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Original Article

Evaluating high serum digoxin concentration risk factors, interaction between direct oral anticoagulant agents and digoxin

Yüksek serum digoksin konsantrasyonu risk faktörlerinin değerlendirilmesi, direkt oral antikoagülan ajanlar ve digoksin arasındaki etkileşim

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ABSTRACT

Aim: Digoxin is an anti-arrhythmic drug that also has a positive inotropic property. It is mainly used to control heart rate in nonvalvular atrial fibrillation, and improve ejection fraction in heart failure. In recent years, the frequency of digoxin and a combination of new drug using has been increasing. Therefore, to assess the pharmacokinetic interaction between direct oral anticoagulant agents and cardiovascular drugs is necessary for intoxications.

Material and Methods: Patients Serum Digoxin Concentrations levels and digoxin intoxications were evaluated according to risk factors investigated retrospectively Patients Serum Digoxin Concentrations levels <1 ng/ml is accepted as low, 1-2 ng/ml therapeutic range, 2.1-2.4 ng/ml is high and >2.4 ng/ml toxicity.

Results: The study consisted of 248 females (60.2%) and 160 males (39.2%). The mean age of the patients was 70.5 years. The average age of patients was 70.5 years. Serum digoxin concentrations of 408 patients; 44.81% were detected in the low therapeutic range, 34.41% in the therapeutic range, 6.23% in the high therapeutic range, 14.55% in the toxic therapeutic range. The mean glomerular filtration rate was 58.45, and the mean Serum Digoxin Concentration was 1.36 ng/ml. The statistically significant relationship between age and Patients Serum Digoxin Concentration was 16.3% ($p < 0.05$). There was a statistically significant relationship between Glomerular Filtration Rate and Serum Digoxin Concentrations; one increased and the other decreased ($p < 0.05$). In patients without atherosclerotic heart disease, Serum Digoxin Concentration was significantly lower than those with atherosclerotic heart disease($p < 0.05$). Serum Digoxin Concentrations were significantly higher in patients treated with rivaroxaban, the proportions of which differ significantly from each other at the 0.05 level.

Conclusion: Nowadays, the frequency of using digoxin and direct oral anticoagulants together is increasing. The narrow therapeutic level of digoxin necessitates close monitoring due to drug-drug interactions.

Keywords: Serum digoxin concentration; drug interaction; direct oral anticoagulant

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ÖZ

Amaç: Digoksin, pozitif inotropik özelliğe sahip anti-aritmik bir ilaçtır. Esas olarak valvüler olmayan atriyal fibrilasyonda kalp hızını kontrol etmek ve kalp yetmezliğinde ejeksiyon fraksiyonunu iyileştirmek için kullanılır. Son yıllarda digoksin ve yeni ilaç kombinasyonlarının kullanım sıklığı artmaktadır. Bu nedenle, doğrudan oral antikoagülan ajanlar ile kardiyovasküler ilaçlar arasındaki farmakokinetik etkileşimi değerlendirmek, zehirlenmeler için gereklidir.

Gereç ve Yöntemler: Hastalar Serum Digoksin Konsantrasyonları seviyeleri ve digoksin intoksikasyonları retrospektif risk faktörlerine göre değerlendirildi. Serum Digoxin Konsantrasyonu seviyeleri <1 ng / ml düşük, 1-2 ng / ml tedavi aralığı, 2.1-2.4 ng / ml yüksek ve> 2.4 ng / ml toksisite olarak kabul edilmektedir.

Bulgular: Çalışma 248 kadın (% 60,2) ve 160 erkek hastadan (% 39,2) oluşturuldu. Hastaların ortalama yaşı 70,5 idi. 408 hastanın serum digoksin konsantrasyonları; % 44.81'i düşük terapötik aralıkta, % 34.41'i terapötik aralıkta, % 6.23'ü yüksek terapötik aralıkta, % 14.55'i toksik terapötik aralıkta saptanmıştır. Ortalama glomerüler filtrasyon hızı 58.45 ve ortalama Serum Digoxin Konsantrasyonu 1.36 ng / ml idi. Yaş ile Serum Digoxin Konsantrasyonu arasındaki istatistiksel olarak anlamlı ilişki % 16,3 idi (p <0,05). Glomerüler Filtrasyon hızı ve Serum Digoxin konsantrasyonu arasında istatistiksel olarak anlamlı bir ilişki vardı; biri artarken diğeri azaldı (p <0,05). Aterosklerotik kalp hastalığı olmayan hastalarda Serum Digoxin konsantrasyonu, aterosklerotik kalp hastalığı olanlardan anlamlı olarak düşüktü (p <0.05). Serum Digoksin konsantrasyonları, rivaroksaban ile tedavi edilen hastalarda anlamlı olarak daha yüksekti ve bunların oranları 0.05 düzeyinde birbirinden önemli ölçüde farklıydı.

Sonuç: Günümüzde digoksin ve direkt oral antikoagülanların birlikte kullanım sıklığı artmaktadır. Digoksinin terapötik düzeyinin dar olması, ilaç-ilaç etkileşimleri nedeniyle yakın takibi gerektirir.

Anahtar kelimeler: Serum digoksin konsantrasyonu; ilaç etkileşimi; direkt oral antikoagülan

Introduction

Digitalis, a cardiac glycoside extracted from Digitalis lanata and Digitalis purpura, was discovered in 1785 by botanist Sir William Whitgering.[1] Digoxin, a pharmaceutical purified form, is widely used to treat atrial fibrillation, atrial flutter, and heart failure.[2]

Heart failure (HF) is a cardiovascular disease that causes significant morbidity and mortality in worldwide.

Digoxin increases myocardial contractility and slightly prolongs the duration of contraction. Digoxin improves tissue perfusion and myocardial functions by increasing cardiac contractility and stroke volume as a positive inotropic agent. Digoxin is recommended by the guidelines for the management of HF in patients with reduced ejection fraction (EF) (i.e., HFrEF) who still have persistent symptoms despite optimal medical therapy (evidence class B).[3] The ACC / AHA guideline recommends digoxin to treat heart failure in patients with symptomatic low ejection fraction (EF) (i.e., HFrEF) despite optimal drug therapy(4). Factors such as advanced age, renal dysfunction, and individual variability in serum concentrations are important risk factors for digoxin toxicity. [5,6]

The Digitalis Investigation Group (DIG) is a double-blind, placebo-controlled, large, randomized trial investigating the effect of digoxin on hospitalization and mortality. In the digoxin group, the rate of hospitalizations for worsened heart failure was reduced by 6% (p <0.001).[7] Kotecha et al. showed that low-dose digoxin might be an alternative to beta-blockers to reach safe heart rate control in patients with permanent AF.[8]

Direct oral anticoagulant agents(DOACs); includes the thrombin inhibitor dabigatran and factor Xa inhibitors, rivaroxaban, apixaban and edoxaban. DOACs are used in the secondary prophylaxis and treatment of venous thromboembolism and pulmonary embolism and reduce the risk of stroke and systemic embolism in non-valvular atrial fibrillation.[9] Today, the combined use of DOAC and digoxin in the treatment steps of atrial fibrillation is gradually increasing, leading to drug interactions.[10-12]

Pharmacokinetics deals with absorption, distribution, metabolism, and excretion events related to drug delivery. Membrane transport proteins play an essential role in plasma concentration changes in drugs, and P-glycoproteins (P-

gp) are the most well-known permeability glycoproteins in cardiovascular medicine.[13] P-gp, the first discovered member of the ABC (ATP-binding cassette) carrier family, is an ATP-dependent efflux pump, and its substrates are xenobiotics and drugs. Digoxin and many direct oral anticoagulant agents are known P-gp substrate. The substrate with a strong affinity for P-gp can compete with the weak substrate, reducing the poorly affinity substrate's efflux affects serum substrate concentrations.[14-16]

This study aimed to evaluate the relationship between drugs used concomitantly and concomitant diseases in patients with high serum digoxin concentrations. This study aimed to assess the relationship between concomitant medications and comorbidities in patients with high serum digoxin concentrations.

Material and Methods

Serum Digoxin concentrations(SDC) levels of patients were evaluated according to risk factors associated with high serum digoxin concentrations and digoxin intoxication admitted our hospital between January 2016-March 2019 retrospectively.

Glomerular filtration rate (GFR) of the patients was measured using the Chronic Kidney Disease-Epidemiology Collaboration Equation(CKD-EPI) formula. The patients were divided into five subgroups of choronic kidney disease according to their CKD-EPI values. Group 1 ≥ 90 ml/dk/1.73 m2, Group 2= 60-89 ml/dk/1.73 m2, Group 3= 59-30 ml/dk/1.73 m2, Group 4=15-29 ml/dk/1.73 m2, and Group 5 <15 ml/dk/1.73 m2.

Serum Digoxin concentrations(SDC)levels <1 ng/ml is accepted as low, 1-2 ng/ml therapeutic range, 2.1-2.4 ng/ml is high and >2.4 ng/ml toxicity. Serum Digoxin concentration Immuno-inhibition test was used for the quantitative determination of digoxin in human serum on Beckman Coulter OSR6424 analyzers. An immunoinhibition test was used to quantify digoxin in human serum on Beckman Coulter OSR6424 analyzers. The principle of measuring digoxin from a sample inhibits the agglutination reaction by competing with microparticle-bound digoxin for antibody. The device automatically measures the digoxin concentration of each sample.

Cardiac ejection fraction (EF) of patients were evaluated by Echocardiography (GE Vivid S5) in the Cardiology clinic. Left Ventricular EF was calculated from biplane Simpson's formula using 2D echocardiography.

This study was approved by Local Ethics Committee (2019/246). The study was conducted in compliance with the principles of the Declaration of Helsinki. Infromed constents were taken from all participants.

Statistical Analysis

IBM SPSS Statistics 25 (Version 25.0, IBM Armonc New York, US.) was used for statistical analysis. The results of tests were expressed as the number of observations (n), mean ± standard deviation, median and min-max values. The results of the homogenity (Levene's Test) and normality tests(Shapiro Wilk) were used to decide which statistical methods to apply in the comparison of the study groups. Normally distributed and with homogeneous variances groups were compared two groups by Student's t test. According to those tests results parametric test assumptions were not available for some variables, so the comparisons of two independent groups were performed by Mann-Whitney U test. Two continuous variables, the relationship between Pearson Correlation Coefficient In the case of providing the prerequisites for parametric tests were evaluated by Spearman correlation coefficient. For the significance level of the tests, $p < 0.05$ and $p < 0.01$ were accepted.

Results

Serum Digoxin concentration was measured in 661 patients in 39 months in the Cardiovascular Surgery Clinic of Konya Training and Research Hospital. Patients with incomplete information about risk factors in hospital records were excluded from the study.

Of the 408 SDC values, 248 (60.2%) belonged to women, and 160 (39.2%) SDC values belonged to men. Patients mean age was 70.5 years old. The average Ejection Fraction (EF) was 47.6(17-70). There were 60 (14.7%) patients with EF: 30 and less, 107 (26.2%) patients with EF: 31-45, 132 (32.4%) patients with EF: 46-55, 109 (26.7%) patients with above EF: 56. The mean glomerular filtration rate (GFR) was 58.45, and the mean Serum Digoxin Concentration was 1.36 ng/ml (0.01-7.96ng / ml). Percentage of accompanying diseases; Diabetes Mellitus 20.6%, Thyroid disease 2.2%, COPD 16.5%, Renal failure 8.8%, Hypertension 16.9%, Atherosclerotic heart disease (ASKH) 8.6% , Heart valve disease 5.4%, Hyperlipidemia 13.3%, Cerebrovascular event was 7.7%. Table-1 shows the cardiovascular medications that patients regularly use when digoxin concentration is measured.

GFR was significantly higher in patients without atherosclerotic heart disease than those with atherosclerotic heart disease ($p < 0.05$). Serum digoxin levels were significantly lower in patients without atherosclerotic heart disease than those with atherosclerotic heart disease ($p < 0.05$).

There is a statistically significant relationship between age and digoxin, one of which increases while the other increases by 16.3%. There is a statistically significant ($p < 0.01$) relationship

between Digoxin and GFR, one increasing and the other decreasing 14.7% (Table-2).

26.9% (110) of the patients were using Warfarin sodium, and 38.5% (158) were using DOAC. Table-4 shows the distribution of patients numbers using oral anticoagulants according to Serum Digoxin Concentrations. SDCs were significantly higher in patients receiving rivaroxaban compared to other direct oral anticoagulants. Drugs whose proportions are significantly different from each other at the 0.05 level(Table-3).

Table 1. The cardiovascular medications that patients regularly use when digoxin concentration is measured.

Cardiovascular drugs	Patients (n:408)	Percentage (%)
Beta blocker	276	17.0
Calcium-Channel Blocker	170	10.5
HMG-CoA Inhibitors Statins	80	4.9
ACE veya ARB	184	11.3
Diuretics	297	18.3
Warfarin sodium	110	6.8
Direct Oral Anticoagulants		
Rivaraxaban	69	4.3
Apixaban	52	3.2
Dabigatran	29	1.8
Edoxaban	8	0.5

Table 2. Correlation between Age, GFR and EF

n=408	Age	EF	GFR
r	0,163	-0,017	-0,147
p	0,001**	0,739	0,003**

** p< 0,01

Table 3. SDCs were significantly higher in patients receiving rivaroxaban, compared to other direct oral anticoagulants.

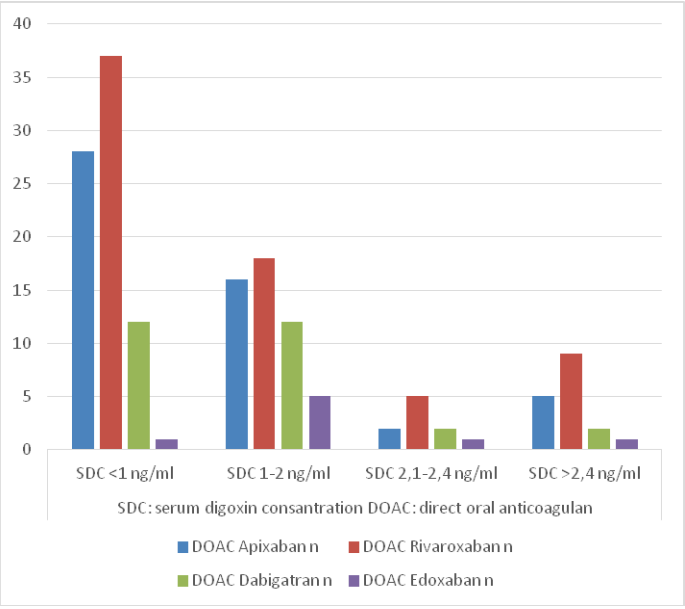
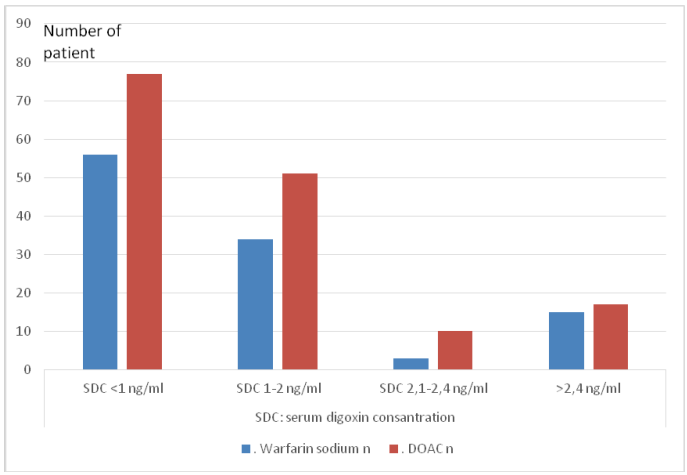


Table 4. Distribution of patients number, using oral anticoagulants according to Serum Digoxin Concentrations.



Discussion

Digital glycosides are a group of positive inotropic cardiac drugs with potential dangers as well as medical benefits. Glycosides with a very narrow safety margin are in cardiovascular drugs that can sometimes show intoxication symptoms at the treatment dose. In the landmark DIG study [8], SDC between 0.5 and 2.0 ng / ml was noted therapeutic, and this is still the standard reference range used at the hospital and in the most independent laboratories. However, published posthoc analyzes of the DIG study have shown that serum digoxin concentrations of 1.0 – 2.0 ng / mL, considered therapeutic, may have adverse effects on hospitalization and survival. In response to this, US guidelines [20, 21] currently advised a target SDC of < 1.0 ng / ml, while European guidelines [22] do not have a specific recommendation.

The lowest SDC range reported in the DIG trial (i.e., 0.5–0.7 ng/mL) was associated with the low-risk all-cause mortality compared with the placebo. Adams et al. [23], in terms of clinical outcomes in the DIG study, SDC up to 0.9 ng / mL was associated with reduced mortality, while SDC of 1.5 ng / mL and above was associated with increased mortality. In our study, GFR, an indicator of kidney function, was low while serum digoxin concentrations were high. This study demonstrates that clinicians should monitor GFR regularly, and serum digoxin dose adjustment should be made according to GFR in patients with heart failure and using digoxin.

Warfarin has more monitoring requirements, frequent follow-up, interactions with drugs and food, making compliance difficult. DOACs quickly gained popularity over warfarin as an anticoagulation strategy due to dosing simplicity,

lack of monitoring requirements, and an expanding list of indications. In our study, the use of DOACs (38,5%) was higher than warfarin (26,9%).

Patient comorbidities and drug-drug interactions, which affect the systemic exposure of medications, need to be considered when managing patients on digoxin therapy. P-gp is a member of transporter proteins called permeability glycoproteins. It is one of the most well-characterized human efflux transporters. P-gps have an extremely broad substrate specificity that can transport many different chemical structures and pharmacological drugs and alter drugs' efficacy and safety. Apixaban, edoxaban, and rivaroxaban are P-GP substrates; digoxin, a cardiac glycoside, is both an intestinal and renal P-glycoprotein substrate[24,25]. In this study, SDCs were significantly higher in patients receiving rivaroxaban compared to other direct oral anticoagulants. Studies assume that the combination of digoxin and rivaroxaban will lead to competition for the P-glycoprotein carrier.

Since our study is retrospective, the dosage and timing of drug use of the patients are unknown. The results reveal that potential pharmacokinetic interactions between digoxin and DOAC should be investigated.

Conclusion

Warnings about drug safety in the elderly are essential, and new drugs, like DOACs related to the cardiovascular system, have been introduced in recent years. DOAC and digoxin are used together to treat cardiovascular comorbidities with congestive heart failure, usually accompanied by AF. Drug dose adjustment with Serum Digoxin Concentration measurement is useful for preventing intoxications. Healthcare professionals should have sufficient knowledge of potential drug interactions.

Declaration of conflict of interest

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