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# Evaluation of the Relationship of Serum Digoxin Levels with Demographic Data

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## Abstract

**Objective:** We aimed to compare serum digoxin levels and demographic data of patients who presenting with digoxin intoxication.

**Materials and Methods:** This is a retrospective study. Patients admitted to the emergency room with suspected digoxin intoxication included into the study. Patients with missed data, and patients younger than 18 years were excluded.

**Results:** A total of 118 patients were investigated in our retrospective study. Among these, 38 (%32,2) were men and 80 were female (%67,8). Patients with a digoxin level above 2 ng/mL were evaluated for intoxication. Digoxin intoxication was detected in 31 patients (26.3%). Of 31 patients with digoxin intoxication, 19 (61.2%) were hospitalized. Patients who had digoxin intoxication admission complaints were fatigue in 6 patients (19,35%), nausea in 4 patients (12,9%), bradycardia in 4 patients (12,9%), and general condition disorder in 4 patients (12,9%).

**Conclusion:** Blood level in digoxin intoxication may not always be decisive. in suspected digoxin intoxication cases, a detailed anamnesis, physical examination, ECG findings routine electrolyte and other blood tests should be examined and cardiology should be consulted.

**Key words:** Digoxin intoxication, digoxin levels, demographic data, emergency service

## Özet

**Amaç:** Digoksin zehirlenmesi ile başvuran hastaların serum digoksin düzeylerini ve demografik verilerinin karşılaştırılması amaçlanmıştır.

**Gereç ve Yöntem:** Bu çalışma retrospektif olarak planlanmıştır. Acil servise şüpheli digoksin zehirlenmesi şikayeti ile başvuran hastalar çalışmaya dahil edildi. Verilerine ulaşılamayan veya 18 yaşından küçük hastalar çalışma dışı bırakıldı.

**Bulgular:** Retrospektif çalışmamızda toplam 118 hasta incelendi. Bunlardan 38'i (% 32,2) erkek, 80'i kadındı (% 67,8). Digoksin seviyesi 2 ng / mL'nin üzerinde olan hastalar zehirlenme açısından değerlendirildi. Digoksin zehirlenmesi 31 hastada (% 26.3) tespit edildi. Digoksin zehirlenmesi olan 31 hastanın 19'u (% 61,2) hastaneye yatırıldı. Digoksin intoksikasyon başvuru şikayeti olan hastalar 6 hastada (% 19,35) yorgunluk, 4 hastada (% 12,9) bulantı, 4 hastada (% 12,9) bradikardi ve 4 hastada (12,9) genel durum bozukluğu mevcuttu.

**Sonuç:** Digoksin zehirlenmesinde kan seviyesi her zaman belirleyici olmayabilir. Şüpheli digoksin zehirlenmesi vakalarında, ayrıntılı bir anamnez, fizik muayene, EKG bulguları rutin elektrolit ve diğer kan testleri incelenmeli ve kardiyoloji kliniğine konsültasyon planlanmalıdır.

**Anahtar kelimeler:** Digoksin zehirlenmesi, digoksin seviyeleri, demografik veriler, acil servis

## Introduction

Digital glycosides shows the inotropic effect by inactivating Na-K ATPase pump by binding to specific receptors in the cell membrane. Sodium - Calcium exchange increases intracellular calcium ion concentration; calcium increases contractility and occurs a positive inotropic effect. This physiological state increases cardiac output and stroke volume. Ejection fraction increases, ventricular wall tension decreases, heart rate decreases and oxygen consumption decreases. Kidney blood flow and glomerular filtration rate increases, edema decreases. With parasympathetic effect, the ventricular response is suppressed in supraventricular tachycardia[1-4]. Digoxin is absorbed from the gastrointestinal system by passive diffusion, excreted by glomerular filtration from the kidneys, very few are metabolized in the liver and undergoes renal tubular secretion. Safe dosage range are narrow medications[4]. Sinoatrial block, AV block, atrial and ventricular arrhythmias, ectopia, hyperkalemia, confusion, nausea, anorexia and color vision disorders are among the side effects. Tissue levels and blood levels are different, even at the treatment dose of poisoning findings can be observed. Toxicity is associated with tissue level. While the blood levels of digoxin are generally high in acute toxicities, digoxin blood level in chronic toxicities is normal or slightly higher. Factors affecting the occurrence of toxicity findings

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in chronic poisoning; metabolic and electrolyte abnormalities, hypokalemia, hypomagnesemia, hypercalcemia, myocardial ischemia, old age, renal dysfunction, liver disease, hypothyroidism, chronic obstructive pulmonary disease, drug interactions[4-7].

Today, it is used in the treatment of heart failure and atrial fibrillation[8, 9]. Intravenous digoxin or amiodarone with grade IIa (level of evidence B) was recommended to slow the heart rate in a new-onset high-speed AF-Acute or Chronic Heart Failure[10]. Digoxin concentration according to DIG (Digitalis Investigation Group) study data; mortality increased in patients with ≥1,2 ng / mL[11].

According to the ACC (American College of Cardiology); digoxin should be started at doses between 0.125 and 0.25 mg / day. Therapeutic serum concentrations were 0.6-1.2 ng / mL. In older patients, the use of digoxin at low doses (day-by-day or 0.125 mg daily) was suggested in patients with impaired renal function or low body mass index[4, 12].

Digoxin intoxication is an important health problem in our country that causes mortality and morbidity. In this study we aimed to compare serum digoxin levels and demographic data of patients who presenting with digoxin intoxication.

## Materials and Methods

This was a retrospective study including patients over 18 years of age who were admitted to the Clinic of Emergency Medicine of University of University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey with suspected digoxin intoxication between 01.01.2017 and 01.01.2019.

On admission to the emergency department, blood samples were evaluated. With digoxin level in the blood, urea, creatinine, potassium, calcium and magnesium levels, hospitalization, ECG findings and mortality status were evaluated.

The data obtained were analyzed using the SPSS v25 (SPSS Inc, Chicago, IL) program package. The Kolmogorov-Smirnov and the Shapiro-Wilk tests were used to analyze the compliance to the normal distribution, and the chi-square and t-tests were used for the remaining analyses. The quantitative data were expressed as mean, standard deviation (SD) and median (minimum – maximum value), and the qualitative data were expressed as case number (n) and percentages (%). The outcomes were evaluated in 95% confidence interval and the significance was accepted at a level of $p<0.05$.

## Results

A total of 118 patients were investigated in our retrospective study. Among these, 38 (%32,2) were male and 80 were female (%67,8). The median age was 76,5 (70,0 – 83,0). 53 (44.9%) patients were hospitalized. Of these, 23 (43.3%) were male; 30 (56.6%) were female. 65 (55.1%) patients were discharged. Two patients (1.7%) died during hospitalization. One of them was male and the other was female. (Table.1)

**Table 1.** Demografic Data-Digoxin Levels-Laboratory Findings

| | | Normal | High | Total |
|---|---|---|---|---|
| **Age** | | 75,0 (69,0 – 82,0) | 80,0 (74,0 – 85,0) | 76,5 (70,0 – 83,0) |
| **Gender** | Female | 55 (%46,6) | 25 (%21,2) | 80 (%67,8) |
| | Male | 32 (%27,1) | 6 (%5,1) | 38 (%32,2) |
| **Digoxin Levels** | | 0,73 (0,42 – 1,16) | 2,81 (2,42 – 3,74) | 1,06 (0,57 – 2,12) |
| **BUN** | | 49,20 (38,50 – 79,15) | 72,70 (48,11 – 109,00) | 53,50 (38,50 – 85,60) |
| **Creatinin** | | 0,90 (0,80 – 1,30) | 1,10 (0,99 – 1,91) | 1,04 (0,80 – 1,50) |
| **Potasium** | | 4,3 (3,9 – 4,8) | 4,8 (4,2 – 5,3) | 4,40 (4,00 – 5,00) |
| **ECG Finding** | No | 23 (%19,5) | 4 (%3,4) | 27 (%22,9) |
| | Yes | 64 (%54,2) | 27 (%22,9) | 91 (%77,1) |
| **Hospitalization** | No | 53 (%44,9) | 12 (%10,2) | 65 (%55,1) |
| | Yes | 34 (%28,8) | 19 (%16,1) | 53 (%44,9) |
| **Mortality** | No | 85 (%72,0) | 31 (%26,3) | 116 (%98,3) |
| | yes | 2 (%1,7) | 0 (%0) | 2 (%1,7) |

**Table 2.** Digoxin Levels and Hospitalization

| | | Hospitalization | | Total |
|---|---|---|---|---|
| | | No | Yes | p=0.033 |
| **Digoxin Levels** | Normal | 53 | 34 | 87 |
| | High | 12 | 19 | 31 |
| **Total** | | 65 | 53 | 118 |

Patients with a digoxin level above 2 (ng/ml) were evaluated for intoxication. Digoxin intoxication was detected in 31 patients (26.3%). 25 (%21,2) of them were female; 6 (%5,1) of them were male. Of 31 patients with digoxin intoxication, 19 (61.2%) were hospitalized. Of these, 5 (16.1%) were male; 14 (45.1%) were female. Patients with high digoxin levels had significantly higher hospitalization rates (p=0.033). (Table.2)

The admission complaints of patients, who had digoxin intoxication, were fatigue in 6 patients (19,35%), nausea in 4 patients (12,9%), bradycardia in 4 patients (12,9%), and general condition disorder in 4 patients (12,9%). 4 patient was unconsciousness (12.9%) and 3 patients had shortness of breathness (9.6%) One patient was admitted with seizure, one patient with chest pain, one patient with dizziness, one patient with edema and one patient with aphasia (3.2%).

The most common ECG finding was Atrial fibrillation (AF). 12 patients (38.7%) had AF. 5 patients (16,12 %) had bradycardia. ECG was normal in 4 (12.9%) patients. Comorbidities: coronary artery disease in 6 (19.3%) patients; atrial fibrillation in 5 (16,12%) patients, diabetes mellitus and atrial fibrillation in 3 (9,6%) patients; hypertension, diabetes mellitus and coronary artery disease in 2 (6,4%) patients. There was also diabetes mellitus and congestive heart failure in 2 (6,4%) patients. Patients with abnormal ECG findings had significantly higher hospitalization rates than the others (p=0.007). (Table.3)

## Discussion

Since the safety interval of the digitals is narrow, poisoning is divided into acute and chronic toxicity. In a patient presenting with emergency service, vomiting, weakness, bradyarrhythmia, atrioventricular block and supraventricular arrhythmia, digoxin poisoning should be questioned. Routine blood tests of these patients should be evaluated. These patients should be monitored. However, the severity of signs of intoxication and digoxin blood levels are not always proportional. Because the tissue levels of digoxin are different from blood levels, signs of poisoning can be observed even at the treatment dose. Toxicity is associated with tissue level. While the blood levels of digoxin in acute toxicities are generally high, digoxin blood level in chronic toxicities is normal or slightly high.

It is known that the absorption rate of the standard tablet formulations of digoxin can be as high as 50-70% and the absorption rate of the solution in gelatin capsule can be as high as 100%. Digoxin is excreted primarily by glomerular filtration from the kidneys and metabolized in the liver and conjugated to inactive metabolites. The protein binding rate is low and varies between 20-30%. The distribution of adipose tissue is insignificant. Can cross the blood-brain barrier and the placenta. The distribution volume of digoxin is large and the distribution in adults is approximately 5 L / kg. The half-life at the treatment dose is 36-48 hours. This period may be prolonged in patients with low glomerular filtration rate[1, 4, 6, 7, 13].

**Table 3.** ECG findings and Hospitalization

| | | Hospitalization | | Total |
|---|---|---|---|---|
| | | No | Yes | p=0.007 |
| **ECG Finding** | No | 21 | 6 | 27 |
| | Yes | 44 | 47 | 91 |
| **Total** | | 65 | 53 | 118 |

In the last 2 years, drug levels were studied in 118 patients and only 31 patients had high levels of digoxin. Of the 31 patients, only 19 were hospitalized. Of the 87 patients with normal or low digoxin levels, 34 were hospitalized for various reasons. It should be calculated that some patients may have different history due to neurological problems, and that drug intake may not be fully known by their relatives. Tissue distribution, glomerular filtration rate, acute-chronic toxicity symptoms and differences in digoxin levels should be kept in mind in cases where intoxication is considered.

The most important cardiac finding of digital poisoning is rhythm disturbances manifested as tachyarrhythmias and conduction blocks. The cause of death is usually ventricular tachycardia or ventricular fibrillation. Cardiac glycosides generally cause A-V (atrioventricular) block of all degrees up to the full block, but rarely form a sinoatrial node block. In cases where the patient cannot be monitored by ECG (electrocardiography), if the pulse falls below 60, is considered to be the A-V block[2, 4, 7, 14].

In our study, in inpatients the most common ECG finding was Atrial fibrillation (AF). 12 patients (38.7%) had AF and 5 patients (16,12 %) had bradycardia. Patients with abnormal ECG findings had significantly higher hospitalization rates than the others (p=0.007). However, the normal ECG should not mean that there is no intoxication.

High serum potassium levels in acute digoxin poisoning is a good predictor of organ toxicity. In acute digoxin intoxications, the patient may be asymptomatic within the first few hours[4, 6, 7].

While the level of digoxin blood is generally high in acute toxicity, digoxin blood level in chronic toxicities is normal or slightly high[4, 6, 7]. In a study in which digoxin levels were found to be normal but patients with symptoms and clinically intoxication were considered, coronary artery disease was more common in the toxic group. There was no significant difference in other data.[15]

In another study that investigated the effect of digoxin use on hospital admission and prognosis, 3397 patients with heart failure were treated with digoxin. 3403 patients were treated with angiotensin converting enzyme inhibitors and diuretics. It was determined that digoxin did not decrease mortality but prevented hospitalization and clinical deterioration[16].

This study has certain limitations. Firstly, the relatively low number of evaluated cases may be considered as a limitation. It is necessary to undertake a further study with a higher number of cases to obtain more reliable results. If the drugs used by the patients were known, the rate of hospitalization of patients using drugs that changed serum digoxin levels could also be investigated. This situation also can be considered as a limitation.

## Conclusion

As a matter of fact, blood level in digoxin intoxication may not always be decisive. After a detailed anamnesis, physical examination, ECG findings should be followed, routine electrolyte and other blood tests should be examined and cardiology should be consulted.

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