การศึกษาอาการนำทางคลินิกและผลการรักษาผู้ป่วยที่มีภาวะพิษจากยา digoxin

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Abstract: Clinical Presentations and Outcomes of Digoxin Intoxicated Patients

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Background: Patients with digoxin intoxication are difficult to diagnose because those have non-specific signs and symptoms and serum digoxin level does not correlate with clinical presentations. Until now, there has been lacking data about the clinical manifestations and therapeutic outcomes in these patients. Objective: To demonstrate the clinical presentations and outcomes in patients with digoxin intoxication. Method: This study was a retrospective observational study. The patients with digoxin intoxication were enrolled in Siriraj Hospital. The clinical characteristics and outcomes of these patients were analyzed with descriptive statistics. Result: A total of 30 patients were diagnosed as digoxin intoxication. About one-third of these patients were male. An average age was 70.33 ± 11.75 years. About one third of those had heart failure and one-fourth of those had atrial fibrillation (AF). An average digoxin dose was 0.19 ± 0.10 milligrams/day during toxicity, and an average digoxin level was 3.08 ± 1.56 nanograms/milliliter. Fatigue combined with gastrointestinal (GI) symptoms (40%) were the most common symptoms in patients with digoxin intoxication, while AF with complete heart block (CHB) was the common arrhythmias in those patients. Interestingly, the most common electrolyte disturbance in those was hyponatremia. Most patients improved after supportive treatment, and minority of those were needed with temporary pacemaker insertion (3.33%). Conclusion: The common clinical presentations of patients with digoxin intoxication were fatigue combined with GI symptoms, AF with CHB, and hyponatremia. Most patients improved after supportive treatment.

Keywords: digoxin toxicity, digitalis toxicity, atrial fibrillation, complete heart block

บทคัดย่อ

ภูมิหลัง: ภาวะพิษจาก digoxin นั้นเป็นภาวะที่ได้รับการวินิจฉัยค่อนข้างยาก เนื่องจากมีอาการและอาการแสดงที่ไม่จำเพาะ และระดับ digoxin ในเลือดก็ไม่สัมพันธ์กับอาการทางคลินิกของผู้ป่วยที่มีภาวะพิษจาก digoxin ปัจจุบันยังไม่มีข้อมูลการศึกษาเกี่ยวกับลักษณะทางคลินิกและผลการรักษาผู้ป่วยกลุ่มนี้ วัตถุประสงค์: เพื่อศึกษาอาการนำทางคลินิกและผลการรักษาในผู้ป่วยที่เกิดภาวะพิษจาก digoxin วิธีการ: การศึกษานี้เป็นการศึกษาแบบเก็บข้อมูลสังเกตการณ์ย้อนหลัง โดยเก็บข้อมูลผู้ป่วยที่เกิดภาวะพิษจาก digoxin ที่รักษาใน รพ.ศิริราช ลักษณะทางคลินิกและผลการรักษาของผู้ป่วยเหล่านี้ได้รับการวิเคราะห์โดยใช้สถิติเชิงพรรณนา ผล: ผู้ป่วยที่ได้รับการวินิจฉัยว่ามีภาวะพิษจาก digoxin มีจำนวนทั้งหมด 30 คน ประมาณ 1 ใน 3 ของผู้ป่วยเป็นเพศชาย มีอายุเฉลี่ย 70.33 ± 11.75 ปี ประมาณ 1 ใน 3 ของผู้ป่วยมีหัวใจล้มเหลวและ

ประมาณ 1 ใน 4 ของผู้ป่วยมีหัวใจห้องบนสั่นพลิ้วขนาดยา digoxin ที่ได้รับเฉลี่ย 0.19 ± 0.10 มิลลิกรัมต่อวันในขณะเกิดภาวะพิษจาก digoxin และระดับยา digoxin ในเลือดเฉลี่ย 3.08 ± 1.56 นาโนกรัมต่อมิลลิลิตร อาการอ่อนเพลียร่วมกับอาการทางระบบทางเดินอาหาร (40%) พบมากที่สุดในขณะที่หัวใจห้องบนสั่นพลิ้วร่วมกับ complete heart block เป็นหัวใจเต้นผิดจังหวะที่พบบ่อยในผู้ป่วยกลุ่มนี้ สิ่งที่น่าสนใจคือความผิดปกติของเกลือแร่ในเลือดที่พบมากที่สุดคือภาวะเกลือ sodium ในเลือดต่ำ ผู้ป่วยส่วนมากที่ได้รับการรักษาแบบประคับประคองหลังจากหยุดยาแล้วอาการดีขึ้นและส่วนน้อยที่ได้รับการใส่ temporary pacemaker (3.33%) **สรุป:** อาการที่พบบ่อยในผู้ป่วยภาวะพิษจาก digoxin คืออาการอ่อนเพลียร่วมกับอาการทางระบบทางเดินอาหาร, หัวใจห้องบนสั่นพลิ้วร่วมกับ complete heart block และภาวะเกลือ sodium ในเลือดต่ำ ผู้ป่วยส่วนมากที่ได้รับการรักษาแบบประคับประคองหลังจากหยุดยาแล้วอาการดีขึ้น

คำสำคัญ: ภาวะพิษจาก digoxin, ภาวะพิษจาก digitalis, หัวใจห้องบนสั่นพลิ้ว, หัวใจเต้นช้า

Introduction

Digoxin is a cardiac glycoside that increases cardiac contractility (positive inotropic effect), heart rate control (chronotropic effect) via blockage of Na^+-K^+ ATPs, parasympathetic activity, and enhancing vagal tone, respectively[1,2]. It is commonly used in patients with heart failure (HF)[3-4] or atrial fibrillation (AF)[5-6] in clinical practice. It is a water-soluble drug and 75% excrete by kidney, and 25% excrete by hepatic metabolism and bile[1]. In patients with creatinine clearance 80 milliliters/minute or more, its half-life is 36 hours, and its volume of distribution is 7 liters/kilograms. However, it has a longer half-life in those with renal impairment (up to 120 hours or 5 days), while it has a shorter half-life in those with hyperthyroidism (24 hours or 1 day)[7].

Digoxin is widespread use in patients with HF or AF, but it has a narrow therapeutic index. Nevertheless, digoxin level is not correlated to its toxicity. Previous study has demonstrated that digoxin level was above 2 nanograms (ng)/milliliter (mL) was associated with its toxicity[8]. However, some patients have signs and/or symptoms or new cardiac arrhythmia consistent with digoxin intoxication such as premature ventricular complexes (PVCs), paroxysmal atrial tachycardia (PAT) with block, AF with complete heart block (CHB) etc[9-10] when their digoxin levels are below 2 ng/mL. To date, lack of data confirms the association between digoxin intoxication and its level.

Moreover, digoxin has many drug-drug interactions such as quinidine, calcium channel blockers, amiodarone, propafenone etc[7]. Risk of its toxicity increases in patients with hypokalemia, hypomagnesemia, or hypercalcemia.

This study was conducted to demonstrate the clinical presentations and outcomes in patients with digoxin intoxication.

Materials and methods

This study was retrospectively enrolled patients with digoxin intoxication treated in Siriraj Hospital. Patients who did not use digoxin for at least 7 days before digoxin intoxication were excluded.

Clinical signs and/or symptoms were compatible with digoxin intoxication if patients had fatigue, color visual changes, anorexia, nausea, vomiting, diarrhea or arrhythmias consistent with its toxicity such as bigeminy PVCs, PAT with block, non-paroxysmal junctional tachycardia, bidirectional ventricular tachycardia, AF with CHB. Digoxin intoxication was diagnosed if those patients had the above clinical signs and/or symptoms or arrhythmias, and they improved after digoxin discontinuation. Outcomes in this study included hospitalization and length of stay. The study protocol was approved by Siriraj Institutional Review Board (No. Si600/2008).

The demographic and clinical data were interpreted by using descriptive statistics. The categorical data are presented as frequency and percentage. The continuous variables are presented as mean ± standard deviation.

Results

A total of 30 patients with digoxin intoxication were recruited. An average age was 70.33 ± 11.75 years. About one-third of those were male gender. About one-thirdof those had HF, and one-fourth of those had AF. An average digoxin dose was 0.19 ± 0.10 milligrams/day during toxicity and an average digoxin level was 3.08 ±

1.56 ng/mL. Baseline characteristics were shown in Table 1.

Fatigue combined with gastrointestinal (GI) symptoms (40%) was the most common symptoms in patients with digoxin intoxication (Table 2) while AF with CHB was the common arrhythmias in those patients (Table 3). Interestingly, the most common electrolyte disturbance in those was hyponatremia (Table 4).

All patients with digoxin intoxication were hospitalized, and an average length of stay was 13.60±11.20 days. Most patients improved after supportive treatment, and minority of those was needed with temporary pacemaker insertion (3.33%). Management in these patients was shown in Table 5.

Table 1 Baseline characteristics of the patients

Demographic data	Total n = 30 n (%) or mean ± SD
Age (years)	70.33 ± 11.75
Male gender	10 (33.33)
Serum creatinine (mg/dL):	
- Baseline serum creatinine (mg/dL)	1.66 ± 0.82
- Serum creatinine during digoxin intoxication (mg/dL)	1.72 ± 0.97
Dose during digoxin intoxication (mg/day)	0.19 ± 0.10
Duration before digoxin intoxication (years)	2.75 ± 6.35
Digoxin level during hospitalization (ng/mL)	3.08 ± 1.56
Medical history:	
- Previous stroke/TIA	9 (30.00)
- Coronary artery disease	15 (50.00)
- Valvular heart disease	9 (30.00)
- Dilated cardiomyopathy	1 (3.33)
- Heart failure	11 (36.67)
- Atrial fibrillation	23 (76.67)
- Diabetes mellitus	10 (33.33)
- Hypertension	17 (56.67)
- Dyslipidemia	7 (23.33)
- Chronic kidney disease	6 (20.00)
- Liver cirrhosis	4 (13.33)
- Hashomoto's thyroiditis	3 (10.00)
- Hyperthyroidism	2 (6.67)
- Malignancy	4 (13.33)
Indication of digoxin:	
- Atrial fibrillation alone	18 (60.00)
- Heart failure alone	2 (6.67)
- Atrial fibrillation combined with heart failure	3 (10.00)
- Unknown	7 (23.33)

n = numbers, SD = standard deviation, mg = milligram, ng = nanogram, mL = milliliter, TIA = transient ischemic attack

Table 2 Signs and/or symptoms of patients with digoxin intoxication

Signs and/or symptoms	Total n = 30 n (%)
Fatigue	6 (20.00)
GI symptoms	4 (13.33)
Color visual changes	1 (3.33)
Concomitant fatigue and GI symptoms	12 (40.00)
Concomitant fatigue and confusion	1 (3.33)
Concomitant GI symptoms and visual changes	1 (3.33)
Other symptoms	5 (16.67)

n = numbers, GI = gastrointestinal

Table 3 Arrhythmias in patients with digoxin intoxication

Arrhythmias	Total n = 30 n (%)
AF combined with CHB	14 (46.67)
Junctional rhythm	3 (10.00)
Slow rate of AF	5 (16.67)
Occasional premature ventricular complex	1 (3.33)
Atrioventricular block	2 (6.67)

n = numbers, AF = atrial fibrillation, CHB = complete heart block

Table 4 Electrolyte disturbances in patients with digoxin intoxication

Electrolyte disturbances	Total n = 30 n (%)
Hyponatremia	16 (53.33)
Hypernatremia	1 (3.33)
Hypokalemia	5 (16.67)
Hyperkalemia	7 (23.33)
Hypomagnesemia	6 (20.00)
Hypocalcemia	1 (3.33)

n = numbers

Table 5 Management in patients with digoxin intoxication

Management	Total n = 30 n (%)
Supportive treatment	24 (80)
Atropine	3 (10)
Temporary pacemaker insertion	1 (3.3)
Dopamine	1 (3.3)
Endotracheal intubation	1 (3.3)

n = numbers

Discussion

To date, digoxin is widespread use in patients with HF or AF, but it has a narrow therapeutic index. This study revealed signs and symptoms in patients with digoxin intoxication, and it was common use in those with AF (60%) while the minority of those patients used digoxin for treatment of HF.

There are several non-specific signs and symptoms in patients with digoxin intoxication, such as fatigue, GI symptoms, etc. Only visual color changes are the specific symptoms in those patients, but they appeared in the late stage of the disease. This study demonstrated visual color changes were a minority of clinical presentation (6.67%) which was similar to previous studies by Jitapunkul S et al[8] and Abad-Santos F et al[11]. Those studies found the visual color changes in 5.6% and 7.3% of patients, respectively.

Fatigue combined with GI symptoms (40%) was the most common symptoms in this study that was different from previous study by Jitapunkul S et al[8] and Abad-Santos F et al[11]. Those studies found nausea and/or vomiting in 88.9% and 58.5% of patients, respectively. These non-specific symptoms were careful in patients receiving digoxin.

AF with CHB was the common arrhythmias in those patients (46.67%), similar to previous study by Jitapunkul S et al[8] that found it in 18% of patients. However, a previous study by Abad-Santos F et al[11] found PVCs was the most common arrhythmia (36.6%). In addition, PVCs may be appeared from causes other than digoxin intoxication such as electrolyte disturbances i.e. hypokalemia or hypomagnesemia.

Interestingly, the most common electrolyte disturbance in this trial was hyponatremia (53.33%) while the lower rate of hyponatremia (6.2%) in patients who were hospitalized in the internal medicine ward of Siriraj Hospital among 2005-2007. Hyponatremia may be related to digoxin intoxication. Further study will be conducted to elucidate the association between hyponatremia and digoxin intoxication.

Most patients improved after supportive treatment (80%) and minority of those was needed with temporary pacemaker insertion (3.33%). Although AF with CHB was common in these patients, it was reversible after discontinuation of digoxin, and no need for temporary pacemaker insertion.

However, this study had several limitations. First, this study enrolled small patients because of digoxin intoxication was rare. It limited to apply in general population. Second, some patients with digoxin were excluded from this study because of death. Because strict definition of digoxin intoxication in this study stated that only patients improved after discontinuation of digoxin were enrolled, patients with digoxin who died before cessation of digoxin cannot be exclude its toxicity. Third, this study was retrospective study, so there were some missing data. However, this study demonstrated the provisional data in patients with digoxin intoxication and showed some clinical data related to this condition.

Conclusion

The common clinical presentations of patients with digoxin intoxication were fatigue combined with GI symptoms, AF with CHB, and hyponatremia. Most patients improved after supportive treatment.

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