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Evaluation of therapeutic and toxic levels of serum digoxin concentration: a cross-sectional study from a tertiary hospital

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Abstract. – OBJECTIVE: Digoxin is a cardiac glycoside for treating heart failure and atrial fibrillation. Despite its limited therapeutic range and complex pharmacokinetic properties, this medication continues to be frequently prescribed. This study aimed to evaluate the serum digoxin concentration (SDC) at therapeutic, subtherapeutic, and toxic levels and explore the factors affecting these levels in patients receiving digoxin therapy for heart failure.

PATIENTS AND METHODS: In this descriptive and cross-sectional study, the data were obtained from the electronic system of patients who presented to Afyonkarahisar Health Sciences University. For the SDC, the reference range was accepted as 0.5-0.9 ng/mL, and the upper limit was 2.0 ng/mL. The patient's demographic characteristics, comorbidities, and laboratory findings were evaluated. The Mann-Whitney U test, Chi-square test, and logistic regression analysis were used. $p<0.05$ was considered statistically significant.

RESULTS: The data of 419 patients (mean age: 65.9±16.1 years, 68.5% women) were evaluated. The mean SDC was 1.11±1.01 ng/mL, and it was below 0.5 ng/mL in 24.3% of the patients, 0.5-0.9 ng/mL in 23.4%, 0.9-2 ng/mL in 41.3%, and over 2 ng/mL in 11.1%. Age, male gender, the presence of diabetes mellitus, and high HbA1c values were found to be associated with greater SDC levels, but this was not statistically significant. The presence of renal failure, elevated creatinine and magnesium levels, and potassium, sodium, and calcium levels outside the normal limits significantly increased the SDC. High creatinine and low/high potassium values significantly affected the detection of SDC at the toxic level.

CONCLUSIONS: The measurement of SDC levels holds significance not only in the monitoring of toxicity but also in ensuring adherence to the recommended therapeutic range during therapy. It is recommended to exercise caution in terms of risk factors such as age, kidney function test results, and blood electrolyte levels.

Key Words:
Digoxin, Serum digoxin concentration, Heart failure, Therapeutic concentration, Toxic concentration.

Introduction

Digoxin, derived from the foxglove plant (*Digitalis lanata* and *Digitalis purpurea*), is the oldest cardiac drug. The historical utilization of the foxglove plant can be traced back to ancient civilizations, such as the Greek, Egyptian, and Roman Empires; however, its application in treating heart disorders originated in the 18th century, when William Withering, an English physician, made significant advancements in understanding the medicinal characteristics of this plant[1]. Digoxin continues to be utilized in contemporary medical practice for managing heart failure and atrial fibrillation due to its positive inotropic effects on the cardiac muscle, its ability to reduce the activation of the sympathetic nervous system, and its direct impact on the atrioventricular node[2]. Despite the diminished preference for digoxin as the primary therapeutic choice owing to the prevalence of alternative medications, its efficacy has been substantiated through clinical investigations[3-5], and it has been shown to improve symptoms, quality of life, and exercise intolerance in patients with mild, moderate, or severe heart failure.

Digoxin is a substrate with a high affinity for p-glycoprotein (P-gp) and is primarily eliminated

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from the body by renal excretion[6]. The measurement of serum digoxin concentration (SDC) is conducted due to the intricate pharmacokinetic characteristics of the drug, its limited margin of safety and efficacy within the therapeutic range, and the potential for the development of toxicity[7]. Several factors can potentially impact the SDC, including advanced age, levels of blood electrolytes, drug-drug interactions, comorbidities, and kidney and thyroid dysfunctions[8]. An accurate interpretation of this parameter can be achieved by considering the patient's clinical condition alongside the pharmacokinetic properties of the drug. The proper administration of the appropriate dosage to patients is considered crucial due to its potential to enhance the therapeutic efficacy of the drug, optimize patient treatment outcomes, reduce the length of hospital stay, and eliminate unnecessary healthcare costs[9,10].

Digoxin toxicity manifests as chronic toxicity resulting from either an acute overdose or often a reduction in renal clearance[11]. The toxicity diagnosis is based on exposure history, clinical findings, and electrocardiogram changes[12]. The established threshold for the SDC toxic level is 2 ng/mL; however, it may be necessary to decrease this upper limit for elderly individuals and high-risk patients such as those with renal failure[13].

This study aimed to evaluate the SDC at therapeutic, subtherapeutic, and toxic levels and explore the factors affecting these levels in patients receiving digoxin therapy for heart failure.

Patients and Methods

Setting and Sample

In this descriptive and cross-sectional study, the data were retrospectively obtained from the electronic system of patients who presented to the Research and Application Hospital of Afyonkarahisar Health Sciences University (AFSU) from January 1, 2020, through December 31, 2021.

The study was initiated after the approval of the Afyonkarahisar University of Health Sciences (AFSU) Non-Interventional Research Ethics Committee (2022/448). It was carried out in line with the principles of the Declaration of Helsinki.

Data Collection and Study Variables

The data of patients who presented to the AHSU Medical Biochemistry and Cardiology Department between January 1, 2020, and December 31, 2021, constituted the sample. Each application was evaluated separately because a patient could have presented to the center more than once.

The toxic SDC level was accepted as 10.4% in light of the information obtained from previous studies in the literature. Using the Open Epi program, we calculated the sample size as a minimum of 144 individuals with a 5% deviation and a 95% confidence level[9]. However, we did not apply sample selection and included all patients who received digoxin therapy for heart failure during the planned period and whose SDC levels were measured.

The patient's demographic characteristics, comorbidities, and laboratory findings were recorded. Clinical trials[2] conducted on individuals receiving digoxin treatment for heart failure recommend an SDC of 0.5-0.9 ng/mL. Therefore, we accepted the therapeutic range for digoxin as 0.5-0.9 ng/mL and the upper limit as 2.0 ng/mL.

Statistical Analysis

The conformity of the data to the normal distribution was checked with the Shapiro-Wilk test. Descriptive data were given as a number, percentage, median (interquartile range), and mean (standard deviation) values. According to the median age, the patients were divided into two groups. Creatinine and serum electrolytes were categorized as low, normal, or high. The relationship between dependent and independent variables was evaluated with the Mann-Whitney U and Chi-square tests. Independent variables with a p-value<0.25 in the univariate analysis were included in a multivariate model[14]. SPSS v. 24 (IBM Corp., Armonk, NY, USA) statistical software was used for statistical analysis, and p<0.05 was considered statistically significant.

Results

The mean age of the 419 patients included in the study was 65.9±16.1 years, and 68.5% (n=287) were females. The diagnosis of diabetes mellitus was present in 28.9% (n=121) of the patients, and the diagnosis of renal failure was current in 12.4% (n=52). The mean SDC was found to be 1.11±1.01 ng/mL. The patient's demographic characteristics and laboratory findings are shown in Table I.

The SDC was determined to be below 0.5 ng/mL (subtherapeutic) in 24.3% (n=102) of the patients, 0.5-0.9 ng/mL (therapeutic) in 23.4% (n=98), and 0.9-2 ng/mL in 41.3% (n=173) and over 2 ng/mL (toxic) in 11.0% (n=46). The mean

SDC was 1.15±1.04 ng/mL in patients with low potassium levels, 1.46±1.85 ng/mL in those with high potassium levels, 1.21±0.77 ng/mL in those with low sodium levels, and 1.16±1.06 ng/mL in those with high sodium levels, 1.35±1.53 ng/mL in those with low calcium levels, and 0.83±0.26 ng/mL in those with high calcium levels.

Upon examination of the parameters affecting the SDC, advanced age, male gender, the presence of diabetes mellitus, and high HbA1c values were found to be associated with greater SDC levels, but this was not statistically significant. The presence of renal failure, elevated creatinine and magnesium levels, and potassium, sodium, and calcium levels outside the normal limits were factors that significantly increased the SDC (Table II).

High creatinine and low or high potassium values significantly affected the detection of the SDC at the toxic level (Table III). These factors remained significant in the multivariate analysis (Table IV).

Table I. Demographic characteristics and clinical and laboratory findings of the study group.

Demographic characteristics (n=419)	
Age, median (IQR)	68 (61-75)
Gender, n (%)	
Female	287 (68.5)
Male	132 (31.5)
Clinical characteristics (n=419)	
Diabetes mellitus diagnosis, n (%)	
Yes	121 (28.9)
No	298 (71.1)
Renal failure diagnosis, n (%)	
Yes	52 (12.4)
No	367 (87.6)
Laboratory findings	**Median (IQR)**
Creatinine (mg/dL)	0.93 (0.69-1.19)
Sodium (mmol/L)	139 (136-141)
Calcium (mmol/L)	9.09 (8.58-9.50)
Potassium (mmol/L)	4.50 (4.10-4.90)
Magnesium (mmol/L)	2.05 (1.85-2.25)
HbA1c (%)	6.39 (5.73-7.47)
Serum digoxin concentration (ng/mL)	0.94 (0.50-1.35)

IQR: interquartile range.

Discussion

This study retrospectively assessed the SDC in inpatients and outpatients diagnosed with heart failure and receiving digoxin treatment at a university hospital. In current guidelines, the target SDC is recommended to be 0.5-0.9 ng/mL; however, it is seen that the therapeutic range still needs to be achieved in approximately three-quarters of the patients[2]. Although the targeted range for SDC varies by laboratory, 0.8-2.0 ng/mL has been accepted for many years. In the post hoc analysis of a study conducted by the Digitalis Investigation Group[15], which is the first randomized controlled clinical trial on the use of digoxin in the treatment of heart failure, low SDC was found to be associated with a significant reduction in all-cause mortality and hospitalization rates. Therefore, the existing guidelines[16] suggest that the optimal target SDC should be 0.5-0.9 ng/mL in treating heart failure.

Elevated creatinine is an independent risk factor for detecting SDC at the toxic level. A previous study[17] observed that individuals diagnosed with renal failure or those with compromised renal function test results exhibited a reduced renal excretion of digoxin, leading to an extended half-life of the drug. In addition, heart failure causes a decrease in renal function[18]. In this case, a vicious cycle begins between heart and renal failure. Therefore, digoxin toxicity is more prevalent in patients with renal failure and results in more severe symptoms, especially in hemodialysis cases[19]. Similarly, the current study observed that poor renal function resulted in a significant increase in the SDC.

The presence of either high or low plasma potassium levels was identified as another independent factor that significantly increased the occurrence of SDC and led to its detection at the toxic level. An electrolyte imbalance in the blood increases the patient's sensitivity to digoxin[20]. Digoxin exerts its therapeutic effects in heart failure by inhibiting Na^+/K^+-ATPase in the cell membrane[21]. The Na^+/K^+-ATPase enzyme exhibits an enhanced affinity toward digoxin in hypokalemia, whereas its association with digoxin is diminished in the presence of hyperkalemia[22]. In our study, hyperkalemia and hypokalemia significantly affected the SDC level. Similar to our research, other studies[23,24] also report that potassium levels affected the SDC.

In this study, similar to the results concerning the relationship between the SDC and potassium levels, a significant correlation was found between the SDC and sodium, calcium, and magnesium levels. Electrolytes play a role in the sensitivity

of the heart muscle to digoxin, given that magnesium is a cofactor of the Na^+/K^+-ATPase enzyme and that sodium and calcium affect the $Na^+/Ca2^+$ antiport system[25]. The findings of our study underscore the importance of detecting blood electrolyte levels alongside the SDC.

Advanced age and gender are other factors that increase SDC and heighten the risk of digoxin toxicity[26]. Renal dysfunction that occurs physiologically with older age can cause an increase in the SDC. In addition, the prevalence of comorbidities and the associated potential drug-drug interactions due to polypharmacy are also increasing[27]. Although we found no significant correlation between advanced age and the SDC in our study, we determined the SDC to be higher in older patients, consistent with the literature[28,29]. Furthermore, the SDC was higher among male patients in our study, but this did not reach statistical significance. In contrast, previous studies[23,30,31] have shown that the SDC is higher among women. Although it is considered that this disparity may be linked to the lower glomerular filtration rate observed in women, the precise underlying mechanism still needs to be fully elucidated.

Medicines' pharmacokinetic and pharmacodynamic characteristics may undergo alterations due to diabetes[32]. Diabetes can potentially impact the activity and expression of P-gp during the pathophysiological progression of the disease. In addition, the incidence of renal failure is higher in diabetic patients than non-diabetic patients. This may cause elevated serum levels of drugs mainly eliminated via the kidneys, such as digoxin[33]. Given the available data, the SDC is expected to be high in diabetic patients. In the current study, the SDC was higher in these patients, although there was no statistically significant difference. There are no clinical studies investigating the effects of diabetes on the P-gp protein level or gene expression in humans. In studies conducted with diabetic animal models, researchers[34] acquired data supporting the information, revealing that the SDC was higher in experimental groups. There is a need for comprehensive and large-scale studies investigating the effects of diabetes on the pharmacokinetics of digoxin.

Although the established upper limit for the accepted toxic level for the SDC is 2 ng/mL, some studies[35] have shown that the threshold value is actually 1.2 ng/mL. In our study, accepting 2 ng/mL as the upper limit, the SDC was found to be toxic in 11% of the patients. Similarly, this rate varies between 9 and 17% in the literature[36-40]. In previous studies[23,41,42] conducted in Turkey, this rate has been reported to range from 6.7% to 24.2%. In clinical practice, digoxin toxicity tends to manifest as a chronic condition. It has been reported[43] that 10-20% of patients undergoing digoxin treatment exhibit persistent toxicity. In studies[8,23] conducted in Turkey, this rate has been found to be 6-10%. The results in our study were similar; however, it is noteworthy that despite the reduced use of digoxin for managing both heart failure and atrial fibrillation, digoxin toxicity remains a significant clinical problem. It has also been reported[44,45] that high SDC causes an increase in the risk of hospitalization and mortality.

In this study, the SDC was within therapeutic limits in only one-quarter of the patients. While the current guidelines recommend the target SDC to be 0.5-0.9 ng/mL, we observed that the therapeutic range still needed to be achieved in 77% of

Table II. Evaluation of factors affecting the SDC.

Variables	SDC (ng/mL) mean±SD	p
Age		
<68 years (n=198)	1.09±0.81	0.338
≥68 years (n=221)	1.12±1.27	
Gender		
Female (n=287)	1.07±0.77	0.771
Male (n=132)	1.19±1.49	
Diabetes mellitus diagnosis		
Yes (n=121)	1.12 (0.79)	0.126
No (n=298)	1.09 (1.14)	
Renal failure diagnosis		
Yes (n=52)	1.21 (0.73)	**0.049**
No (n=367)	1.09 (1.09)	
Creatinine		
Normal (n=269)	1.03 (1.12)	**0.001**
High (n=135)	1.26 (0.89)	
Potassium		
Normal (n=311)	1.03 (0.78)	**0.005**
Low or high (n=85)	1.39 (1.72)	
Sodium		
Normal (n=293)	1.09 (1.15)	**0.011**
Low or high (n=106)	1.21 (0.81)	
Calcium		
Normal (n=249)	1.01 (0.69)	**0.021**
Low or high	1.31 (1.48)	
Magnesium		
Normal (n=154)	0.97 (0.75)	**0.043**
High (n=265)	1.18 (1.19)	
HbA1c		
Normal (n=108)	1.07 (0.61)	0.609
High (n=96)	1.10 (0.87)	

Mann-Whitney U test was performed; SDC: serum digoxin concentration; SD: standard deviation.

Table III. Evaluation of the factors affecting SDC detection at the toxic level.

Variables	SDC (ng/mL)		p
	≤2 ng/mL (n=373)	>2 ng/mL (n=46)	
Age			
<68 years (n=98)	174 (87.9)	24 (12.1)	0.479
≥68 years (n=221)	199 (90.0)	22 (10.0)	
Gender			
Female (n=287)	254 (88.5)	33 (11.5)	0.616
Male (n=132)	119 (90.2)	13 (9.8)	
Diabetes mellitus diagnosis			
Yes (n=121)	107 (88.4)	14 (11.6)	0.805
No (n=298)	266 (89.3)	32 (10.7)	
Renal failure diagnosis			
Yes (n=52)	43 (82.7)	9 (17.3)	0.119
No (n=367)	330 (89.9)	37 (10.1)	
Creatinine			
Normal (n=269)	248 (92.2)	21 (7.8)	**0.003**
High (n=135)	111 (82.2)	24 (17.8)	
Potassium			
Normal (n=311)	283 (91.0)	28 (9.0)	**0.005**
Low or high (n=85)	68 (80.0)	17 (20.0)	
Sodium			
Normal (n=293)	262 (89.4)	31 (10.6)	0.324
Low or high (n=106)	91 (85.8)	15 (14.2)	
Calcium			
Normal (n=249)	226 (90.8)	23 (9.2)	0.078
Low or high (n=146)	124 (84.9)	22 (15.1)	
Magnesium			
Normal (n=154)	143 (92.9)	11 (7.1)	0.056
High (n=265)	230 (86.8)	35 (13.2)	
HbA1c			
Normal (n=108)	98 (90.7)	10 (9.3)	0.334
High (n=96)	83 (86.5)	13 (13.5)	

Chi-square test was performed; SDC: serum digoxin concentration.

Table IV. Multivariate analysis of the factors affecting SDC detection at the toxic level.

Variables (n=232)	ß	SE	p	OR (95% CI)
Renal failure	0.008	0.446	0.986	1.008 (0.420-2.419)
Creatinine	0.735	0.354	**0.038**	2.085 (1.042-4.173)
Potassium	0.760	0.347	**0.029**	2.138 (1.082-4.224)
Calcium	0.348	0.334	0.297	1.417 (0.736-2.726)
Magnesium	0.256	0.398	0.519	1.292 (0.592-2.819)

SE: standard error, OR: odds ratio, CI: confidence interval. Reference categories: absence of renal failure and normal values of serum electrolytes.

our patients. This rate is very high for a drug with a narrow therapeutic range and pharmacokinetic variability, such as digoxin. In addition, the SDC was at a subtherapeutic level in 24% of our patients. In previous studies[15,35,44], there was a need for more empirical evidence concerning the efficacy of digoxin at doses lower than 0.5 ng/mL. Nevertheless, various drug trials[45] have demonstrated that low concentrations of digoxin cause treatment failure and a prolonged hospital stay.

Limitations

The most important limitations of this study are the acquisition of data from electronic patient records, the presence of missing data, and the retrospective nature of the evaluation. In addition, we could not evaluate other parameters related to therapeutic drug level monitoring, such as the digoxin dose used, blood sample collection time, SDC measurement indications, and treatment change based on the SDC result.

Conclusions

The measurement of the SDC in patients receiving digoxin therapy is essential not only in the toxicity follow-up but also in maintaining it within the recommended therapeutic range during treatment. Clinicians should be careful regarding risk factors, such as patient age, renal function test results, and blood electrolyte levels. The results of our study are important in drawing attention to the importance of the SDC measurement and disseminating the use of standard guidelines related to the SDC. Prospective and larger-scale clinical studies are warranted to investigate the therapeutic drug-level monitoring of digoxin.

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Conflict of Interest
The authors declare no conflict of interest.

Ethics Approval
The Afyonkarahisar University of Health Sciences (AFSU) Non-Interventional Research Ethics Committee (2022/448) approved the study.

Informed Consent
Informed consent was taken from all cases and the control group participants before inclusion into the study.

Authors' Contributions
All authors contributed to the planning, designing, literature survey, data collection, and active intellectual support.

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Availability of Data and Materials
All data for this study is presented in this paper.

References

1) Fisch C. William Withering: An account of the foxglove and some of its medical uses 1785-1985. J Am Coll Cardiol 1985; 5: 1-2.
2) Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-2200.
3) Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol 1993; 22: 955-962.
4) Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993; 329: 1-7.
5) Collins JF, Egan D, Yusuf S, Garg R, Williford WO, Geller N; DIG Investigators. Overview of the DIG trial. Control Clin Trials 2003; 24: 269-276.
6) Patocka J, Nepovimova E, Wu W, Kuca K. Digoxin: Pharmacology and toxicology-A review. Environ Toxicol Pharmacol 2020; 79: 1-6.
7) Ewy GA. Digoxin: the art and science. Am J Med 2015; 128: 1272-1274.
8) Oncu S, Gelal A, Aslan O, Ucku RS. Appropriateness of digoxin measurement in hospitalized patients. Biochem Med (Zagreb) 2018; 28: 1-8.
9) Aonuma K, Shiga T, Atarashi H, Doki K, Echizen H, Hagiwara N, Hasegawa J, Hayashi H, Hirao K, Ichida F, Ikeda T, Maeda Y, Matsumoto N, Sakaeda T, Shimizu W, Sugawara M, Totsuka K, Tsuchishita Y, Ueno K, Watanabe E, Hashiguchi M, Hirata S, Kasai H, Matsumoto Y, Nogami A, Sekiguchi Y, Shinohara T, Sugiyama A, Sumitomo N, Suzuki A, Takahashi N, Yukawa E, Homma M, Horie M, Inoue H, Ito H, Miura T, Ohe T, Shinozaki K, Tanaka K; Japanese Circulation Society and the Japanese Society of Therapeutic Drug Monitoring Joint Working Group. Guidelines for therapeutic drug monitoring of cardiovascular drugs clinical use of blood drug concentration monitoring (JCS 2015)-Digest Version. Circ J 2017; 81: 581-612.
10) Junaid T, Wu X, Thanukrishnan H, Venkataramanan R. Therapeutic Drug Monitoring. Clinical Pharmacy Education, Practice and Research 2019; 3: 425-435.
11) Ozyıldırım S, Barman HA, Dogan O, Atici A, Mirzayev K, Ebeoglu AO, Yumuk MT, Ikitimur B, Dogan SM, Enar R. The effects of Digoxin use on long-term prognosis in patients with heart failure with reduced ejection fraction. Eur Rev Med Pharmacol Sci 2023; 27: 7226-7234.
12) Chang DW, Lin CS, Tsao TP, Lee CC, Chen JT, Tsai CS, Lin WS, Lin C. Detecting Digoxin Toxicity by Artificial Intelligence-Assisted Electro-

cardiography. Int J Environ Res Public Health 2021; 18: 1-6.

13) Goldberger ZD, Goldberger AL. Therapeutic ranges of serum digoxin concentrations in patients with heart failure. Am J Cardiol 2012; 109: 1818-1821.

14) Masel J, Humphrey PT, Blackburn B, Levine JA. Evidence-Based Medicine as a Tool for Undergraduate Probability and Statistics Education. CBE Life Sci Educ 2015; 14: 1-12.

15) Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003; 289: 871-878.

16) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 accf/aha guideline for the management of heart failure: a report of the American college of cardiology/american heart association task force on clinical practice guidelines and the heart failure society of America. Circulation 2017; 136: 137-161.

17) Hanratty CG, McGlinchey P, Johnston GD, Passmore AP. Differential pharmacokinetics of digoxin in elderly patients. Drugs Aging 2000; 17: 353-362.

18) Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens 2004; 13: 163-170.

19) Kar M, Altıntaş M, Bayar Muluk N, Cingi C. Olfactory function in patients undergoing hemodialysis as assessed by Sniffin' Sticks testing. Eur Rev Med Pharmacol Sci 2023; 27: 1-7.

20) Litonjua MR, Penton S, Robinson C, Daubert GP. Digoxin: the monarch of cardiac toxicities. J Pharm Pract 2005; 18: 57-168.

21) Gheorghiade M, Adams KF Jr, Colucci WS. Digoxin in the management of cardiovascular disorders. Circulation 2004;109: 2959-2964.

22) Abdul-Rahim AH, MacIsaac RL, Jhund PS, Petrie MC, Lees KR, McMurray JJ; On behalf the VICCTA-Heart Failure Collaborators. Efficacy and safety of digoxin in patients with heart failure and reduced ejection fraction according to diabetes status: An analysis of the Digitalis Investigation Group (DIG) trial. Int J Cardiol 2016; 209: 310-316.

23) Ozyigit F, Kocak FE, Arikan I, Genc O. A retrospective analysis about the quality of therapeutic drug monitoring of digoxin. Sch Acad J Pharm 2015; 4: 331-336.

24) Cauffield JS, Gums JG, Grauer K. The serum digoxin concentration: ten questions to ask. Am Fam Physician 1997; 56: 495-503.

25) Prassas I, Diamandis EP. Novel therapeutic applications of cardiac glycosides. Nat Rev Drug Discov 2008; 7: 926-935.

26) See I, Shehab N, Kegler SR, Laskar SR, Budnitz DS. Emergency department visits and hospitalizations for digoxin toxicity: United States, 2005 to 2010. Circ Heart Fail 2014; 7: 28-34.

27) Gosselink AT, van Veldhuisen DJ, Crijns HJ. When, and when not, to use digoxin in the elderly. Drugs Aging 1997; 10: 411-420.

28) Shen JZ, Zhu HJ, Liu H, Luo XM, Jin L, Li DY, Zhang HX, Ge WH. Individualized medication of digoxin based on the serum drug concentration and blood biochemical indexes. Per Med 2020; 17: 23-31.

29) Grześk G, Stolarek W, Kasprzak M, Krzyżanowski M, Szadujkis-Szadurska K, Wiciński M, Grześk E. Therapeutic drug monitoring of digoxin-20 years of experience. Pharmacol Rep 2018; 70: 184-189.

30) Abad-Santos F, Carcas AJ, Ibáñez C, Frías J. Digoxin level and clinical manifestations as determinants in the diagnosis of digoxin toxicity. Ther Drug Monit 2000; 22: 163-168.

31) Aarnoudse AL, Dieleman JP, Stricker BH. Age- and gender-specific incidence of hospitalisation for digoxin intoxication. Drug Saf 2007; 30: 431-436.

32) Dostalek M, Akhlaghi F, Puzanovova M. Effect of diabetes mellitus on pharmacokinetic and pharmacodynamic properties of drugs. Clin Pharmacokinet 2012; 51: 481-499.

33) Cummings ED, Swoboda HD. Digoxin Toxicity. 2023 Mar 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. PMID: 29262029.

34) Zhang LL, Lu L, Jin S, Jing XY, Yao D, Hu N, Liu L, Duan R, Liu XD, Wang GJ, Xie L. Tissue-specific alterations in expression and function of P-glycoprotein in streptozotocin-induced diabetic rats. Acta Pharmacol Sin 2011; 32: 956-966.

35) Adams KF Jr, Gheorghiade M, Uretsky BF, Patterson JH, Schwartz TA, Young JB. Clinical benefits of low serum digoxin concentrations in heart failure. J Am Coll Cardiol 2002; 39: 946-953.

36) Mayan H, Bloom E, Hoffman A. Use of digoxin monitoring in a hospital setting as an essential tool in optimizing therapy. J Pharm Technol 2002; 18: 133-137.

37) Williamson KM, Thrasher KA, Fulton KB, LaPointe NM, Dunham GD, Cooper AA, Barrett PS, Patterson JH. Digoxin toxicity: an evaluation in current clinical practice. Arch Intern Med 1998; 158: 2444-2449.

38) Ragab AR, Al-Mazroua MK, Abdel-Rahman RH. Clinical utility of serum digoxin level in cardiac patients for diagnosis of chronic digitalis toxicity. J Clinic Toxicol 2012; 2: 2161-2195.

39) Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol 2013; 61: 2495-2502.

40) Vella J, Wirth F, Azzopardi LM, Serracino-Inglott A. Serum digoxin concentrations: a retrospective analysis. Pharmacol Cln Toxicol 2018; 6: 1129-1132.

41) Öztürk Z, Çuhadar S. Effects of Age, Gender, and Comorbid Diseases on Serum Digoxin Levels During Digoxin Treatment. Science 2018; 6: 31-36.

42) Yilmaz I, Bilgili S, Bozkaya G. Evaluation of digoxin levels in elderly patients in a training hospital: an 11-year follow-up. Turk Geriatri Derg 2020; 23: 108-117.

43) Campbell TJ, MacDonald PS. Digoxin in heart failure and cardiac arrhythmias. Med J Aust 2003; 179: 98-102.

44) Lopes RD, Rordorf R, De Ferrari GM, Leonardi S, Thomas L, Wojdyla DM, Ridefelt P, Lawrence JH, De Caterina R, Vinereanu D, Hanna M, Flaker G, Al-Khatib SM, Hohnloser SH, Alexander JH, Granger CB, Wallentin L; ARISTOTLE Committees and Investigators. Digoxin and Mortality in Patients With Atrial Fibrillation. J Am Coll Cardiol 2018; 71: 1063-1074.

45) van Lent-Evers NA, Mathot RA, Geus WP, van Hout BA, Vinks AA. Impact of goal- oriented model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. Ther Drug Monit 1999; 21: 63-73.