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ÖZGÜN MAKALE/ORIGINAL ARTICLE

DIGOXIN TOXICITY IN THERAPEUTIC SERUM LEVELS

Terapötik Serum Seviyesinde Digoksin Toksisitesi

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ABSTRACT

Aim: The purpose of this study, to evaluate digoxin toxicity and risk factors leading to digoxin toxicity in patients with therapeutic digoxin levels.

Material and Methods: We studied ninety–five patients with digoxin level was above of the 1.4 ng/mL and below of the 2.0 ng/mL at admission. They were divided into two groups, drug toxicity or nontoxicity, on the basis of both clinical symptoms and electrocardiography recording. The clinical and laboratory data were compared between these groups.

Results: When overall patients' digoxin usage indications were evaluated, it was revealed that 56 patients (58.9%) had been received digoxin only for heart failure, 32 patients (33.6%) only for atrial fibrillation and 20 patients (21%) received digoxin for both conditions. The exact reason for digoxin usage could not be determined in 17 patients (17.9%). When patients were evaluated, no differences in age, gender, medical history other than coronary artery disease and laboratory findings were observed between toxic and nontoxic patients. The medical history of coronary artery disease in toxic patients was significantly higher than in nontoxic patients (p: 0.008). In these variable, no differences were observed except atrial fibrillation (p<0.001), between toxic and nontoxic patients.

Conclusion: In this study, the exact reasons for digoxin use could not be determined in 17 (17.9%) patients. In appropriate usage of digoxin could be increased risk of adverse outcomes and education program may reduce in appropriate use. Clinicians should be aware that signs of toxicity may occur at levels below of the 2.0 ng/mL, and such toxicity is more likely in the presence of atrial fibrillation or coronary artery disease.

Keywords: Digoxin, toxicity, intoxication, serum digoxin levels

ÖZET

Amaç: Bu çalışmanın amacı terapötik seviyede digoksin seviyesi olan hastalarda digoksin toksisitesi ve risk faktörlerini araştırmak.

Metot: Başvuru sırasında digoksin seviyesi 1,4 ng/mL'nin üzerinde ve 2,0 ng/mL'nin altında olan 95 hasta klinik belirti ve elektrokardiyografi kayıtları göz önüne alınarak toksisite olan ve toksisite olmayan olarak iki gruba ayrıldı. Klinik ve laboratuar verileri iki grup arasında karşılaştırıldı.

Bulgular: Tüm hastalar digoksin kullanma endikasyonu açısından değerlendirildiğinde 56 hasta (58,9%) sadece sol kalp yetersizliği, 32 hasta (33,6%) atriyal fibrilasyon ve 20 hasta (21%) her iki durum için kullanıyorlardı. 17 hastada (17,9%) ise digoksin kullanımının net bir nedeni, bulunamadı. Toksik ve toksik olmayan grup arasında yaş, cinsiyet, koroner arter hastalığı dışındaki medikal öykü ve laboratuar bulguları açısından fark yoktu. Sadece koroner arter hastalığı öyküsü anlamlı şekilde toksik grupta fazla saptandı (p:0,008). Atriyal fibrilasyon (p<0,001) dışında toksik ve toksik olmayan hastalar arasında fark yoktu.

Sonuç: Bu çalışmada 17 (17,9%) hastada digoksin kullanımı için net bir endikasyon saptanamamıştır. Uygunsuz digoksin kullanımı istenmeyen yan etkilerin artışına sebep olabilir ve eğitim programları uygunsuz kullanımı azaltabilir. Klinisyenler toksisite belirtilerinin 2,0 ng/mL'nin altında olabileceğinin farkında olmalı ve toksisite koroner arter hastalığı öyküsü ve atriyal fibrilasyon varlığında daha olasıdır

Anahtar kelimeler: Digoksin, toksisite, intoksikasyon, serum digoksin düzeyleri

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INTRODUCTION

Digoxin had been used for the main treatment of heart failure and arrhythmia for many decades (1, 2), until it was shown that the digoxin does not have a survival advantage (3) and further development of effective cardiac drugs has led to diminished utilization. Estimates of digoxin use in heart failure have decreased from approximately 80% to <30% in the past decade (4, 5). Conversely, the absence of downward trend in the incidence of digoxin toxicity and the frequency of emergency department admissions related to digoxin toxicity has remained relatively unchanged (6, 7).

The recommended therapeutic range of digoxin has changed in the past decade after the post hoc analyses of the Digitalis Investigation Group (DIG) study, which found that digoxin at a serum concentration of 0.5-0.9 ng/mL was associated with reduce total mortality (4), while the 2 ng/mL value still has using in aiding the diagnosis of digoxin toxicity, but many patients show signs and/or symptoms of digoxin toxicity even when the serum digoxin concentration (SDC) is below the this value. (8, 9) We recently became aware of a large number of our patients with serum digoxin levels lower than the 2.0 ng/mL, had digoxin toxicity. The purpose of this study was to evaluate in accepted therapeutic range patients to identify risk factors leading to digoxin toxicity in the modern era.

MATERIAL AND METHODS

The medical records of all patients receiving digoxin maintenance therapy at Dışkapı Research and Education Hospital (a tertiary center, 355000 patients' admission yearly) between January 2009 and January 2011 were reviewed. All of the patients were eligible if they were ≥ 18 years old and SDCs above of the 1.4ng/ml and below of the 2.0ng/ml. Data extracted from the medical records included age, demographic features, sign and symptoms, primary and secondary diagnoses, indications for digoxin use, laboratory data including serum creatinine and electrolytes, chest radiography, electrocardiography (ECG) and transthoracic echocardiography (TTE) data. The diagnosis of coronary artery disease was made according to the history of myocardial infarction or interventions (CABG operation or Percutaneous Coronary Interventions). Also diagnosis of chronic kidney disease was made according to the creatinine levels higher than 1.2 mg/ml. Digoxin use was considered in appropriate if the patient had cardiothoracic ratio below to 50% in chest radiography or normal TTE and normal ECG.

Digoxin levels were measured specific radioimmunoassay method (Gammacoat Digoxin, Baxter, France). Digoxin toxicity was defined as the development of signs or symptoms commonly associated with digoxin toxicity that resolved after a decrease in digoxin dosage and/or withdrawal. The occurrence of one or both of following criteria was used to support a diagnosis of digoxin toxicity, and all subjects were involved: (I) nausea, anorexia, vomiting, and/or disturbed color vision (green or yellow halos around lights); and (II) arrhythmias that were not present before the onset of digoxin therapy and/or resolved on withholding of the drug, that is, premature ventricular contraction with

periodic or persistent bigeminy or trigeminy, second-degree AV block of Mobitz type II, AV nodal escape rhythm, paroxysmal atrial tachycardia with block, and non-paroxysmal AV nodal tachycardia at a rate of 100-200 beat/min. The patients who digoxin level was above of the 1.4 ng/mL and below of the 2.0 ng/mL at admission were divided into two groups, drug toxicity or nontoxicity, on the basis of both clinical symptoms and ECG recording by three years experienced cardiologist. The clinical and laboratory data were compared between these groups. Our study was approved by the local ethics committee.

All analyses were conducted using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). Data were shown as mean ± SD or median (IQR), where applicable. The normality of the distribution was evaluated with the Kolmogonov-Smirnow test. Chi-square test was used to compare categorical data. Group means were compared by the student T-test for unpaired data. A two-sided value of p value < 0.05 was considered to be statistically significant.

RESULTS

During the study period, 12.430 digoxin assays were obtained on 5.340 patients. One hundred thirty one patients (%2.4) had serum digoxin concentrations greater than 1.4 ng/mL and lower than 2.0 ng/mL. Complete clinical data were available for 100 of these patients, 5 of whom had an elevated level due to sampling error (SDC drawn within 6 hours of oral dose). Thus, 95 (%2) patients had appropriately sampled digoxin assays with a level greater than level of the 1.4 ng/mL and lower than level of the 2.0 ng/mL. The overall average of age was 70.1±10.2 years with 50 (52.6%) of the patients ≥75 years old. The patients mean SDC was 1.6 ng/mL. Digoxin toxicity was the primary reason for admission at emergency service in 20 of these cases. Heart failure (n: 30) and slow or fast atrial fibrillation (n: 25) were other frequent reasons for admissions.

Twenty-two patients had both ECG and clinical features suggestive of digoxin toxicity, while eleven patients had clinical symptoms alone. Clinical features of digoxin toxicity included nausea, anorexia and vomiting (n: 32) and disturbed color vision (n: 3). One patient was asymptomatic at admission and had ECG features of digoxin toxicity. Withdrawal of digoxin was associated with improvement in ECG (paroxysmal atrial tachycardia with block). Frequent ECG features of concomitant digoxin toxicity were ventricular premature contraction and periodic or persistent bigeminy or trigeminy (n: 22). Table 1 summarizes the demographic and clinical data for toxic and nontoxic patients. When data patients were evaluated, no differences in age, gender, medical history other than coronary artery disease, laboratory findings were observed between toxic and nontoxic patients. The only medical history of coronary artery disease in toxic patients was significantly higher than in nontoxic patients (p: 0.008).

Table 1: Demographic and Clinical Data in Patient with SDCs>1.4 ng/mL and<2.0 ng/Ml*

	DigoxinToxic(N=34)	NonToxic (N=61)	P value
No. of patient (%)	34 (35.8)	61(64.2)	
Age (yr)	74.3±10.6	74.0±10.3	0.883
Female % (n)	50 (17)	62 (38)	0.172
Medical history% (n)			
Coronary artery disease	76.4 (26)	49.2 (30)	**0.008**
Hypertension	70 (24)	68.8 (42)	0.526
Diabetes mellitus	35.2 (12)	24.5 (15)	0.191
Chronic kidney disease	35.2 (12)	37.7(23)	0.494
Laboratory findings			
SDC (ng/mL)	1.6 (1.4-1.9)	1,6 (1.4-1.9)	0.423
Creatinine (mg/dL)	1.4 ± 0.5	1.4 ± 0.6	0.666
Potassium (mEq/dL)	4.8 ± 0,9	4.8 ± 1.0	0.655
Calcium (mEq/dL)	9.1 ± 1,6	9.3 ± 1.3	0.408

BUN: blood urea nitrogen; SDC: serum digoxin concentration. *Data are presented mean ± SD or range and % (n).

When overall patients' digoxin usage indications were evaluated, it was revealed that 56 patients (58.9%) had been received digoxin only heart failure, 32 patients (33.6%) only atrial fibrillation and 20 patients (21%) received digoxin both conditions. The exact reason for digoxin use could not be determined in 17 patients (17.9%). **Table 2** summarizes digoxin usage indication for toxic and nontoxic patients. In these variable no differences were observed other than atrial fibrillation (p<0.001), between toxic and nontoxic patients.

Table 2: Digoxin usage indications for Toxic and Nontoxic Patients

	Toxic(N=34)	Nontoxic(N=61)	P value
Atrialfibrillation	76.4% (26)	9.8% (6)	**<0.0001**
Heartfailure	52.9% (18)	62.2% (38)	0.251
Other	35.2% (12)	24.6% (15)	0.191

Other groups consist of both atrial fibrillation and heart failure patients (n: 20) and digoxin use indications could not be determined patients (n: 17). *Data are presented % (n).

DISCUSSION

In the modern era, the evolution of knowledge regarding the clinical use of digoxin has resulted in a declining frequency and a different profile of digoxin toxicity. Toxicity is usually associated with an elevated SDC simply because they received a dosage that was too high (according to their renal function) or an electrolyte abnormality such as hypokalemia (10, 11). SDCs are not always a good indicator of toxicity, there is some overlap in 'therapeutic' and 'toxic' levels (12). This overlap zone (SDCs 1.4-2.0 mg/mL) is not evaluated

properly yet. In our study, this overlap zone of the patients' ratio was 2.4%.

The clinicians should be aware of that the signs of the toxicity of digoxin may occur at below the serum level of the 2.0 ng/mL. Also, it is more encountered in the presence of comorbid conditions such as myocardial ischemia, hypokalemia and hypercalcemia (5, 11, 13). In our study, we found that in patients with SDCs between 1.4 and 2.0 mg/mL, AF and Coronary Artery disease was found associated with the toxicity. Beller et al suggested that myocardial ischemia, itself may cause inhibition of sodium pump providing myocardial tissue more sensitive to the arrhythmogenic effects of digitalis, even at lower SDC (14). Therefore, digoxins hould be used in very low doses or not be used at all in patients with acute coronary syndromes or significant ischemia. The effect of digoxin or other rate –control drugs on mortality in atrial fibrillation (AF) has not been examined in randomized clinical trials. Post hocanalysis of the atrial fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial data reported in 2004 and 2012 suggested that digoxin use was associated with higher all-cause mortality (15, 16). In this study, we found digoxin in toxication was higher in patient with AF despite the SDC below to 2.0 ng/mL ($p<0.001$). This may explain the higher mortality in patients with AF in AFFIRM post hoc analysis.

In our study, the exact reasons for digoxin use could not be explained in 17 (17.9%) patients. We think about that the indications for digoxin therapy were not appropriate; the digoxin therapy might have been administered only for temporarily occurred AF and did not persist. Biteker et al. reported that the 40% of patients use the digoxin in an inconvenient indication (17). In appropriate usage of digoxin can increase the risk of adverse outcomes and education program may be required.

There were some limitations for this study. Firstly, creatinine levels were similar between the toxic and nontoxic groups, but lack of eGFR data of patients has limitation that must be addressed in the future studies. Secondly, this was a retrospective study and the study population was from a single center. However, in the modern era digoxin levels not evaluate routinely so patients with high normal level SDC is becoming extremely rare and it is hard to recruit these cases.

In conclusion, digoxin has cost-effectiveness and easy available worldwide, therefore digoxin should not be considered a drug of past but rather a drug of present and even one of the future. Clinicians should be aware that signs of toxicity may occur at levels below of the 2.0 ng/mL, and such toxicity is more likely in the presence of atrial fibrillation or coronary artery disease. Prospective studies are warranted in order to confirm these associations.

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