Journal of Clinical Toxicology
ISSN: 2161-0495

Ragab et al., J Clinic Toxicol 2012, 2:9
DOI: 10.4172/2161-0495.1000150

Research Article Open Access

Clinical Utility of Serum Digoxin Level in Cardiac Patients for Diagnosis of Chronic Digitalis Toxicity

Ahmed Refat Ragab[1,2]*, Maha Khalid Al-Mazroua[1,2], and Rania Hamed Abdel-Rahman[1]

[1]*Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Mansoura University, Egypt*
[2]*Dammam Regional Poison Control Center-Eastern Region, Kingdom of Saudi Arab*

Abstract

Digitalis toxicity is a complication of the digitalis therapy. It could occur also due to the patient taking in a much larger dose of the drug than prescribed. The general symptoms of Digitalis toxicity are typically gastro-intestinal, neurologic and non-specific cardiac type manifestations that are strikingly similar to the clinical picture of primary Congestive Heart Failure (CHF) making a diagnosis of chronic digitalis toxicity in particular relatively difficult. Serum digoxin measurement is today becoming a crucial subject of concern because of the narrow therapeutic window of digoxin besides increasing mortality and morbidity due to its intoxication. The present work is focused on evaluating the clinical value of Serum Digoxin Concentrations (SDCs) in relation to appropriate assessment of chronic digitalis toxicity in cardiac patients. The current study was conducted in the form of a cross-sectional Electronic Medical Record (EMR) review study of patients presently on continuous prescriptions for digoxin with there being zero gaps in therapy for at least 10 days prior to SDC result entered into the Online Analytical Toxicology Request Result (OTARR). There was also a complete clinical examination report as well as a review of the results of serum potassium concentration, liver and kidney functions. Patients with digoxin toxicity (11.9%) had a significantly higher mean SDC (2.75 ± 1.2) than those with subtherapeutic (0.67 ± 0.17 ng/mL) or eutherapeutic SDC (1.19 ± 0.26 ng/mL) (p value ≤ 0.05). About 12% of the total cases showed an abnormal serum potassium concentration of electrolyte fluctuations. From this, one can conclude that a regular monitoring of serum digoxin level would be seen as mandatory for the verification of digoxin's therapeutic effects and then the subsequent prevention and early diagnosis of chronic toxicity.

Keywords: Serum digoxin concentration; Cardiac patients; Digitalis toxicity

Introduction

Digoxin, a purified cardiac glycoside, is widely prescribed as medications despite there being several adverse drug reactions due to it [1]. Although digitalis preparations have been used therapeutically for over two centuries, it is still quite difficult to diagnose digoxin toxicity. The various symptomatic indications with regard to toxicity are still non-specific, in the same way as are electrocardiographic changes. At a specific given Serum Digoxin Concentration (SDC) 'Therapeutic' and 'toxic' concentrations do overlap. For instance, a patient may be able to control ventricular response without any adverse effects, while another may exhibit toxicity. Therapeutic drug monitoring steps up the patient care and are very likely a contributing factor to the suspected decrease in digoxin toxicity; Yet, elevated concentrations are not the only reasons for toxicity [2].

There is a tendency to overlook Digoxin intoxication because of its variable bioavailability and because of differences in its gastrointestinal absorption, distribution and excretion [3]. Moreover, it has also shown a narrow therapeutic window which could possibly heighten the risk factors of toxicity in patients being treated with digoxin therapy with a ratio of 5 to 35 % in hospitalized patients [4,5].

It was observed that in cardiac patients, the therapeutic range for digoxin was in the range from 0.9 to 2.2 mg/ml [6]. Also, the serum digoxin levels below and above this range were quite ineffective and toxic as well. There are many arrhythmias along with several other extra cardiac side-effects, right from headaches, nausea and vomiting to death [4].

According to a statement made by the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Heart Failure in 2009, once the therapeutic range has been reached, it is advisable to go in for SDC measurement. It is also considered proper to bring about a change in a toxicity-provoking physiologic parameters, like decreased renal function; after the introduction or discontinuation of an interacting drug; in order to assess clinical response; to assess adherence; or in the presence of clinical signs of digoxin toxicity [7,8].

The present work aims at evaluating the clinical value element of Serum Digoxin Concentrations (SDCs) with regard to appropriate assessment of chronic digitalis toxicity in cardiac patients at Dammam Regional Poison Control Center.

Subjects and Methods

Study setting

This work was conducted as a cross sectional, (Electronic Medical Review) EMR database review study at Damamm Regional Poison Control Center–Eastern Region, KSA.

Inclusion criteria

Adult patients monitored for SDC in two hospitals (Dammam Medical Complex and Qatif Central Hospital) that were participating

***Corresponding author:** Ahmed Refat Ragab, Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Mansoura University, Egypt, E-mail: ahmedrefat1973@yahoo.com

Received November 26, 2012; **Accepted** December 26, 2012; **Published** December 28, 2012

Citation: Ragab AR, Al-Mazroua MK, Abdel-Rahman RH (2012) Clinical Utility of Serum Digoxin Level in Cardiac Patients for Diagnosis of Chronic Digitalis Toxicity. J Clinic Toxicol 2:150. doi:10.4172/2161-0495.1000150

in a year-long period from the beginning of April, 2011 until the end of March, 2012.

Study population parameters

Investigators noted down important and detailed information of all the patients, like their age, and sex as well as their patient code, in-patient or out-patient admission status and medical service type.

Indications for digoxin treatment, clinical manifestations and electro-cardiographic changes were consistent with digoxin toxicity and this information was recorded. Digoxin toxicity, if any was diagnosed and also reported.

SDCs assays for adult patients were recorded along with crucial information digoxin dosing data, including dose, route of administration, date of the first and last dose, and the timing of the blood sample relative to the last dose of digoxin (2, 4, 6, 8 and 10 hours after dosing).

At present, the status of electrolytes, renal and liver function values were evaluated at the same time of estimating the SDC. Important laboratory activities and investigations such as blood urea nitrogen, serum creatinine concentration, both serum ALT and AST levels were also conducted.

Assay procedure

The received blood samples were centrifuged at 3000 rpm for 5 minutes. Immediate measurement of serum digoxin level was done by immunoassay technology using the Abbott TDx system (Abbott Laboratories, Abbott Park, Ill; assay sensitivity range is 0.3-6.4 nmol/L [0.2-5.0 ng/mL].

Grouping of the studied patients

The studied cases were divided into 3 groups according to the obtained serum digoxin level as follows:

Group A: patients with therapeutic serum digoxin level 0.9–2.2 ng/mL.

Group B: patients with subtherapeutic serum digoxin level<0.9 ng/mL.

Group C: patients with toxic serum digoxin level>2.2 ng/mL.

Electronic medical records review process

Three reviewers conducted the entire review process – 'pharmacists'. Taking the help of individual patient records, the individual patient records were accessed by way of medical record number access into the EMR. Predefined data points fed into a standard type Excel worksheet was set up on a share drive that was password protected which was to be used by every single reviewer in order to get the abstraction data information. Then every patient was reviewed on an independent basis to be reviewed for agreement purpose followed by checks carried out by the third reviewer to see if there were still any other discrepancies identified. Data extractors had to have total agreement amongst themselves. The study was approved by the Medical Ethics Committee of the Dammam Regional Poison Control Center/ Ref No 13/2012.

Statistical analysis:

There was a statistical analysis of the entire data with the help of the present SPSS statistical package Version 19. This data was further presented as mean ± Standard Deviation of Means (S.D.M). There was also a comparison exercise done between the two groups that was carried out with the help of t-test and p value was considered statistically significant if <0.05.

Results

The current work comprised of 217 patients (78 males and 139 females with mean age ± SD: 63.18 ± 19 years). Therefore, a total of 217 SDCs was requested in the entire 12-month (1 year) study period.

Table 1 show the different characters of the patients. These patients were studied and analyzed against vital benchmarks like age, sex, admission status. Another notices in Table 1 the digoxin levels and dosing data with regard to the medical indication for digoxin, its dosage, as well as the time of sampling and route of administration.

Atrial fibrillation and heart failure were the commonest conditions (69.6%) consistent with indications of digoxin therapy in this study whereas sole diagnosis as heart failure was found in 23.5% of our case series. The mean daily digoxin dosage was 0.17.

In the present work, about 95.8% of patient's samples were taken 6 hours or later after the last dose. Digoxin levels were measured 6 hours or later to avoid any wrong assessment caused by the distribution characters of digoxin.

Table 2, showed the manifestations of digoxin toxicity, associated electrocardiographic changes, liver and renal functions as well as potassium level. The commonest symptoms and ECG signs in the subtherapeutic group were abdominal pain and atrial fibrillation (16.4% and 12.6%) respectively. On the other aspect, the commonest symptoms in the toxic group and eutherapeutic group were palpitation and dysnoea (26.5% and 4.55) respectively.

There were laboratory experiments done which led to findings

Age in years mean (range)	63.8 ± 19	
Sex	Male 78 (36%)	Female 139 (64%)
Admission Status Inpatient Outpatient	No 183 34	% 84.3% 15.7%
Renal functions status Stable "Normal Laboratory Findings" Unstable " Marked abnormal Laboratory Findings"	 169 48	 77.9% 23.1%
Liver functions status Stable "Normal Laboratory Findings" Unstable " Marked abnormal Laboratory Findings"	 191 26	 88% 12%
Potassium level Normal Level (3.5-5.5 mEq) Hypokalaemia (<3.5 mEq) Hyperkalaemia (>5.5 mEq)	 191 22 4	 88% 10.2% 1.8%
Indication for digoxin: n (%)		
Heart failure		51 (23.5%)
Both Atrial Fibrillation and Heart Failure		151 (69.6%)
Others e.g. Myocardial Infarction, Ventricular Septal Defet Complication, Other types of cardiac arrhythmia		15 (6.9%)
Digoxin Dosage: mg/day Mean (range) 0.17 (0.01 – 0.625		
Time of Sample:		
At 2 hrs		3 (1.4%)
At 4 hours		6 (2.8%)
At 6 hours		200 (92.1%)
At 8 hours		6 (2.8%)
At 10 hours		2 (0.9%)
Route of administration:		
Oral		194 (89.4%)
IV		23 (10.6%)

Table 1: Morphological, biochemical and digoxin dosing characteristics of the studied Patients and (n=217).

		No. (%) of Patients		
		Subtherapeutic Digoxin Level (< 0.9 ng/mL) (n= 103)	Therapeutic Digoxin Level (0.9-2.2 ng/mL) (n=88)	Toxic Digoxin Level (>2.2 ng/mL) (n=26)
Any Symptoms & or ECG changes		95 (92.2%)	44(61.3%)	25 (96.2%)
Symptoms				
	Anorexia	2 (1.9%)	1(1.3%)	2 (7.6%)
	Nausea	1 (1.9%)	0(0%)	6 (23.1%)
	Vomiting	5(4.9%)	2(2.2%)	5 (19.2%)
	Abdominal Pain	17 (16.4%)	1(1.3%)	5(19.2%)
	Diarrhea	1 (0.97%)	0(0%)	4 (15.3%)
	Dizziness	7(6.7%)	2(2.2%)	2 (7.6%)
	Headache	4 (3.8%)	2(2.2%)	1 (3.8%)
	Confusion	16 (15.5%)	0(0%)	0 (0%)
	Visual Changes	1(0.97%)	0(0%)	1 (3.8%)
	Palpitation	6(5.8%)	3(3.4%)	7 (26.9%)
	Cough	1(0.97%)	0(0%)	1(3.8%)
	Dyspnoea	10 (9.7%)	4(4.5%)	4(15.3%)
Electrocardiographic Changes				
	Atrial Fibrillation	13 (12.6%)	8(9%)	7 (26.9%)
	Bradycardia (<50 beats/min)	5 (4.9%)	3(3.4)	2(7.6%)
	Junctional Tachycardia	0(0.0%)	1(1.3%)	0(0%)
	Sustained ventricular tachycardia	1(0.97%)	0(0%)	0(0%)
	Sinus arrest	4(3.8%)	0(0%)	1(3.8%)
	Heart block	0(0%)	1(1.3%)	4(15.3%)

Table 2: Frequency of Symptoms and or Electrocardiographic Changes in Patients with Abnormal Digoxin Concentration (n= 129).

detected with regard to the different SDCs. These were presented in Table 3. While patients with digoxin toxicity showed a majorly higher mean SDC, those that did not, were seen to be having sub-therapeutic or eutherapeutic SDC (P value ≤ 0.05).

It was also observed that there was a drastic decrease in the serum levels of BUN, creatinine, AST and ALT and a much higher and distinct decrease in the serum K level when compared with sub-therapeutic SDCs group.

Patients with digoxin toxicity (11.9%) had a significantly higher mean SDC (2.75 ± 1.2) than those with subtherapeutic (0.67 ± 0.17) or eutherapeutic SDC (1.19 ± 0.26) (p value ≤ 0.05). Laboratory findings detected in relation to different SDCs were also presented in Table 3. Patients with digoxin toxicity had a significantly higher mean SDC than those with subtherapeutic or eutherapeutic SDC (P value ≤ 0.05). There was a significant decrease in serum levels of BUN, AST and ALT (P value ≤ 0.05) and a highly significant decrease in the serum K level when compared with a subtherapeutic SDCs group (P value ≤ 0.01).

In the present work result, impaired renal functions were detected in forty eight patients while twenty six cases showed disturbed liver functions with a significant decrease in mean serum levels of AST (130.2 ± 45.9) and ALT (93.7 ± 32.5). In the digoxin intoxicated group, there was a significant increase in serum levels of BUN (171.5 ± 91.3) and creatinine (1.97 ± 1.86).

Moreover, hypokalaemia and hyperkalaemia were found in 10.2% and 1.8% of cases respectively. There was a highly significant decrease in the serum K level in the toxic dioxin group when compared with a subtherapeutic SDCs group.

Figure 1 illustrates the indication of requesting SDC. About 54.8% of patients were part of routine assessment to check for routine indication of toxicity. About 39.2% had suspected toxicity while the rest requests had suspected failure of therapy (3.2%) and below average compliance (2.8%).

Figure 2 showed the relationship between different categories of SDC as well as the reason for requesting Digoxin level. Almost half the requests-52% of the routine requests identified abnormal SDCs (6% toxic levels and 46% sub-therapeutic level).

Figure 3 shows the percentages of patients needing dosage adjustment of digoxin and/or interval. About 24% of the cases needed readjustment of dose or interval. Twenty four percent of the studied

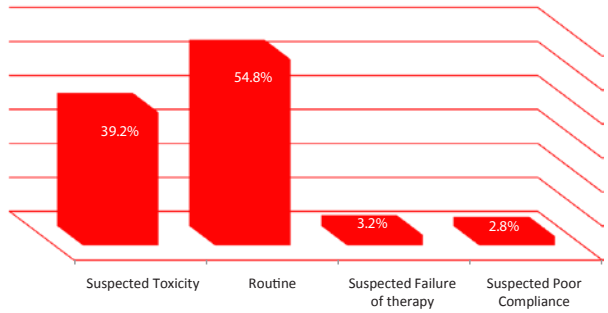
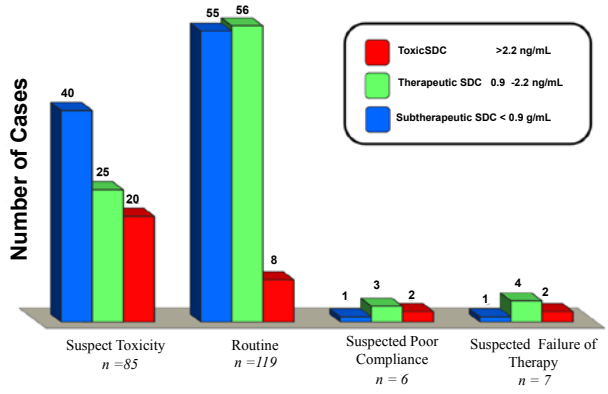


Figure 1: The indication of requesting serum digoxin concentration "SDC" (n=217).



SDC=Serum Digoxin Concentration

Figure 2: Relationship between different categories of SDC and the reason for requesting digoxin level (n=217).

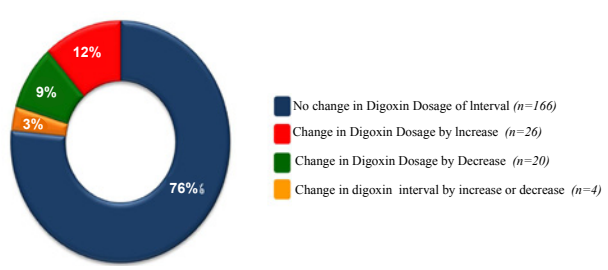


Figure 3: Doughnut Chart of percentages of patients requiring readjustment of digoxin dosage and/or interval (total n=217).

	Therapeutic SDC Group (n =88)		Subtherapeutic SDC Group (n=103)		Toxic SDC Group (n=26)	
	Total Group		Total Group		Total Group	
	Inpatient (n= 77)	Outpatient (n=11)	Inpatient(n=84)	Outpatient(n=19)	Inpatient(n=23)	Outpatient(n=3)
SDL (ng/mL) Mean ± SD	1.19 ± 0.26		0.67 ± 0.17		2.75 ± 1.2*	
	1.18 ± 0.59	126.6 ± 0.56	0.66 ± 0.4	0.52 ± 0.34	0.06 ± 0.8	1.06 ± 0.8
	All Groups (1.02 ± 0.8)					
Blood urea nitrogen (mg/dl) Mean ± SD	62.6 ± 36.2		57.77 ± 41.3		171.5 ± 91.3*	
	67.2 ± 41.3	30.9 ± 11.4	61.3 ± 49.2	39.4 ± 35.1	212.9 ± 191.2	23.83 12.4
Serum creatinine (mg/dl) Mean ± SD	1.58 ± 1.16		1.61 ± 1.51		1.97 ± 1.86	
	1.6 ± 1.1	1.2 ± 0.7	1.7 ± 1.6	0.8 ± 0.43	2.3 ± 1.9	0.8 ± 0.4
Serum potassium (mEq/L) Mean ± SD	4.2 ± 1.05		5.3 ± 1.3		3.9 ± 1.1**	
	4.3 ± 0.8	4.2 ± 0.6	5.7 ± 1.4	2.9 ± 1.8	4.1 ± 0.8	3.4 ± 1.7
Serum ALT (IU/L) Mean ± SD	57.8 ± 19.2		52.81 ± 49.8		93.7 ± 32.5*	
	61.7 ± 16.23	32.6 ± 7.4	58.95 ± 8.11	45.45 ± 12.11	108.7 ± 36.1	39.8 ± 20.3
Serum AST (IU/L) Mean ± SD	62.08 ± 25.9		42.9 ± 23.7		130.2 ± 45.9*	
	66.30 ± 19.4	30.6 ± 9.3	47.14 ± 27.3	19.4 ± 14.2	156.4 ± 41.1	35.3 ± 27.1
* P < 0.05% / ** P ≤ 0.01%						
Number (%) of studied cases laboratory findings according to different digoxin concentrations (n= 217)						
Blood urea nitrogen (mg/dl) (10-20 mg/dl)						
No (%) within normal range No (%) above normal range No (%) > triple the normal range	50 (56.8%) 32 (36.4%) 6 (6.8%)		77 (74.8%) 21 (20.4%) 5 (4.8%)		16 (61%) 6 (23.7%) 4 (15.3%)	
Serum creatinine (mg/dl) (0 .5 -1.1 mg/dl)						
No (%) within normal range No (%) above normal range No (%) > triple the normal range	50 (56.8%) 32 (36.4%) 6 (6.8%)		77 (74.8%) 21 (20.4%) 5 (4.8%)		16 (61%) 6 (23.7%) 4 (15.3%)	
Serum potassium (mEq/L) (3.5-5.5 mEq/l)						
No (%) Hypokalamia (<3.5 mEq/L) No (%)within normal range No(%)Hyperkalaemia(>5.5 mEq/L)	17 (19.3%) 69 (78.4%) 2 (2.3%)		13 (14.7%) 85 (82.5%) 5 (5.6%)		5 (19.2%) 19 (73.2%) 2 (7.6%)	
Serum ALT (IU/L) (5-40 IU/L)						
No (%) within normal range No (%) above normal range No (%) > triple the normal range	72 (81.9%) 11 (12.5%) 5 (5.6%)		67 (65%) 15 (13.5%) 21 (20.5%)		16 (61.5%) 6 (23.5%) 4 (15%)	
Serum AST (IU/L) (5-50 IU/L)						
No (%) within normal range No (%) above normal range No (%) > triple the normal range	65 (73.8%) 14 (16%) 9 (10.2%)		67 (66%) 16 (15.5%) 19 (18.5%)		20 (77%) 3 (11.5%) 3 (11.5%)	

Table 3: aboratory findings detected in relation to different SDC (n= 217).

cases required readjustment of dose or interval. On the other aspect, most of SDC results obtained in the study (76%) did not lead to clinical action, such as dose adjustment, drug holding and or interval changes. A considerable percentage reaching 24% of the studied cases required readjustment of dose by an increase in 12% or decrease in about 9% and interval changes (3%).

Discussion

This study presently being conducted consisted of 217 patients (36% males and 64% having a mean age ± SD: 63.18 ± 19 years). About 129 patients (59.4%) exhibited at least one sign, symptom, or an electro-cardiographic change that hinted at digoxin toxicity (20.2%) or sub-therapeutic digoxin level (79.8%). It was seen that the most common symptom associated with digoxin toxicity was high palpitation. Moreover, the toxic digoxin level was connected to non-statistically major and many more episodes of palpitation, nausea, vomiting and abdominal pain. At the same time, more or less the same results were observed in another study by Zibzeenezhad and Gharchehm [9]. It was also seen that the patients admitted to emergency departments because of digoxin intoxication complained of various problems. This included problems ranging from mild gastrointestinal complaint to syncope caused by severe bradycardia. What is of essence is that none of these complaints are specific to digoxin intoxication [5].

In current circumstances, there were many electro-cardiographic occurrences and alterations that happened to a great extent in cardiac patients who had toxic digoxin level than in cases with sub-therapeutic level. Therefore, one had to depend on Atrial fibrillation and heart block to identify the most frequent finding in toxic cases. It became the norm to check the patient for any arrhythmia occurring in a patient who has received digoxin. Premature ventricular beats and atrial fibrillation were the mostly encountered ECG changes found in the study conducted by Kirilmaz et al. [5].

All studied cases called for SDCs. About 88 patients were found to be eutherapeutic without any manifestations of toxicity. Those having digoxin toxicity (11.9%) with a higher mean SDC (2.75 ± 1.2) than those with sub-therapeutic (0.67 ± 0.17) or eutherapeutic SDC (1.19 ± 0.26).

The current work presently has a lot of the overall incidence of digoxin toxicity and was at 11.9%, higher than that found previously by Mahdyoon et al. [10]. After having conducted a detailed sample of 994 heart failure patients, it was seen that 56% had digoxin, diagnosis

of digoxin intoxication was seen to have affected just 5% of cases. Also, Garg et al. [11]. observed the incidence of hospitalization for presumed digoxin toxicity was about 0.9% in the placebo group with and only 2% in the digoxin group.

The 3 groups indicated similar factors such as age and sex. The mean SDCs were also situated within the normal range in different age groups. As against this, Miura et al. [12] studied the connection between SDC values and the incidences of digoxin toxicity in 899 Japanese cardiac patients receiving digoxin. Advancing age was also seen to be one of the predisposing factors for digoxin toxicity, which the authors suggested that the SDC therapeutic range for patients aged 70 years or older should be redefined as 0.5- 1.4 ng/ ml.

According to Goldberger and Goldberger [13] toxicity has risks that are likely to occur with serum concentrations >2 ng/ml and is almost certain at >3 ng/ml. As per another analysis, it was also seen that SDCs>1.2 ng/ml could possibly be harmful [14]. The serum digoxin level for chronic heart failure is recommended at not more than 0.6-1.2 ng/ml [15].

Several large clinical study initiatives demand a redefinition of the generally-accepted safe, and therapeutic range for digoxin therapy of 0.9 ng per mL to 2.2 ng/mL [16]. As seen in another report, this once accepted SDC therapeutic range was challenged by showing the symptom relief for heart failure at SDCs between 0.5 ng/mL and 0.8 ng/mL [2]. Similarly, the present results clarified that 52 cases (20.1%) showed SDC ranged between (0.5-0.9 ng/mL) without any kind of manifestations just for routine follow up.

It has been widely accepted that deteriorating renal functions and electrolyte abnormalities (hypokalemia) predispose patients to digoxin toxicity [17]. Our study deals with all these factors except creatinine. This element differed majorly ($P<0.5$) between the toxic and sub-therapeutic groups. Although the serum creatinine levels showed a tendency to be higher in patients with toxic digoxin concentration than those without intoxication, creatinine is not the best predictors of renal function, and creatinine clearance would have likely been more indicative [18].

A majority of SDC results obtained in the study (76%) did not lead to clinical action, such as dose adjustment, drug holding and or interval changes. A huge percentage of around 24% of the studied cases required re-adjustment of dose by an increase in 12% or decrease in about 9% and interval changes (3%). These findings were completely different from another study conducted by Orrico et al. [19] who clarified that the majority of SDCs ordered in their medical group setting for stabilizing cardiac patients provided little clinical action with just only one case who needed a dose lowering.

Summary and Conclusion

The results of this study indicated that the SDCs measured in cardiac patients receiving digoxin therapy is appropriate as it could provide highly useful information which could ameliorate the clinical decision concerning diagnosis of chronic digoxin toxicity. Furthermore, clinical manifestations of digoxin toxicity were not sufficient to be used for evaluation of drug toxicity separately. Hence, it is recommended that periodical monitoring of serum digoxin levels should be mandatory in all patients receiving digoxin especially when considering the narrow therapeutic index of this drug.

References

1. Winter ME (2009) Basic Clinical Pharmacokinetics (5thedn), Baltimore MD: Lippincott Williams & Wilkins.
2. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM (2003) Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 289: 871-878.
3. Gilman GA, Rall TW, Neis AS (2001) The Pharmacological Basis of Therapeutics (10th Edn), McGraw Hill.
4. Caspi O, Zylber-Katz E, Gotsman O, Wolf DG, Caraco Y (1997) Digoxin intoxication in a patient with end-stage renal disease: efficacy of digoxin-specific Fab antibody fragments and peritoneal dialysis. Ther Drug Monit 19: 510-515.
5. Kirilmaz B, Saygi S, Gungor H, Onsel Turk U, Alioglu E, et al. (2012) Digoxin intoxication: An old enemy in modern era. J Geriatr Cardiol 9: 237-242.
6. Kelly RA, Smith TW (1992) Recognition and management of digitalis toxicity. Am J Cardiol 69: 108G-118G.
7. Cañas F, Tanasijevic MJ, Ma'luf N, Bates DW (1999) Evaluating the appropriateness of digoxin level monitoring. Arch Intern Med 159: 363-368.
8. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, et al. (2009) 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 119: 1977-2016.
9. Zibzeenezhad M and Gharchehm M (2007) The applicability of International Reports Toxicity to Iranian Patients. Iranian Cardiovascular Reasearch Journal 1: 1.
10. Mahdyoon H, Battilana G, Rosman H, Goldstein S, Gheorghiade M (1990) The evolving pattern of digoxin intoxication: observations at a large urban hospital from 1980 to 1988. Am Heart J 120: 1189-1194.
11. [No authors listed] (1997) The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 336: 525-533.
12. Miura T, Kojima R, Sugiura Y, Mizutani M, Takatsu F, et al. (2000) Effect of aging on the incidence of digoxin toxicity. Ann Pharmacother 34: 427-432.
13. Goldberger ZD, Goldberger AL (2012) Therapeutic ranges of serum digoxin concentrations in patients with heart failure. Am J Cardiol 109: 1818-1821.
14. Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, et al. (2005) Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol 46: 497-504.
15. Kockova R, Skvaril J, Cernohous M, Maly M, Kocka V, et al. (2011) Five year two center retrospective analysis of patients with toxic digoxin serum concentration. Int J Cardiol 146: 447-448.
16. Winter ME (2009) Basic Clinical Pharmacokinetics (5thedn), Baltimore, MD: Lippincott Williams & Wilkins.
17. Katzung BG, Parmley WW (2004) Drugs used in heart failure In: Basic & Clinical Pharmacology (9th edn), Katzung BG, New York: McGraw Hill.
18. Piergies AA, Worwag EM, Atkinson AJ Jr (1994) A concurrent audit of high digoxin plasma levels. Clin Pharmacol Ther 55: 353-358.
19. Orrico KB, Wu M, Wilson AR (2011) Assessment of the appropriateness of serum digoxin concentration measurement in a medical group setting. J Manag Care Pharm 17: 695-700.