5 In the intestine, P-gp limits the oral bioavailability of most drugs that act as its substrate. It transports the absorbed molecule back to the luminal surface of the enterocyte, where it is pumped back into the lumen of the intestine, thereby preventing it from reaching the systemic circulation.6,7 Digoxin has been well documented as a P-gp substrate.8,9 Ledipasvir/sofosbuvir (Harvoni®), a new treatment for hepatitis C, also interacts with P-gp. Ledipasvir is an inhibitor of the P-gp that may increase intestinal absorption of co-administered substrates such as digoxin.10 Here, we report a case of digoxin toxicity due to initiation of ledipasvir/sofosbuvir.

Case presentation

A 69-year-old male with a past medical history of non-ischemic cardiomyopathy, ventricular tachycardia/fibrillation (VT/VF), bi-ventricular implantable cardioverter-
defibrillator (ICD) (BiV-ICD) implantation, permanent atrial fibrillation, and cirrhosis due to chronic hepatitis C was admitted to the hospital because of an ICD shock. He was taking amiodarone 200 mg daily for his history of VT/VF and digoxin 0.125 mg daily for atrial fibrillation and HF. He had normal renal function, and digoxin levels ranged from 1.1 to 1.4 ng/ml. One month prior to admission, he began ledipasvir/sofosbuvir therapy for his hepatitis C. At that time, it was decided that the patient would continue on his current doses of amiodarone and digoxin.

Two weeks after initiation of ledipasvir/sofosbuvir therapy, he developed loss of appetite and mild nausea for which he was given ondansetron. Two weeks later, the patient’s symptoms intensified with poor appetite, persistent nausea/vomiting, dizziness, blurry vision, and difficulty concentrating. At this point, there was concern for digoxin toxicity, and he was instructed to discontinue digoxin. The following day, he had an episode of abrupt syncope for which he did not seek medical attention. Remote monitoring of the patient’s BiV-ICD revealed an episode of VT/VF for which an ICD shock was delivered (Figure 1), and the patient was instructed to come to the hospital for evaluation. On presentation, the patient was still experiencing poor appetite, nausea/vomiting, and vision/cognitive dysfunction despite abstinence from digoxin for 3 days. An electrocardiogram showed atrial fibrillation with ventricular paced complexes. Telemetry revealed frequent PVCs. Please give PVC in full, including bidirectional PVCs (Figure 2). A serum digoxin level was obtained and found to be elevated at 3.1 ng/ml. Given the patient’s symptoms, frequent ectopy, and elevated serum digoxin level, he was diagnosed with digoxin toxicity that was likely the cause of his VT/VF arrest. He was treated with digoxin immune Fab, which quickly led to improvement in his symptoms and resolution of his ventricular ectopy.

**Discussion**

Digoxin is a water-soluble drug, and its elimination is dependent on renal excretion. It has a narrow therapeutic index and several factors predispose to the risk of digoxin toxicity, such as increased bioavailability, increased volume of distribution, and reduction of digoxin clearance due to renal impairment. As a P-gp substrate, digoxin is susceptible to numerous drug–drug interactions. The quinidine–digoxin interaction is the most extensively studied cardiovascular drug–drug interaction, which was initially recognized in 1978. Quinidine inhibits P-gp, resulting in increased serum digoxin levels and greater risk of toxicity. Inhibitors of P-gp, such as quinidine, amiodarone, clarithromycin, diltiazem, and verapamil, increase digoxin concentration in plasma, whereas inducers of P-gp, such as rifampin, St John’s wort, and carbamazepine, decrease digoxin concentration. Knowledge of these interactions in patients with AF and HF can help ensure the establishment of safe and effective treatment through optimal dosing and monitoring to prevent digoxin toxicity.

Digoxin’s primary mechanism of action is through inhibition of the sodium–potassium adenosine triphosphatase (ATPase) causing an increase in intracellular sodium concentration, which in turn causes a decrease in calcium efflux via the sodium–calcium exchanger. The net effect of digoxin therapy is 1) shortening of the cardiac action potential causing slower heart rates, and 2) increasing intracellular calcium concentration leading to increased myocardial contractility. Digoxin also has autonomic effects, including inhibition of sympathetic nervous outflow and enhanced parasympathetic tone. Through its autonomic effects, digoxin decreases automaticity, prolongs the effective refractory period, and slows conduction velocity through the atroventricular (AV) node.

The most common symptoms associated with digoxin toxicity, particularly among elderly people, include cognitive changes, anorexia, nausea/vomiting, dizziness, and vision changes. Numerous dysrhythmias may be encountered with digoxin toxicity. Owing to increased automaticity from increased intracellular calcium concentrations, patients may experience supraventricular tachycardia or an accelerated junctional rhythm. Various degrees of heart block may also be observed due to decreased AV conduction. Ventricular arrhythmias are also associated with digoxin toxicity. Premature ventricular contractions, as well as ventricular bigeminy/trigeminy, are the most common ventricular arrhythmias encountered. However, in severe cases, patients may experience VT, which rarely can manifest as bidirectional VT, a pathognomonic sign of digoxin toxicity. In this case, our patient experienced most of these typical symptoms of digoxin toxicity (cognitive changes, nausea/vomiting, vision changes, anorexia, ventricular ectopy with bidirectional PVCs and, ultimately, VT/VF).

In the era of an aging patient population and the continued use of digoxin in patients with refractory symptoms of AF and/or HF, it is of utmost importance to study the drug–drug interactions with digoxin and to monitor patients for potential digoxin toxicity. Indeed, our patient was being managed with two known P-gp inhibitors (amiodarone and ledipasvir/sofosbuvir), and monitoring of serum digoxin levels or an empiric reduction in digoxin dosing may have prevented the toxic effects observed.

Furthermore, there exists some evidence that digoxin may not have clinical benefit in the modern era of heart failure management and, in fact, may lead to increased mortality in the management of HF and AF. However, digoxin still remains widely prescribed for these indications and is still endorsed in both the current AF and HF guidelines, where it holds a Class I recommendation for rate control of AF in patients with HF, a Class Ila recommendation for rate control of AF patients without HF, and a Class Ila recommendation for the management of HF with reduced ejection fraction (HFrEF) in order to prevent hospitalizations.

Here we report the first case of digoxin toxicity caused by the co-administration of ledipasvir/sofosbuvir, a known P-gp inhibitor. Given the narrow therapeutic range of digoxin and evidence showing increased mortality with elevated serum digoxin levels, this case highlights the
Figure 1: Intracardiac Electrocardiogram (EGM) showing initiation of ventricular tachycardia/fibrillation and shock.
importance of monitoring serum digoxin levels or empirically adjusting its dose, particularly when introducing a medication, which may interact with digoxin.

References


