Ain Shams Journal of Forensic Medicine and Clinical Toxicology
January 2013, 20: 51-60

Correlation between Serum Digoxin Concentration and Impaired Renal or/and Hepatic Functions in Cardiac Patients

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Abstract Digitalis toxicity is characterized by gastrointestinal, neurologic and non-specific cardiac manifestations with striking similarities to the clinical picture of primary congestive heart failure (CHF) making 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. This study comprised of 217 adult patients (78 males and 139 females) with mean age ± SD (63.18 ±19 years). There were high concentrations of digoxin which led to unstable renal and liver functions. 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 concentration 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 (Winter, 2009). 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 is very likely a contributing factor to the suspected decrease in digoxin toxicity; Yet, elevated concentrations are not the only reasons for toxicity (Mordasini et al., 2002; Rathore et al., 2003).

There is a tendency to overlook Digoxin intoxication because of its variable bioavailability and because of differences in its gastrointestinal absorption, distribution and excretion (Gilman et al., 2001). 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 (Caspi et al., 1997; Kirilmaz et al., 2012).

It was observed that in cardiac patients, the therapeutic range for digoxin was in the range from 0.9 to 2.2 mg/ml (Kelly and Smith, 1992). Also, the serum

digoxin concentrations 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 up to death (Caspi et al., 1997).

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 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 (Cañas et al., 1999; Jessup et al., 2009).

The present work aims at raising the precautions against digoxin toxicity in renal and hepatic impairment cardiac patients and evaluating the clinical value element of serum digoxin concentrations (SDCs) with regard to appropriate assessment of chronic digitalis toxicity.

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

Exclusion criteria

Patients aged less than 18 years old, severe heart failure, severe hepatic failure, severe hypertension, a history of acute digitalis toxicity that resulted from intention ingestion of digoxin therapy, patients presently on interrupted prescriptions for digoxin or patient there being zero gaps in therapy for less than 10 days prior to SDC result were excluded from the study.

Study population parameters

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

Indications for digoxin treatment, clinical manifestations and electrocardiographic 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 functions values were evaluated at the same time of estimating the SDC. Important laboratory activities and investigations such as blood urea nitrogen, serum creatinine concentration, and 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.

The studied cases were divided into 2 groups according to the stability of hepatic and renal functions as follows (Pincus and Abraham 2006):

- **Stable liver and renal functions**: Normal laboratory finding or slightly increased.
- **Unstable liver and renal functions**: Abnormal laboratory findings "More than a triple fold of the upper border of normal range".

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 access by way of medical record number access into the EMR. Pre-defined 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 them. The study was approved by the Medical Ethics Committee of the Dammam Regional Poison Control Center with complete confidentiality of patient information records as maintained by keeping patients names anonymous.

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 (S.D.). 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 were requested in the entire 12-month (1 year) study period.

Tables (1) and (2) show the different characters of the patients. These patients were studied and analyzed against vital benchmarks like age, gender, admission status, manifestations of digoxin toxicity, associated electro-cardiographic changes, liver and renal functions as well as levels of potassium. In this case, about eighty-eight patients were excluded for being identified and later confirmed as 'eutherapeutic' and classified as bearing "no toxicity".

There were laboratory experiments done which led to findings 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 potassiumlevel when compared with sub-therapeutic SDCs group.

One notices in Table (4) the digoxin concentrations and dosing data with regard to the medical indication for digoxin, its dosage, as well as the time of sampling and route of administration.

Figure (1) illustrates the indication of requesting SDC. About 54.8% of patients were part of routine assessment to check for indications of toxicity. About 39.2% had suspected toxicity while the rest of the 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 concentration. 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.

Table1: Statistical analysis of age, gender, admission status, renal functions status, liver functions status, and serum potassium level in the studied patients (n=217).

Age in years mean (range)	63.8± 19	
Gender	Male 78 (36%)	Female 139 (64%)
Admission Status	No	%
Inpatient	183	84.3%
Outpatient	34	15.7%
Renal functions status		
Stable	169	77.9%
Unstable	48	23.1%
Liver functions status		
Stable	191	88%
Unstable	26	12%
Serum potassium level		
Normal Level (3.5-5.5 mEq)	191	88%
Hypokalaemia (<3.5 mEq)	22	10.2%
Hyperkalaemia (>5.5 mEq)	4	1.8%

Table 2: Percentages of symptoms and or electrocardiographic changes in patients with abnormal digoxin concentration (n= 129).

	No. (%) of Patients	
	Subtherapeutic Digoxin Concentration (< 0.9 ng/mL) (n= 103)	**Toxic Digoxin Concentration (>2.2 ng/mL) (n=26)**
Associated Symptoms &/or ECG changes	95 (92.2%)	25 (96.2%)
Symptoms		
Anorexia	2 (1.9%)	2 (7.6%)
Nausea	1 (1.9%)	6 (23.1%)
Vomiting	5(4.9%)	5 (19.2%)
Abdominal Pain	17 (16.4%)	5(19.2%)
Diarrhea	1 (0.97%)	4 (15.3%)
Dizziness	7(6.7%)	2 (7.6%)
Headache	4 (3.8%)	1 (3.8%)
Confusion	16 (15.5%)	0 (0%)
Visual Changes	1(0.97%)	1 (3.8%)
Palpitation	6(5.8%)	7 (26.9%)
Cough	1(0.97%)	1(3.8%)
Dyspnoea	10 (9.7%)	4(15.3%)
Electrocardiographic Changes		
Atrial Fibrillation	13 (12.6%)	7 (26.9%)
Bradycardia (50 beats/min)	5 (4.9%)	2(7.6%)
Junctional Tachycardia	0(0.0%)	0(0%)
Sustained ventricular tachycardia	1(0.97%)	0(0%)
Sinus arrest	4(3.8%)	1(3.8%)
Heart block	0(0%)	4(15.3%)
Eighty eight (88) patients were eutherapeutic and classified as "no toxicity" (Serum digoxin concentration = 0.9 – 2.2 ng/mL).		

Table 3: Statistical analysis correlating serum digoxin concentration (SDC), blood urea nitrogen, serum creatinine, serum potassium, ALT, and AST between studied groups (n= 217).

	Therapeutic SDC Group (n =88)	**Subtherapeutic SDC Group (n=103)**	**Toxic SDC Group (n=26)**
SDL (ng/mL) Mean ± SD	1.19 ± 0.26	0.67 ± 0.17	2.75 ± 1.2*
	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*
Serum creatinine (mg/dl) Mean ± SD	1.58±1.16	1.61± 1.51	1.97±1.86
Serum potassium (mEq/L) Mean ± SD	4.2±1.05	5.3±1.3	3.9±1.1**
Serum ALT (IU/L) Mean ± SD	57.8±19.2	52.81±49.8	93.7±32.5*
Serum AST (IU/L) Mean ± SD	62.08±25.9	42.9±23.7	130.2±45.9*

** $P < 0.05$; ** $P \leq 0.01$*

Table 4: Digoxin dosing data in the studied patients (n=217).

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 defect 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 hours	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%)

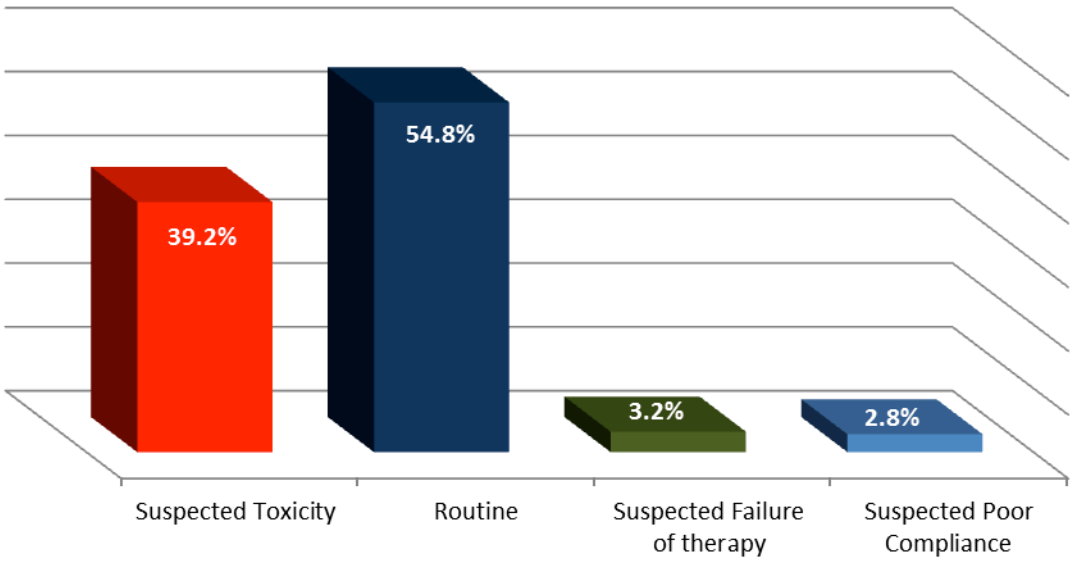

Figure 1: The indication of requesting serum digoxin concentration "SDC" (n= 217).

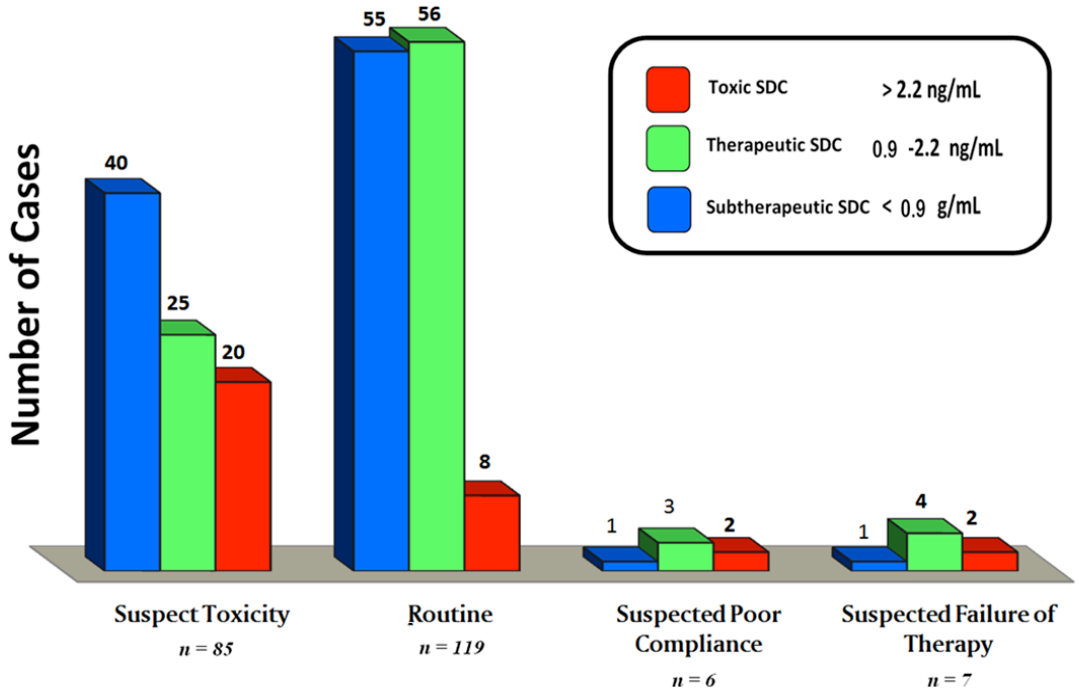

Figure 2: Relationship between different categories serum digoxin concentration (SDC) and the reason for requesting it (n= 217).

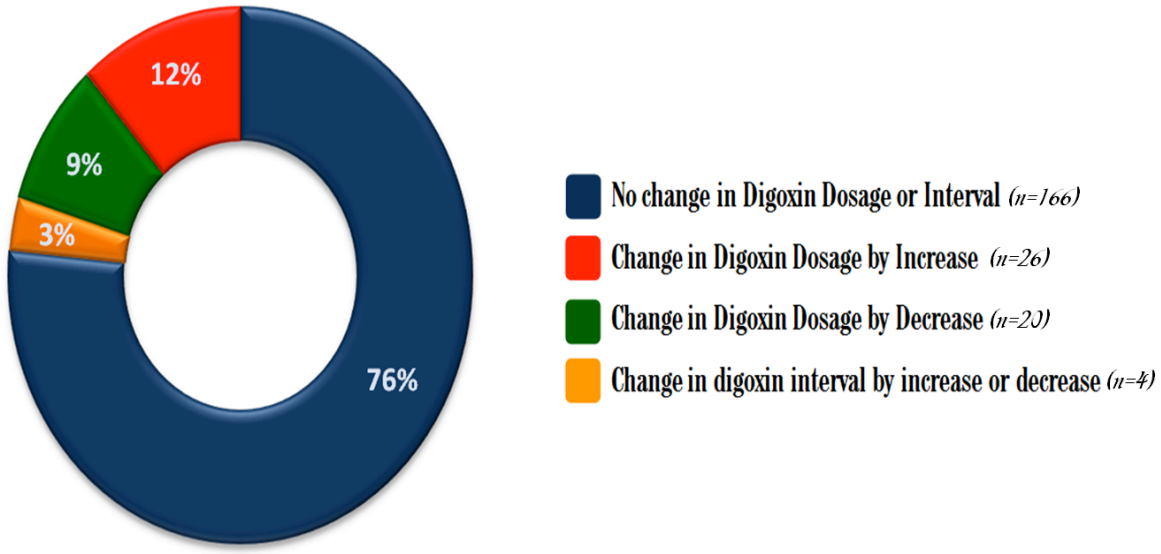

Figure 3: Doughnut Chart of percentages of patients requiring readjustment of digoxin dosage and/or interval (total n= 217).

Discussion

This study presently being conducted consisted of 217 patients (36% males and 64% having mean age ± SD: 63.18 ±19 years). About 129 patients (59.4%) exhibited at least one sign, symptom, or an electrocardiographic change that hinted at digoxin toxicity (20.2%) or sub-therapeutic digoxin concentration (79.8%). It was seen that the most common symptom associated with digoxin toxicity was high palpitation. Moreover, toxic digoxin concentration 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 (2007). 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 (Kirilmaz et al., 2012).

According to Kanji and MacLean (2012) digitalis toxicity creates a toxidrome that is accompanied by gastrointestinal, neurologic, electrolyte, and non-specific cardiac manifestations. Even in today's modern times, chronic toxicity is not easy to identify. This is largely because of its non-specific manifestations. Naturally, serum glycoside concentrations are extremely vital for effective diagnosis in this kind of population. Also, Koda-Kimble et al. (2005) believed that it was proper predictors of an elevated SDC that helped in understanding clinical signs and symptoms of digoxin toxicity were only fair predictors of an elevated SDC (> 2mg/ml).

In current circumstances, there were many electrocardiographic occurrences and alterations that happened to a great extent in cardiac patients who had toxic digoxin concentration than in cases with sub-therapeutic concentration. 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., 2012).

That digoxin reversibly halts the sodium-potassium pump and thus inhibits sodium from being pumped out of cells and potassium from being pumped in. Moreover, potassium competes with digoxin in terms of respect to binding to the Na, K pump. Therefore, as the serum potassium concentration is reduced for example by diuretics, the inhibition of the Na, K pump by digoxin is further facilitated (Katzung and Parmley, 2004). In consequence, the depletion of intracellular potassium might occur, and is connected digoxin-induced arrhythmia (Wang et al., 2010).

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 overall incidence of digoxin toxicity and was at 11.9%, higher than that found previously by Mahdyoon et al. (1990). 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. (1997) 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 gender. The mean SDCs were also situated within the normal range in different age groups. As against this, Miura et al. (2000) 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 factor 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 Goldbergerand Goldberger (2012), 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 (Adams et al., 2005). The serum digoxin concentration for chronic heart failure is recommended at not more than 0.6-1.2 ng/ml (Kockova et al., 2011).

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 (Winter, 2009). 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 (Rathore et al., 2003). 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.

As part of the present work, it was seen that 48 patients had impaired renal functions whereas 26 cases indicated disturbed liver functions and a sharp decrease in the mean serum levels of AST (130.2±45.9) and ALT (93.7±32.5). With regard to the digoxin intoxicated group, one noticed a substantial hike in the serum levels of BUN (171.5±91.3) and creatinine (1.97±1.86). Marik and Fromm (1998) thus observed that the mean creatinine level was about 3. As for the other side, Kirilmaz et al. (2012) reported relatively lower levels of urea and creatinine levels (1.5± 0.6).

Moreover, hypokalaemia and hyperkalaemia were seen in 10.2% and 1.8% of cases respectively. A huge decrease was observed in the serum potassium level in the toxic digoxin group when compared with sub-therapeutic SDCs group.

It has been widely accepted that deteriorating renal functions and electrolyte abnormalities (hypokalemia) predispose patients to digoxin toxicity (Goldbergerand Goldberger, 2012). 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 (Piergies et al., 1994).

Serum creatinine and potassium are known to better correlate with digoxin toxicity (Orrico et al., 2011).Binding of digoxin to the Na/K-ATPase transport system is inhibited by high levels of potassium. Thus, hypokalaemia increase digoxin toxicity, and hyperkalaemia is claimed to be protective (Dawson and Buckley, 2011).

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 contrast, Kirilmaz et al. (2012) reported that 50.7% of patients received digoxin for only heart failure. The authors also stated that 23.7% of patients were on the drug for atrial fibrillation while 25.4% received digoxin for both conditions. Daily digoxin dose taken by most patients was 0.25 mg.

The present study used about 95.8% of patients' samples that were taken 6 hours or later after the last dose. The concentrations of digoxin concentrations were measured 6 hours or later so as to avoid any wrong assessment caused by the distribution characters of digoxin. Also, samples taken after 6 hours enable more accurate estimation of the body's digoxin burden (Dasgupta, 2008; Dawson and Buckley, 2011). The frequency of digoxin concentrations determined before 6 hours after intake was relatively low in our study (4.2%) denoting that a responsible physician is not ignorant of this aspect.

In the case of Digoxin, there is quite a long initial distribution phase of about 4-8 hours that lasts 4–8 hours indicating distribution from the central compartment to peripheral tissues compartments. The elevated digoxin plasma concentrations during the distribution phase are mostly clinically irrelevant and might prompt clinicians to unnecessary actions such as adjusting the digoxin dose (Mulder et al., 2010).

Routine indication (54.8%) was seen to be the most widely-used reason for requesting SDC in the current research while 39.2% had suspected toxicity. Other requests concerned suspected failure of therapy (3.2%) and poor compliance (2.8%). Sidwell et al. (2003) studied the utility of 100 SDCs drawn at Christchurch Hospital in New Zealand and categorized 53% of requests as routine indication without clear landmark to the accurate and correct therapeutic range.

A majority of SDC results obtained in 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 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. (2011) who clarified that the majority of SDCs ordered in their medical group setting for stabilized cardiac patients provided little clinical action with just only one case who needed dose lowering.

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 concentrations should be mandatory in all patients receiving digoxin especially when considering the narrow therapeutic index of this drug.

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الملخص العربي

العلاقة بين مستوى الديجوكسين و الاضطرابات في وظائف الكبد والكلى في مرضى القلب

أحمد رفعت رجب[1،2] و مها خالد المزروع[2] و رانيا حامد عبد الرحمن[1]

إن التسمم بالديجيتاليس (digitalis) يتميز بأعراض في كل من الجهاز الهضمي، والعصبي، وبعض المظاهر القلبية الغير مميزة مع وجود تشابه كبير في تلك الأعراض مع الحالة الإكلينيكية لقصور القلب الاحتقاني الأولى مما يجعل تشخيص السمية المزمنة للديجيتاليس على وجه الخصوص صعبا نسبيا. ولذلك فإن إجراء قياسات الديجوكسين يعد نقطة جوهرية في تلك الحالات نتيجة لضيق النافذة العلاجية للديجوكسين بالإضافة لزيادة معدلات الإعياء والوفيات الناجمة عن التسمم من هذا الدواء.

والهدف من هذا العمل هو تقييم الفائدة الإكلينيكية لقياس تركيزات الديجوكسين ومدى تناسبها مع تشخيص السمية المزمنة للديجيتاليس في مرضى القلب. وقد أجريت هذه الدراسة عن طريق مراجعة السجلات الطبية الإلكترونية لمرضى القلب والذين يعالجون بالديجوكسين دون توقف لمدة لا تقل عن 10 أيام قبل إدخال نتيجة قياس تركيز الديجوكسين في الطلب التحليلي للسموم على الإنترنت مع أخذ التقرير الإكلينيكي الكامل للمرضى ونتائج وظائف الكلى والكبد وقياسات تركيز البوتاسيوم.

وقد اشتملت هذه الدراسة على 217 مريضا بالغا (78 من الذكور و139من الإناث) وكان متوسط أعمارهم (63.18 ± 19 عاما). وقد تبين وجود اختلال في وظائف الكلي والكبد لدى هؤلاء المرضى مما ساهم في ارتفاع مستويات الديجوكسين. كما أظهرت النتائج وجود انخفاض في تركيز البوتاسيوم في حوالي 12٪ من المرضى.

ويمكن أن نخلص من هذه الدراسة إلى أن التقييم المنتظم لمستوى الديجوكسين في مرضى القلب يعتبر ضرورة ملحة للتحقق من مدى فاعلية الآثار العلاجية وكذلك الوقاية والتشخيص المبكر للسمية المزمنة لهذا الدواء.

1 قسم الطب الشرعي والسموم الإكلينيكية كلية الطب جامعة المنصورة، مصر
2 المركز الإقليمي لمراقبة السموم بالدمام. المنطقة الشرقية، المملكة العربية السعودية