DIGOXIN TOXICITY WITH NORMAL DIGOXIN AND SERUM POTASSIUM LEVELS: BEWARE OF MAGNESIUM, THE HIDDEN MALEFACTOR

Mamatha Punjee Raja Rao, MBBS,* Prashanth Panduranga, MRCP,† Kadhim Sulaiman, FRCP† and Mahmood Al-Jufaili, FRCP*C

*Department of Emergency Medicine and †Department of Cardiology, Royal Hospital, Muscat, Oman

Reprint Address: Mamatha Punjee Raja Rao, MBBS, Department of Emergency Medicine, Royal Hospital, Post Box 1331, Muscat-111, Sultanate of Oman

Abstract—Background: In recent years, digoxin use has been on the decline, with decreased incidence of digoxin toxicity. Hence, digoxin toxicity, when it occurs, remains an elusive diagnosis to emergency physicians. Objective: To present a case of digoxin toxicity with normal levels of digoxin and serum potassium, but with severe hypomagnesemia. Case Report: A 66-year-old woman presented with junctional tachycardia and ectopic atrial tachycardia. She was known to have congestive cardiac failure on diuretic therapy. Her serum digoxin level was within the normal range (2.4 mmol/L [normal = 1.9–2.6]) along with a normal serum potassium level (3.9 mmol/L [normal = 3.5–5]). However, there was severe hypomagnesemia (0.39 mmol/L [normal = 0.65–1.25]) precipitating digoxin-induced dysrhythmia, which responded well to intravenous magnesium therapy. Conclusion: This case reiterates that digoxin toxicity can occur in patients with normal digoxin and potassium levels, and in such patients, magnesium needs to be checked and treated to prevent potentially life-threatening dysrhythmias. © 2013 Elsevier Inc.

Keywords—digoxin toxicity; hypomagnesemia; hypokalemia; dysrhythmia

INTRODUCTION

Digoxin toxicity can be acute, due to overdose, or chronic, when taken for a prolonged period of time. In the Digitalis Investigation Group trial, the overall incidence of digoxin toxicity was 2% over a 3-year period (1). Recently, the incidence of digoxin toxicity has been decreasing due to less use of digoxin in heart failure patients, and it remains an elusive diagnosis to emergency physicians (2). We present a case of digoxin toxicity presenting with junctional tachycardia and ectopic atrial tachycardia in an elderly patient with congestive cardiac failure.

CASE REPORT

A 66-year-old woman was referred from a health center to the Emergency Department (ED) with a 1-day history of abdominal discomfort, nausea, vomiting, and intermittent palpitations. Her past history was significant for diabetes, hypertension, severe left ventricular systolic dysfunction, and congestive cardiac failure. She was being treated for the last 6 months with anti-failure medications, and her current medications included furosemide 40 mg twice daily, spironolactone 25 mg once daily, digoxin 0.125 mg once daily, carvedilol 6.25 mg twice daily, and lisinopril 10 mg once daily, along with metformin and calcium supplement.

At presentation, the patient was conscious and oriented with a blood pressure of 145/70 mm Hg, pulse rate of 110 beats/min with no gallop, and a clear chest. Her initial electrocardiogram (ECG) done in the referral
health center demonstrated narrow QRS tachycardia with a heart rate of 130 beats/min with inverted P waves falling on T waves and upright P in aVR (Figure 1, arrowheads), suggestive of junctional tachycardia. An ECG done in our ED demonstrated a narrow QRS tachycardia, peaked P waves with prolonged PR interval at 110 beats/min heart rate, and typical ECG signs of the “digoxin effect” in the form of a scooped appearance of the asymmetric down-sloping ST depression (“reversed tick” sign) (Figure 2). This ECG was suspicious for an ectopic atrial tachycardia with 1:1 conduction. In view of the patient taking digoxin, she was suspected to have digoxin toxicity, and her blood was sent for routine blood tests along with digoxin levels. All of the patient’s blood investigations were reported as normal, including free digoxin level (2.4 nmol/L [normal = 1.9–2.6] using Abbott AxSYM analyzer; Abbott Laboratories, Abbott Park, IL). Her troponin T was negative, serum potassium was 3.9 mmol/L (normal = 3.5–5), creatinine was 91 μmol/L (normal = 45–90), calculated glomerular filtration rate (GFR) was 54 mL/min/1.73 m², and brain natriuretic peptide was 2017 pg/mL (normal = 20–285). These results initially ruled out digoxin toxicity and suggested that the dysrhythmia may be due to underlying cardiomyopathy. However, in view of the ECG changes being highly suspicious for digoxin toxicity, her magnesium and calcium levels were requested. The calcium level was normal, but the serum magnesium level was low at 0.39 mmol/L (normal = 0.65–1.25). She was diagnosed to have digoxin toxicity precipitated by hypomagnesemia.

Figure 1. Twelve-lead electrocardiogram demonstrating a narrow QRS tachycardia with a heart rate of 130 beats/min with inverted P waves falling on T waves (arrow), and upright P in aVR suggestive of a junctional tachycardia.

Figure 2. Twelve-lead electrocardiogram (ECG) illustrating a narrow QRS tachycardia, peaked P waves with prolonged PR interval at 110 beats/min heart rate, and typical ECG signs of the “digoxin effect” in the form of a scooped appearance of the asymmetric down-sloping ST depression (“reversed tick” sign; arrow). This ECG is suggestive of an ectopic atrial tachycardia with 1:1 conduction.
The patient was admitted and was treated with intravenous magnesium sulfate 2 g in 100 mL saline over 60 min. The digoxin was discontinued. After 1 h of infusion, her rhythm changed to sinus with a heart rate of 70 beats/min and a prolonged PR interval (Figure 3). The P wave morphology was different between the second ECG and third ECG, suggesting that her second ECG showed ectopic atrial tachycardia. A further magnesium sulfate infusion of 5 g (approximately 40 mEq) in 500 mL saline was given for 24 h. Repeat serum magnesium at 6 h was 0.67 mmol/L. Her thyroid-stimulating hormone level was normal. The patient was discharged after 72 h of observation, with no recurrence of any dysrhythmia. At discharge, digoxin level was 1.4 nmol/L and magnesium level was 1.1 mmol/L.

DISCUSSION

In a relatively recent study, digoxin toxicity was identified in 0.04% of all admissions (2). The incidence rate for digoxin toxicity-related admissions was 48 per 100,000 prescriptions, which corresponds to 1.94 admissions for toxicity per 1000 treatment-years. Women had a 1.4-fold higher risk of intoxication than men. In patients taking digoxin in recommended doses (0.125 to 0.25 mg once daily), digoxin toxicity can occur when they are exposed to precipitating factors such as hypokalemia, hypomagnesemia, or hypothyroidism, even though the serum digoxin level is within normal limits (3). In addition, drug-to-drug interactions can increase digoxin level (e.g., quinidine, verapamil, spironolactone, flecainide, amiodarone, erythromycin, clarithromycin) and cause digoxin toxicity (3). Furthermore, elderly age, female gender, low muscle mass, and reduced GFR can predispose to digoxin toxicity in patients taking a normal recommended dose (3,4).

Hypokalemia or hypomagnesemia sensitize the myocardium to digoxin even when digoxin levels are within the normal range (Lanoxin product information; Aspen Pharma, St. Leonards, NSW, Australia). Digoxin directly inhibits sodium-potassium ATPase pump in the membrane of cardiac myocyte, causing an increase in intracellular sodium and calcium (through a sodium and calcium exchanger) with subsequent increase in myocardial contractility (5). Hypokalemia increases digoxin cardiac sensitivity because potassium and digoxin compete for the same ATPase-binding site (5). This leads to a decrease in atrioventricular (AV) node conduction, and an increase in automaticity (increased intracellular calcium) and ectopic pacemaker activity. In addition, there is an increase in vagal tone (inhibits sodium-potassium ATPase pump in vagal afferent fibers), causing bradycardia and AV blocks. Magnesium is a cofactor of the sodium-potassium ATPase pump (6). Hypomagnesemia increases myocardial digoxin uptake, further inhibiting sodium-potassium ATPase pump activity (6). Hypomagnesemia is associated with hypokalemia in 40–60% and hypocalcemia in 40% of toxicity cases (7). However, hypomagnesemia can produce intracellular potassium depletion in the presence of normal serum potassium levels (8). It is known that long-term digoxin users often have hypokalemia or hypomagnesemia, presumably due to diuretic usage in patients with congestive heart failure (5).

Even though this patient had several risk factors for digoxin toxicity, including elderly age, female gender, and a moderately reduced GFR, it was the diuretic-induced hypomagnesemia that precipitated digoxin-induced junctional and atrial tachycardia. This patient did not manifest serum hypokalemia due to the co-administration of a potassium-sparing diuretic and angiotensin-converting enzyme inhibitor. However, it is possible that the

Figure 3. Twelve-lead ECG post-magnesium sulfate infusion for digoxin-induced dysrhythmia demonstrating sinus rhythm with a heart rate of 70 beats/min and prolonged PR interval with ST depression suggestive of digoxin effect.
hypomagnesemia was associated with intracellular potassium depletion, leading to digoxin-related dysrhythmias (8). Enhanced automaticity and impaired conduction are the hallmarks of digitalis toxicity (9). Digoxin can cause any type of dysrhythmia, but especially the following: frequent premature ventricular complexes; atrial fibrillation with slow, regular ventricular rate or complete AV block; non-paroxysmal junctional tachycardia; atrial tachycardia with block; and bidirectional ventricular tachycardia (9,10).

Normal levels of serum digoxin and the absence of hypokalemia (the most common precipitant of digoxin-induced dysrhythmias) initially led to the conclusion that the dysrhythmias may be due to underlying cardiomyopathy. However, magnesium was found to be very low and magnesium replacement resulted in conversion to sinus rhythm without the need for any anti-dysrhythmic agents. Management of digoxin toxicity involves withdrawal of the medication as well as administration of digoxin-specific Fab antibodies for life-threatening cardiovascular compromise (9,10). In addition, it is necessary to treat precipitating conditions such as replacement of electrolyte deficiencies. In the patient presented here, treatment of hypomagnesemia resulted in conversion of atrial tachycardia to sinus rhythm without the need for Fab antibodies. Magnesium therapy requires monitoring of serum levels and is contraindicated in patients with bradycardia or AV block, or severe renal failure.

CONCLUSION

This case reiterates that digoxin toxicity can occur in patients with normal digoxin and potassium levels, and in such patients, magnesium must be monitored and treated to prevent potentially life-threatening dysrhythmias.

REFERENCES