PHARMACOLOGICAL THERAPY

FELLOWS CASE OF THE MONTH

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

MICHAEL A. VALENTINO, MD, PhD¹, JAD AL DANAF, MD² and DANIEL FRISCH, MD¹

¹Division of Cardiology, Thomas Jefferson University Hospital, Philadelphia, PA

²Division of Internal Medicine, Thomas Jefferson University Hospital, Philadelphia, PA

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.

ISSN 2156-3977 (print)
ISSN 2156-3993 (online)

© 2016 Innovations in Cardiac
Rhythm Management

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-

The authors have no conflicts of interest relevant to this study to disclose.

Manuscript received March 21, 2016, Final version accepted April 7, 2016.

Address correspondence to: Michael A. Valentino, MD, PhD, Thomas Jefferson University Hospital, Division of Cardiology, 925 Chestnut St., Mezzanine, Philadelphia, PA 19107.

E-mail: Michael.Valentino@jefferson.edu

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.^{11,12} 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.¹³ 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) lengthening of the cardiac action potential causing slower heart rates, and 2) increasing intracellular calcium concentration leading to increased myocardial contractility.^{12,14–16} 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 atrioventricular (AV) node.¹²

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.^{17–21} 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,² a Class IIa recommendation for rate control of AF patients without HF,² and a Class IIa recommendation for the management of HF with reduced ejection fraction (HFrEF) in order to prevent hospitalizations.¹

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.

Figure 2: Telemetry tracing showing ventricular paced complexes (*), PVCs (†), and bidirectional PVCs (‡).

importance of monitoring serum digoxin levels or empirically adjusting its dose, particularly when introducing a medication, which may interact with digoxin.

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147–e239.
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):2246–2280.
3. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC. Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. *Proc Natl Acad Sci USA*. 1987;84(21):7735–7738.
4. Chandra P, Brouwer KLR. The complexities of hepatic drug transport: Current knowledge and emerging concepts. *Pharm Res*. 2004;21(5):719–735.
5. Cummins CL, Jacobsen W, Benet LZ. Unmasking the dynamic interplay between intestinal P-glycoprotein and CYP3A4. *J Pharmacol Exp Ther*. 2002;300(3):1036–1045.
6. Igel S, Drescher S, Mürdter T, et al. Increased absorption of digoxin from the human jejunum due to inhibition of intestinal transporter-mediated efflux. *Clin Pharmacokinet*. 2007;46(9):777–785.
7. König J, Müller F, Fromm MF. Transporters and drug-drug interactions: Important determinants of drug disposition and effects. *Pharmacol Rev*. 2013;65(3):944–966.
8. Lin JH, Yamazaki M. Clinical relevance of P-glycoprotein in drug therapy. *Drug Metab Rev*. 2003;35(4):417–454.
9. Pedersen KE, Christiansen BD, Klitgaard NA, Nielsen-Kudsk F. Effect of quinidine on digoxin bioavailability. *Eur J Clin Pharmacol*. 1983;24(1):41–47.
10. Harvoni (ledipasvir/sofosbuvir) (prescribing information). Foster City, CA; Gilead Sciences Inc. 2015. http://www.gilead.com/-/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf.
11. Iisalo E. Clinical pharmacokinetics of digoxin. *Clin Pharmacokinet*. 1977;2(1):1–16.
12. Eichhorn EJ, Gheorghade M. Digoxin. *Prog Cardiovasc Dis*. 2002;44(4):251–266.
13. Fromm MF, Kim RB, Stein CM, Wilkinson GR, Roden DM. Inhibition of P-glycoprotein-mediated drug transport: A unifying mechanism to explain the interaction between digoxin and quinidine [see comments]. *Circulation*. 1999;99(4):552–557.
14. Chaggar PS, Shaw SM, Williams SG. Is foxglove effective in heart failure? *Cardiovasc Ther*. 2015;33(4):236–241.
15. Dec GW. Digoxin remains useful in the management of chronic heart failure. *Med Clin North Am*. 2003;87(2):317–337.
16. Maury P, Rollin A, Galinier M, Juilliere Y. Role of digoxin in controlling the ventricular rate during atrial fibrillation: A systematic review and a rethinking. *Res Reports Clin Cardiol*. 2014;5:93–101.
17. Freeman J V, Reynolds K, Fang M, et al. Digoxin and risk of death in adults with atrial fibrillation: The ATRIA-CVRN study. *Circ Arrhythm Electrophysiol*. 2015;8(1):49–58.

18. Whitbeck MG, Charnigo RJ, Khairy P, et al. Increased mortality among patients taking digoxin--analysis from the AFFIRM study. *Eur Heart J*. 2013;34(20):1481-1488.
19. Butler J, Anand IS, Kuskowski MA, et al. Digoxin use and heart failure outcomes: Results from the Valsartan Heart Failure Trial (Val-HeFT). *Congest Heart Fail*. 16(5): 191-195.
20. Hallberg P, Lindbäck J, Lindahl B, Stenestrand U, Melhus H, RIKS-HIA group. Digoxin and mortality in atrial fibrillation: A prospective cohort study. *Eur J Clin Pharmacol*. 2007;63(10):959-971.
21. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: A systematic review and meta-analysis of the literature. *Eur Heart J*. 2015;36(28):1831-1838.