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Serum Urea and Creatinine Levels are Better Predictors of Mortality than Serum Potassium Levels in Chronic Digoxin Toxicity

Turgay Yılmaz Kilic, MD[1*]; Murat Yesilaras, MD[2]; Ibrahim Toker, MD[3]; Ozge Duman Atilla, MD[2]; Feriyde Caliskan, MD[1]; Selim Ekinci, MD[4]

[1]*Attending Physician of Emergency Medicine, Department of Emergency Medicine, Tepecik Training and Research Hospital, Izmir, Turkey*
[2]*Associate Professor of Emergency Medicine, Department of Emergency Medicine, Tepecik Training and Research Hospital, Izmir, Turkey*
[3]*Attending Physician of Emergency Medicine, Emergency Service, Tire State Hospital, Izmir, Turkey*
[4]*Attending Physician of Cardiology, Department of Cardiology, Tepecik Training and Research Hospital, Izmir, Turkey*

[*]***Corresponding author***
Turgay Yılmaz Kilic, MD
Department of Emergency Medicine, Tepecik Training and Research Hospital, Gaziler Caddesi, Yenisehir, 35120, Izmir/Turkey
Tel. 2324696969; Fax: 2324594788; E-mail: turgayyilmaz.kilic@gmail.com

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ABSTRACT

Objective
Hyperpotassemia is known to have critical importance in acute digoxin intoxication. However, few studies have focused on the effects of serum urea, creatinine and potassium levels on the clinical prognosis of chronic digoxin intoxication. Our aim in this study was to investigate the relationship between serum urea, creatinine and potassium levels and mortality in patients with chronic digoxin toxicity.

Methods
Between January 2010 and May 2015, patients with chronic digoxin toxicity with serum digoxin levels of 2 ng/mL and above were screened retrospectively. Patients were divided into two groups according to their serum digoxin levels; Group 1 consisted of patients with digoxin levels between 2-4.9 ng/mL, Group 2 consisted of patients with digoxin levels of 5 ng/mL and above. The relationship between serum potassium, urea and creatinine levels and mortality was examined.

Results
Of the 307 patients were included, 10.1% (n = 31) were found to have died. In the analysis of survivors and non-survivors, the areas under the receiver operating characteristic curve were found to be 0.64, 0.73, 0.66 and 0.83 for serum digoxin, urea, creatinine and potassium values, respectively. The odds ratios calculated for the determined cut-off values were 2.8 for digoxin≥3.05 ng/mL, 4.8 for potassium≥5 mmol/L, 9.7 for creatinine≥1.75 mg/dL and 9.4 for urea≥100 mg/dL.

Conclusion
In patients with chronic digoxin toxicity, serum urea and creatinine values predict mortality better than serum potassium and digoxin levels.

Keywords
Digoxin toxicity, mortality, potassium, creatinine, urea.

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INTRODUCTION

Digoxin is a cardiotonic drug that produces positive inotropic, negative chronotropic and negative dromotropic effects by sodium-potassium ATPase inhibition.[1,2] The most important factor limiting its use is its narrow therapeutic index.[3] Though digoxin use has decreased in the last few decades, the number of digoxin toxicity cases has not decreased accordingly.[4]

Compared with acute digoxin toxicity, chronic digoxin toxicity is more frequent. The majority of these patients are diagnosed and treated in the emergency departments (ED) where they initially present. Therefore, it is important for emergency physicians to predict the prognosis of patients with chronic digoxin toxicity.

Hyperpotassemia is the most common electrolyte abnormality observed in digoxin toxicity and is associated with poor prognosis.[4] Especially in acute digoxin poisoning, hyperpotassemia has critical importance. In addition to elevated serum potassium (K+) levels, increased serum creatinine and urea levels have also been reported to be cardiotoxic.[5] However, the effect of potassium, creatinine and urea elevation on the clinical course of chronic digoxin poisoning has not been fully elucidated.[6,7,8] Our aim in this study was to investigate the relationship between serum urea, creatinine and potassium levels and mortality in patients with chronic digoxin toxicity.

MATERIALS AND METHODS

This retrospective study was conducted between June 2010 and May 2015 at a tertiary urban ED with an annual admission rate of nearly 200,000. Ethical committee approval was waived due to the retrospective nature of the study.

The institutional electronic medical record system was searched to identify patients 18 years and older whose serum digoxin levels were measured during their ED visit. All electronic and paper medical records of the patients were reviewed by 2 emergency medicine specialists and a cardiologist. Patients with acute digoxin toxicity and patients with serum digoxin levels below 2 ng/dL who have a low possibility of chronic digoxin toxicity were excluded. In addition, patients with hemolyzed blood samples (causing a false elevation of serum K+) and patients whose laboratory results (serum K+, urea, creatinine, and digoxin levels) were missing in the medical records were not included in the study.

Excessive digoxin ingestion within 24 hours prior to ED admission was defined as acute digoxin toxicity. The diagnosis of chronic digoxin toxicity was based on clinical and/or electrocardiographic (ECG) manifestations accompanying elevated serum digoxin concentrations (≥2 ng/mL). Hyperpotassemia was defined as serum K+≥5 mmol/L in a non-hemolyzed blood sample. Abnormal ECG findings were defined as documented in the medical records. The patients were divided into two groups according to their serum digoxin levels; Group 1: digoxin level 2-4.9 ng/mL, and Group 2: digoxin level ≥5 ng/mL. The age, gender; history of exposure (acute vs chronic); the initial serum blood samples results: serum digoxin, potassium, creatinine and urea levels; electrocardiographic manifestations; patients outcome (survive vs non-survive) and mortality time were recorded on the data collection form.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 22.0 (SPSS Inc., IL, USA). The power of the study (98%) was calculated according to the relationship between serum potassium levels and mortality. The Kolmogorov-Smirnov test showed non-normal distribution. Qualitative data were expressed in terms of frequency. Quantitative data were expressed as median and interquartile range (IQR). For the analysis of quantitative data, Mann-Whitney U test and Spearman correlation test were used. For the analysis of qualitative data, Chi-square test was used. Receiver operating characteristic (ROC) analysis was performed to determine the threshold values for serum digoxin, K+, urea and creatinine levels in survivors and non-survivors. All statistical analyses were performed at a 95% confidence interval. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 2052 patients whose digoxin levels were measured during their ED evaluation were enrolled. Of these, 1716 patients with serum digoxin levels below 2 ng/mL were excluded from the study. In addition, 24 patients whose serum K+ levels were not available, 2 patients whose creatinine levels were not available and 3 patients with acute toxicity were excluded from the study. As a result, the study was conducted with 307 patients.

The median age was 76 years (IQR:14, range:47-107) and 68.1% of the patients (n=209) were female. The relationships between gender, age, serum digoxin level, and mortality are shown in Table 1. The median mortality time was 4 (IQR=11; min:0, max: 54) days. The median serum creatinine level was 1.4 mg/dL (IQR:0.8; range:0.1-13), the median serum urea level was 67 mg/dL (IQR:52; range:14-432) and the median serum K+ level was 4.6 mmol/L (IQR:1; range:3.1-8.8).

In 9.4% (n=29) of patients, serum digoxin levels were found to be 5 ng/mL and above. The median serum digoxin levels of the patients in the first and second groups were 2.7 ng/mL (IQR:1.3) and 5.8 ng/mL (IQR:1.9), respectively. Regarding the serum digoxin levels, 26 (9.4%) patients in the first group and 5 (17%) patients in the second group were found to have died (p=0.192). The patients data of the two groups are presented in Table 2.

No significant correlation was found between serum digoxin and K+ values (r=0.081, p=0.078). It was found that 10.1% (n=31) of the patients had died. The median serum digoxin levels were 3.6 ng/mL (IQR:2.1) in patients who had died and 2.8 ng/mL (IQR:1.5) in patients who survived (p=0.009). Serum urea, creatinine and K+ levels of the survivors and non-survivors are presented in Table 3.

Receiver operating characteristic analysis was performed

Table 1. *The association between gender and age factors with blood digoxin levels and mortality.*

	Female (n)	Male (n)	p value (two sided)	Age (median, year) (IQR)	p value (two sided)
Group 1 (Digoxin 2-4.9 ng/ml)	**189 (%61.6)**	**89 (%29)**	1	76 (14)	0.273
Group 2 (Digoxin≥5 ng/ml)	**20 (%6.5)**	**9 (%2.9)**		78 (13)	
Dead patients	**21 (%6.8)**	**10 (%3.3)**	1	81 (8)	0.026
Alive patients	**188 (%61.2)**	**88 (%28.7)**		76 (14)	

Table 2. *The electrolytes and renal function tests of patients in groups 1 and 2.*

	Group 1 (n=278, %90.6) (median, mg/dl) (IQR)	Group 2 (n=29, %9.4) (median, mg/dl) (IQR)	p value (two sided)
Potassium (mmol/L)	**4.6 (1)**	**5 (1.5)**	**0.177**
Sodium (mmol/L)	**136 (7)**	**135 (10)**	**0.633**
Calcium (mg/dl)	**9.1 (0.9)**	**9.2 (1.1)**	**0.114**
Creatinin (mg/dl)	**1.4 (0.7)**	**1.8 (1.5)**	**0.001**
Urea (mg/dl)	**65 (46)**	**119 (131)**	**<0.001**

Table 3. *The electrolytes and renal function tests of dead and alive patients.*

	Dead patients (n=31, %10.1) (median, mg/dl) (IQR)	Alive patients (n=276, %89.9) (median, mg/dl) (IQR)	p value (two sided)
Potassium (mmol/L)	**5.4 (1.4)**	**4.6 (0.9)**	**<0.001**
Sodium (mmol/L)	**134 (12)**	**136 (6)**	**0.064**
Calcium (mg/dl)	**8.7 (0.9)**	**9.1 (0.8)**	**0.005**
Creatinin (mg/dl)	**2.3 (1.8)**	**1.4 (0.7)**	**<0.001**
Urea (mg/dl)	**123 (147)**	**65 (44)**	**<0.001**

Table 4. *The odd ratios for determined cutting values.*

	Odd Ratio	Confidence interval	p value (two sided)
Digoxin≥3.05 ng/ml	**2.0**	**1.0-4.3**	**0.083**
Potassium≥5.0 mmol/L	**4.8**	**2.2 - 10.6**	**<0.0001**
Creatinin≥1.75 mg/dl	**7.2**	**3.2 - 16.4**	**<0.0001**
Urea≥100 mg/dl	**9.4**	**4.1 - 31.5**	**<0.0001**
Calcium≤8.86 mg/dl	**3.1**	**1.4 - 6.7**	**0.004**

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DISCUSSION

Our aim in this study was to investigate the relationship between serum digoxin, urea, creatinine, K+ levels and mortality in patients with chronic digoxin toxicity (serum digoxin level≥2 ng/mL). The relationship between these parameters and mortality was determined to determine the threshold values for serum digoxin, K+, urea and creatinine levels of the survivors and non-survivors. The areas under the ROC curve and confidence intervals for serum digoxin, K+, urea and creatinine levels were measured as 0.643 (0.544-0.742), 0.729 (0.625-0.832), 0.830 (0.765-0.895) and 0.791 (0.705-0.878), respectively. Based on these data, the cut-off values were defined as values with the closest sensitivity and specificity. The odds ratios (OR) for the determined cut-off values are presented in Table 4.

by examining the OR values calculated for the cut-off values derived from the ROC curve. Serum urea and creatinine levels were found to be more strongly associated with mortality compared to serum potassium levels. No significant relationship was found between digoxin level and mortality.

Hyperpotassemia is a major manifestation of acute glycoside toxicity caused by the inhibition of sodium-potassium-ATPase in heart and skeletal muscles, leading to an increase in extracellular potassium.[4,8] However, hyperpotassemia itself is not regarded as a cause of mortality.[2] Theoretically, because it triggers dysrhythmias, hyperpotassemia is considered to have cardiotoxic effects on patients with chronic digoxin intoxication.[8] In their study, Manini et al. have reported that elevated serum potassium levels in chronic digoxin intoxication are fatal, even for patients receiving Fab therapy.[8] In our study, the relationship between mortality and hyperpotassemia was found to be much stronger than the relationship between mortality and digoxin (OR:4.4 vs. 2, respectively).

Digoxin use has been associated with an overall 21% increased relative risk in all-cause mortality compared to patients not receiving this medication.[9] Serum digoxin elevation is shown to be correlated to mortality and cardiotoxicity in hospitalized patients.[5, 10] Rathore et al. demonstrated that digoxin levels higher than 1.2 ng/mL are significantly associated with increased mortality.[11] According to the threshold values derived from the ROC curve in our study, mortality rates did not differ between patients with high and low levels of digoxin.

The cause of toxicity in most digitalized patients is the reduced digoxin clearance caused by renal insufficiency.[8] Chan et al have reported that in patients with end-stage renal failure, increased digoxin levels are associated with mortality.[12] Another study has reported that patients with digoxin poisoning who develop cardiotoxicity have high serum urea and creatinine levels.[5] In our study, urea and creatinine were found to be much strongly related to mortality than potassium.

LIMITATIONS

Because of the retrospective design of this study, it was not possible to ascertain whether the cause of death in non-survivors was digoxin toxicity. Patients were not evaluated for using other medication such as quinidine, verapamil, and propafenone, which may elevate serum digoxin levels. Patients showing signs and symptoms of chronic digoxin toxicity were not included in the study if their digoxin levels were lower than 2 ng/mL. Therefore, the results obtained from this study should not be used as a basis for patients with chronic digoxin toxicity whose serum digoxin level is less than 2 ng/mL. In addition, the results obtained from this study should not be generalized to pediatric patients with chronic digoxin toxicity. The treatment protocols applied to patients with chronic digoxin toxicity were not examined in this study. Another important limitation of this study is its single-centered retrospective design.

CONCLUSION

In patients with chronic digoxin toxicity, serum urea and creatinine values predict mortality better than serum potassium and digoxin levels.

CONFLICTS OF INTEREST

In patients with chronic digoxin toxicity, serum urea and creatinine values predict mortality better than serum potassium and digoxin levels.

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