



Digoxin intoxication: An old enemy in modern era

Bahadır Kirilmaz¹, Serkan Saygi¹, Hasan Gungor², Ugur Onsel Turk³, Emin Alioğlu³, Serdar Akyuz⁴, Fatih Asgun⁵, Istemihan Tengiz³, Ertugrul Ercan¹

¹Department of Cardiology, Canakkale Onsekiz Mart University, Medical Faculty, Canakkale 17100, Turkey

²Department of Cardiology, Odemis State Hospital, Izmir 35750, Turkey

³Department of Cardiology, Central Hospital, Izmir 35580, Turkey

⁴Department of Cardiology, Yunus Emre State Hospital, Eskisehir 26190, Turkey

⁵Department of Cardiovascular Surgery, Canakkale Onsekiz Mart University, Medical Faculty, Canakkale 17100, Turkey

Abstract

Objectives Although development of new treatment modalities limited digoxin usage, digoxin intoxication is still an important issue which could be easily overlooked. In this report, we analyzed a case series definitively diagnosed as digoxin intoxication in the modern era. **Methods** We analyzed 71 patients hospitalized with digoxin intoxication confirmed by history, complaints, clinical and electrocardiograph (ECG) findings, and serum digoxin levels > 2.0 ng/mL, during a five year period. The demographic and clinical data, indications for digoxin use, digoxin dosage, concurrent medications, laboratory data, hospital monitoring, and ECG findings were obtained from all patients. **Results** Thirty-eight of 71 patients (53.5%) had symptoms of heart failure during admission or later. Sixty-four percent of patients were older than 75 years. The percentage of females was 67%. Atrial fibrillation, hypertension and gastrointestinal complaints were more frequent in the females (64% in females, 30% in males, $P = 0.007$; 81% in female, 52% in males, $P = 0.01$; 50% in female, 17.3% in males, $P = 0.008$, respectively). The mortality rate during the hospital course was 7%. **Conclusions** This report demonstrated the reduced mortality rates in patients with digoxin intoxication over the study period. Gastrointestinal complaints are the most common symptoms in this population.

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1 Introduction

Digoxin has been used to treat heart failure and arrhythmia for many years. Although a number of sophisticated management options and new therapeutic agents utilized to treat patients with heart failure have been developed in recent years, digoxin, a well-tolerated and inexpensive drug which has widely been used for a long time, is one of the most frequently prescribed drugs and still remains as the first choice of treatment.^[1–3] However, it has a narrow therapeutic dose range and can easily reach toxic levels in the blood stream, increasing the intoxication risk. The mortality rate of digoxin intoxication has been reduced due to new treatment modalities and decreased usage of digoxin. However, digoxin is still the one of the most frequently prescribed drugs and therefore digoxin intoxication could be overlooked. Furthermore, discrimination of

digoxin intoxication may be difficult because the clinical presentation of disease can occur in different forms, and electrocardiograph (ECG) records are not specific. In this report, we aimed to investigate the clinical features, treatment, and outcomes of patients hospitalized for digoxin intoxication in the modern era.

2 Methods

A total of 71 patients, hospitalized for digoxin intoxication during five years were included into the study. Digoxin intoxication was confirmed by history, complaints, clinical and ECG findings, and serum digoxin levels > 2.0 ng/mL. Patients with normal serum digoxin levels were excluded. The hemodynamic condition, findings of physical examination, New York Heart Association (NYHA) class, and ECG records of all patients were recorded on admission. The following information was obtained from the patients or relatives of the patients during admission: demographic features including age and weight, complaints, existing diseases and clinical conditions, etiology of heart failure, if it present, previous treatment details, including name and number of drugs

Correspondence to: Hasan Gungor, MD, Department of Cardiology, Odemis State Hospital, Izmir, Turkey. E-mail: drgungorhasan@yahoo.com

Telephone: +90-232-5445113

Fax: +90-232-54466 32

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taken by the patient, and digoxin dosage. The time of last digoxin dose received by patient was especially recorded. Biochemical and hematological analyses, including serum levels of urea, creatinine, sodium, potassium, magnesium, albumin and hemoglobin were recorded. Serum digoxin levels of patients were measured on admission and at the 72nd hour after admission. We measured digoxin levels by a specific radioimmunoassay method (Gammacoat Digoxin, Baxter, France). Daily ECG assessments were performed and recorded in all patients. Transthoracic echocardiographic examinations were performed on the study group according to the criteria of American Society of Echocardiography, including measurements of left ventricular ejection fraction, diameters of cardiac chambers, wall thicknesses, and color and flow Doppler analyses of valves.^[4] Mean hospitalization time, treatment, complications occurred throughout the hospital course and modes of death were also recorded.

Statistical analysis was performed using a commercial computer program (NCSS/PASS Dawson Edition, Number Cruncher Statistical Systems, Kaysville, Utah). Numerical variables were expressed as mean \pm SD, and frequencies were done as number and percentage. Numerical variables were compared using *t*-test, and categorical variables were done using chi-square test. Statistical significance was accepted at the level of $P \leq 0.05$.

3 Results

3.1 Baseline characteristics of patients

Forty-eight of 71 patients were female (67.6%) and 23 were male (32.4%). The overall average of age was 76 ± 9.5 years with 64.4% of the patients ≥ 75 years old. Average body weight of the patients was 63.7 ± 13.9 kg. Complaints of the patients admitted at emergency service were dyspnea, gastrointestinal complaints (nausea, vomiting, abdominal pain), weakness, vertigo, pre-syncope or syncope and visual disturbances, respectively, and none of them were specific complaints. Diseases detected in patients were chronic congestive heart failure, essential hypertension, atrial fibrillation, coronary artery disease, diabetes mellitus, hyperlipidemia and chronic obstructive pulmonary disease. It was found that 38 of 71 patients (53.5%) had symptoms of heart failure during admission or later. Diminished mental status, including difficulty in cooperation, was detected in 19 patients (26.8%) during admission. Average number of drugs, except digoxin, regularly received by the patients was determined to be 4.8. It was found that the percentage of patients receiving three or more drugs was 88.7%. Baseline characteristics were summarized in Table 1.

Table 1. Baseline characteristics of study group (n = 71).

| | |
|--|-----------------|
| Age (yrs) | 76.0 \pm 9.1 |
| Weight (kg) | 63.7 \pm 13.9 |
| Female gender | 48 (67%) |
| Complaints | |
| Palpitation | 15 (21.1%) |
| Gastrointestinal complaints | 28 (39.4%) |
| Dyspnea | 36 (50.7%) |
| Pre syncope | 17 (23.9%) |
| Weakness | 21 (29.6%) |
| Previous medication | |
| Number of drugs | 4.8 \pm 1.8 |
| Aspirin | 46 (64.8%) |
| Diuretics | 35 (49.3%) |
| Potassium sparing diuretics | 26 (36.6%) |
| Angiotensin converting enzyme inhibitors | 32 (45.1%) |
| Angiotensin receptor blockers | 14 (19.7%) |
| Beta blockers | 17 (23.9%) |
| Statins | 15 (21.1%) |
| Calcium channel blockers | 11 (15.5%) |
| Nitrate | 24 (33.8%) |
| Previous digoxin dosage | |
| 0.25 mg/d | 63 (88.7%) |
| 0.125 mg/d | 8 (11.3%) |
| History of patients | |
| Systolic heart failure | 55 (77.5%) |
| Atrial fibrillation | 38 (53.5%) |
| Coronary artery disease | 32 (45.1%) |
| Hypertension | 51 (71.8%) |
| Diabetes mellitus | 23 (32.4%) |
| Hyperlipidemia | 19 (26.8%) |
| Obstructive lung disease | 12 (16.9%) |
| NYHA class | |
| Class I and II | 56 (78.9%) |
| Class III and IV | 15 (21.1%) |
| Laboratory findings | |
| Urea (mg/dL) | 79.7 \pm 44.9 |
| Creatinine (mg/dL) | 1.5 \pm 0.6 |
| Creatinine clearance | 37.7 \pm 16.7 |
| Sodium (mEq/L) | 137.1 \pm 5.3 |
| Potassium (mEq/ L) | 4.6 \pm 0.8 |
| Magnesium (mEq/ L) | 2.2 \pm 0.5 |
| Albumin (mg/dL) | 3.5 \pm 0.6 |

Data are presented as mean \pm SD or n (%).

3.2 Indications of digoxin treatment

When initial indications for drug usage were explored, it was revealed that 36 patients (50.7%) have been receiving digoxin for only heart failure, 17 patients (23.7%) have been doing so for only atrial fibrillation, and 18 patients (25.4%) for both conditions. The mean control digoxin level measured

at 72 h after admission was 1.73 ng/mL in all patients, but was 1.41 ng/mL in 66 surviving patients at discharge. Indications of digoxin therapy, digoxin levels on admission and at the 72nd h, and echocardiographic measurements of group were summarized in Table 2.

Table 2. Etiology of heart failure, serum digoxin level, and echocardiographic findings of patients after admission (n = 71).

| | |
|---|-------------|
| Etiology of heart failure | |
| Ischemic | 29 (40.8%) |
| Non-ischemic | 15 (21.1%) |
| Unknown | 27 (38.1%) |
| Digoxin level on admission (ng/mL) | 3.40 ± 1.20 |
| Digoxin level at 72 nd h (ng/mL) | 1.7 ± 0.9 |
| Left ventricle ejection fraction (%) | 40.5 ± 13.5 |
| Left atrial diameter (mm) | 48.2 ± 7.1 |
| Heart rate (/min) | 70.7 ± 32.0 |

3.3 Hospital course of patients

Mean hospitalization time in the patients with digoxin intoxication was 12 days (11.7 days in females and 12.7 days in males). Daily ECG assessments of the patients were performed during the hospital course. Baseline heart rhythms on ECGs recorded in the emergency service were atrial fibrillation with mean ventricular rate in 22 patients (31.0%), sinus rhythm or pacing in 20 (28.2%), atrial fibrillation with low ventricular rate in 16 patients (22.5%), atrial fibrillation with high ventricular rate in six patients (8.5%), nodal rhythm or complete atrioventricular heart block in four patients (5.6%), ventricular tachycardia in two patients and supraventricular tachycardia in one patient. Thirty-three patients suffered additional arrhythmic events, such as ventricular tachycardia, nodal rhythm, frequent premature ventricular beats and supraventricular tachycardia. Two patients had bidirectional ventricular tachycardia, and one patient had posterior fascicular ventricular tachycardia. Temporary pacing was required in 10 patients (3 males and 7 females) according to their clinical and hemodynamic status and ECG findings, and the indications of temporary pacing in these patients were atrial fibrillation with slow ventricular rate in five patients, nodal rhythm with slow ventricular rate or complete atrioventricular heart block in three patients, and severe sinus bradycardia in two patients (Table 3). Two patients already had permanent pacemakers during admission.

Table 3. Hospital course of patients (n = 71).

| | |
|--------------------------------------|------------|
| Temporary pacemaker implantation (n) | 10 (14.1%) |
| Hospitalization day (day) | 12.0 ± 8.5 |
| Mortality (n) | 5 (7.0%) |

3.4 Characteristics of patients according to the gender

Atrial fibrillation and hypertension were more frequent in the females (Atrial fibrillation: 64% in females, 30% in males, $P = 0.007$; hypertension: 81% in female, 52% in males, $P = 0.01$). Gastrointestinal complaints were more common in females (50% in females, 17.3% in male patients, $P = 0.008$). Mortality rates were similar between male and female patients.

3.5 Mortality rate

Five patients died during management (mortality rate 7.0%). Four patients died of arrhythmic event and one patient died of pulmonary insufficiency caused by pulmonary infection. Cause of death in four patients was ventricular fibrillation following ventricular tachycardia. An emergent temporary pacemaker was implanted in one of these patients, but he did not survive (Table 3).

4 Discussion

In this report, we analyzed a case series hospitalized with the diagnosis of digoxin intoxication between 2001 and 2008. Published studies analyzing patients with definitively diagnosed digoxin intoxication are limited. Distinct from previous studies, only patients with definitively diagnosed as digoxin intoxication confirmed by complaints, serum digoxin levels, physical examination, and ECG findings were included in the present study. Digoxin is one of the most prescribed drugs with advantages, including cost-effectiveness and well-tolerance, and the disadvantage of a mainly narrow therapeutic range.^[1,3] In studies performed in the 1970s, it was reported that 23% of patients on digoxin therapy were admitted to hospitals for digoxin intoxication.^[5-7] Over the years digoxin intoxication rates reduced, as defined in Digitalis Investigation Group (DIG) study, and the hospitalization rate for digoxin intoxication was 2%.^[8]

As expected, the mean age was high in our series, with no differences between sexes. The patients over 75 years-old represented two thirds of all cases. Eighty percent of the patients receiving digitalis products are over 85 years-old, and it was reported that digoxin usage rate in this group aged over 85 years is 25%.^[9] Especially in elder population, digoxin intoxication is more frequent because of decreased renal function, higher rate of accompanying disorders, and drugs using to treat these additional diseases.^[10,11] An important issue in digoxin usage is that intoxication may occur in patients with hypopotassemia, hypomagnesaemia, hypercalcaemia, hypoxia, acidosis, acute and chronic lung disease, hypothyroidism and myocardial ischemia, even if they have a serum digoxin level in normal ranges.^[12,13] In our analyses, 67% of patients were female, as expected. This

was explained by the lower muscle mass and lower body weight of women. Our results were in concordance with previous reports.^[14] In the DIG study, the raised mortality rate associated with elevated serum digoxin levels in female patients with low ejection fraction was observed, and the authors proposed that digoxin should be administered in relatively low dosages in women.^[8] The patients admitted to emergency services due to digoxin intoxication have a wide range of complaints. This spectrum varies from mild gastrointestinal complaint to syncope caused by severe bradycardia, and any of these complaints is not specific to digoxin intoxication. Symptoms are generally originated from vagal tonus augmented by digoxin. In our series, we found that gastrointestinal complaints including nausea, vomiting, and abdominal pain were more frequent in women.

Congestive heart failure and atrial fibrillation were found to be the most frequent diagnosis consistent with indications of the drug in our study. More frequent, additional diseases were essential hypertension and diabetes mellitus, also consistent with the mean age of patients. The number of drugs used by the patients was high as expected, and was positively correlated with the age and the number of diseases diagnosed in these patients. It was important that the percentage of patients receiving three or more drugs was nearly 90%. Elevated number of drugs used by the patients on digoxin treatment facilitates the intoxication. Also, decreased renal function by the age and the drugs used to treat heart failure, including diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, facilitate the intoxication. In our series, usage rates of these drugs were very high. Daily digoxin dosage taken by the most patients with these drugs was 0.25 mg. But this dosage may not be high when the age and renal functions of these patients is considered. It is important that favorable results associated with low dose digoxin were found in the DIG study.^[8] Especially in elder and female patients, digoxin should be suggested in low dosages. Most of the patients using digoxin had systolic heart failure, and the cause of systolic heart failure in approximately half of these patients was ischemic heart disease. Also in the literature, it has been confirmed that most of the patients receiving digoxin have ischemic heart disease.^[8,15] This situation, accompanied by a high serum digoxin level, may be a risk factor facilitating life-threatening dysrhythmias. In contrast to expectations, a larger number of the patients had moderate symptoms (78% of patients had NYHA class I and II) according to the NYHA classification. Left ventricular hypertrophy and left atrial dilatation detected by the echocardiographic examination were the frequently observed findings.

Mean urea and creatinine levels were relatively lower in the present study (1.5 ± 0.6). The mean creatinine level was

about 3.0 in the report by Marik.^[14] Higher mortality rates demonstrated in that study could be explained by the higher baseline creatinine levels of patients compared to our report. Renal functions and age are independent predictors of intoxication.^[16] As mentioned especially in heart failure guidelines, intense usage of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics in this patient group and adverse renal effects of them should be kept in mind. Digoxin should be administered in low doses in elder population who are susceptible to diminished renal function. Low dose digoxin administration in the population with high intoxication risk is also suggested by the authors of DIG study.^[8] The mean serum digoxin levels of our patients were over 2.0 ng/mL which is the nomogram value given for the serum digoxin level by Jelliffe.^[17] Higher mortality rates has been found in patients with increased serum digoxin concentration above the therapeutic range.^[18,19] This special status, which is intoxication with a normal serum digoxin level, can cause misdiagnoses.^[20-22] Digoxin levels were measured eight hours following the last digoxin dose to avoid any wrong assessment caused by the distribution characteristics of digoxin.^[23]

ECG changes caused by digoxin intoxication include an arrhythmia spectrum varied from asymptomatic rare premature ventricular beats to life-threatening complete atrioventricular blocks, bradycardia, ventricular tachycardia and fibrillation.^[20] It should be kept in mind that any arrhythmia occurring in a patient receiving digoxin should be accepted as a sign of intoxication. More frequently determined ECG changes during admission and throughout the management were atrial fibrillation and premature ventricular beats in our series. Two patients had bi-directional ventricular tachycardia which is typical for digoxin intoxication.^[24]

Mortality rate of digoxin intoxication in the literature is varied, but it is generally reported between 20% and 30%.^[25-29] The mortality rate of intoxication in our series was 7%. Death of more severe cases before admission, and the wide serum digoxin level spectrum of our patients, may cause a low mortality rate compared with the literature data. In 1998, Marik *et al.*^[14] analyzed 82 patients with manifest digoxin intoxication. The mortality rate in their series was 28%. Ten years later, another study investigating 1,286 patients with digoxin intoxication was reported by Aarnoudse *et al.*^[30] They found a mortality rate of 7.7% ($n = 99$) similar with our results (7%, $n = 5$). Great experiences about the side effects of digoxin and the development of new treatment modalities for heart failure limited the digoxin usage and intoxication rates over the years. However, the mortality rate reported in the present study revealed that the clinical importance

of digoxin intoxication should not be underestimated. Treatment of intoxication is a difficult course.

In conclusion, despite its side effects, digoxin is still the one of the most effective drugs in the treatment of heart failure. Increased knowledge about the side effects, reduction of dosage, and development of new treatment modalities for heart failure reduced the digoxin intoxication rates over the years. However, we thought that the mortality rate reported in this study should not be underestimated. Clinical and laboratory parameters used to diagnose digoxin intoxication, and to determine the prognosis may not sufficiently help the clinician. For this reason, it seems that clinical suspect in the patients with higher intoxication risk is the best way to diagnose digoxin intoxication. As we found in our study, elder and female patients are at greater risk. Appropriately adjusted digoxin doses based on the patient characteristics and indications are important to prevent this complication and mortality.

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