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OPTIMIZATION OF DIGOXIN THERAPEUTIC DRUG MONITORING (TDM): A PROSPECTIVE DIAGNOSTIC DIGITALIS TOXICITY OF 217 PATIENTS

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ABSTRACT

Digoxin toxicity is obvious as it has narrow therapeutic window. Patients on this drug behave differently with the same dose there is variability in serum digoxin concentration and in therapeutic response. Digoxin toxicities are gastrointestinal, neurological and are manifested simpler to the clinical picture of primary congestive heart failure (CHF) and in chronic digitalis toxicity the diagnosis induced by toxicities are relatively difficult. Due to toxicities of digoxin intoxication, mortality and morbidity is increased. The present work is focused to elaborate the clinical value of serum digoxin concentration (SDCs) in relation to appropriate assessment of chronic digitalis toxicity in cardiac patients. This is a prospective study and patients were on continuous prescription for digoxin. The patients were continuously taking digoxin for 10 days when the sample was drawn for the SDC. Complete clinical examination report as well as review of the results of serum potassium concentration, liver and kidney functions were estimated and assessed. Patients with digoxin toxicity (11.9%) had a significantly higher mean SDC (2.75±1.2) ng/ml than those with sub-therapeutic (0.67±0.17ng/ml) or therapeutic SDC (1.19±0.28ng/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 potassium concentration would be mandatory for the verification of digoxin's therapeutic effects and then the subsequent prevention and early diagnosis of chronic toxicity.

Keywords: Therapeutic Drug Monitoring, Digoxin, Tertiary Care, Cardiacpatients, Therapeutic range, Toxicity, Medical Intensive Care Unit, Serum Digoxin Concentrations.

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 maybe 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 of toxicity [2]. There is 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 narrow therapeutic window which could

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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 ng/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 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 asses clinical response; to asses 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 SKIMS, Soura JK India. Therapeutic drug monitoring was started as an attempt to protect patients against drug toxicity. Digoxin assays were the first to emerge in the market and used by the laboratories[9].After five decades, TDM has evolved a multidisciplinary field of medicine where laboratory and clinical specialists join on the common purpose of personalizing the dosage of therapeutic agents[10][11]. Situations that may be appropriate for TDM include dosage adjustment, confirmation of suspected toxicity, identification of non-compliance management of drug interaction and specific clinical conditions like in the case of uremic patients, patients with liver disease, pediatric and geriatric patients, critically ill patients and pregnant[10][12]. The narrow therapeutic range of digoxin means that small variations in blood concentration may easily result in toxic or sub-therapeutic concentration. To maintain concentration within the therapeutic range requires consistent bioavailability and careful management of factors that may influence bioavailability [13]. It is common practice among cardiologists to prescribe daily digoxin dosage regimen and interrupted dosage regimen. A digoxin holiday is given when the patient is given the dose five or six days a week to minimize digoxin toxicity due to the lack of therapeutic drug monitoring. It is not clear whether this holiday is justified in all cases, since digoxin plasma levels might decrease to below therapeutic levels [14].Several different reports refer to the acceptable range of digoxin. Some authors suggest range between 0.8ng/ml and 2.0ng/ml and others propose range between 0.5 and 1.5ng/ml [15]. Digoxin continues to have an important role in the control of ventricular rate with atrial fibrillation, and as a positive inotropic agent in heart failure. Therapeutic Drug Monitoring (TDM) for digoxin was introduced more than 50 years ago, and resulted in a reduction in the incidence of digoxin toxicity. However, despite a long experience of TDM with this drug, the way in which TDM is performed is often inappropriate as highlighted. Therapeutic Drug Monitoring of digoxin is in appropriately indicated in all countries [16].

MATERIAL AND METHODS

Study setting

It was a prospective study carried out at SKIMS, Soura JK India. Study subjects were routinely coming in OPD and IPD particularly from Cardiology and Medical Intensive Care Unit (MICU). Tertiary care Institute provides the TDM services to the hospital and other associated hospitals in Srinagar city at Jammu and Kashmir State in India. This study was carried out in January 2012 to December 2013 in two years time. Samples were collected after the patients requisition form was properly filled by the concerned doctor. Samples were drawn only when the patient was in steady state or in some cases random sample was drawn.

Inclusion criteria

Adult patients monitored for SDC in one hospital SMHS, Srinagar and SKIMS that were participating for Heart Failure in these two years time, once the therapeutic range has been reached, it in two years long period from the beginning of January 2012, until the end of December, 2013.

Study population parameters

Investigators noted down important and detailed information of all the patients, like their age, 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 (2,4,6,8and10 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, 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

EMIT System assay sensitivity ranges [0.2-5.0ng/mL]. Calibrators 0.2, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 ng/ml with three controls were used along with the samples. Quality control was used to validate the samples as per the protocol. There was minimal error in quantifying the systematic and random error. Interday and intraday error was minimal below 10%.

Clinical Chemistry was carried out at SKIMS, Soura in the department of Biochemistry which is carrying routine investigations round the clock. All the biochemical investigations are being carried out under a thorough check on Auto Analyser. These tests were carried out in the Biochemistry Department: Blood urea nitrogen, Serum creatinine, Serum Potassium, Serum ALT, and Serum AST.

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 0.9–2.2ng/ml

Group B: Patients with sub-therapeutic serum digoxin level<0.9ng/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. Taking the help of individual patient records, the individual patient records were assessed by way of medical record number accession. 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 them. The study was approved by the Medical Ethics Committee of the SKIMS, JK-INDIA.

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 (36%) and 139 females (64%) with mean age ± SD: 57.18 ± 10.90 years). Therefore, a total of 217 SDCs was requested in the entire 24-month (2 years) study period.

Table-1 shows 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 patients samples were taken 6 hours or later after the last dose. Digoxin levels were measured 6 hours later to avoid any wrong assessment caused by the distribution characters of digoxin. Table 2, shows 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 sub-therapeutic 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 therapeutic group were palpitation and dyspnea (26.5% and 4.55%) respectively. There were laboratory experiments done which led to findings detected with regard to the different SDCs, were presented in Table 3A and 3B. While patients with digoxin toxicity showed a majority higher mean SDC, those that did not, were seen to be having sub-therapeutic or therapeutic SDC (P value $\leq$ 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 distinct decrease the serum Potassium level when compared with sub-therapeutic SDC group. Patients with digoxin toxicity (11.9%) had a significantly higher mean SDC (2.75±1.2) than those with sub-therapeutic (0.67±0.17) or therapeutic SDC (1.19 ± 0.26) (p value $\leq$ 0.05). Laboratory findings detected in relation to different SDCs were also presented in Table 3A, 3B. Patients with digoxin toxicity had a significantly higher mean SDC in those with sub-therapeutic or therapeutic SDC (P value <0.05). There was a significant decrease in serum levels of BUN, AST and ALT value < 0.05 and a highly significant decrease in the serum Potassium level when compared with a sub-therapeutic SDCs group (P value $\leq$ 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 toxicity 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% and1.8% of cases respectively. There was a highly significant decrease in the serum Potassium level in the toxic digoxin group when compared with a sub-therapeutic SDCs group.

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

Age in years mean (range)	**57.18+10**	
Sex	Male 78 (36%)	Female 139 (64%)
Admission Status	No. of Patients (%)	
Inpatient	183(84.3%)	
Outpatient	34(15.7%)	
Renal functions status Stable "Normal Laboratory Findings"	169(77.9%)	
Unstable " Marked abnormal Laboratory Findings"	48(23.1%)	
Liver functions status		
Stable "Normal Laboratory Findings"	191(88%)	
Unstable " Marked abnormal Laboratory Findings"	26(12%)	
Potassium level	191(88%)	
Normal Level (3.5-5.5 mEq) Hypokalaemia (<3.5 mEq)	22(10.2%)	
Hyperkalaemia (>5.5 mEq)	4(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 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 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 2. Frequency of symptoms and or electrographic changes in patients with Abnormal Digoxin concentration (n=129)

	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%)
Dyspnea	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 3A. Laboratory findings detected in relation to difference SDC (n=217)

	Therapeutic SDC Group (n=88)		**Sub therapeutic SDC Group (n=103)**		**Toxic SDC Group (n=36)**	
	Total Group		**Total Group**		**Total Group**	
	Inpatients (n=22)	**Outpatients (n=11)**	**Inpatients (n=49)**	**Outpatients (n=19)**	**Inpatients (n=27)**	**Outpatients (n=3)**
SDC(mg/mL) Mean ± SD	1.19 ± 0.26		0.67 ± 0.17		2.75 ± 1.2*	
	1.18 ± 0.59	1.26 ± 0.56	0.66 ± 0.40	0.52 ± 0.34	0.06 ± 0.80	1.06 ± 0.80
	All Groups (1.02 ± 0.80)					
BUN(mg/mL) Mean ± SD	62.6 ± 36.2		57.7 ± 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
S.C.(mg/mL) Mean ± SD	1.58 ± 1.16		1.61 ± 1.5		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
S.K.(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
S.ALT(IU/L) Mean ± SD	57.8 ± 19.2		52.81 ± 49.8		93.7 ± 32.5*	
	61.7 ± 16.2	32.6 ± 7.4	58.9 ± 8.1	45.5 ± 12.1	108.7 ± 36.1	39.8 ± 20.3
S.AST(IU/L) Mean ± SD	62.08 ± 25.9		42.9 ± 23.7		130.2 ± 45.9*	
	66.3 ± 19.4	30.6 ± 9.3	47.1 ± 27.3	19.4 ± 14.2	156.4 ± 41.1	30.3 ± 27.1
*p<0.05, **p ≤ 0.01,S.C, Serum Creatinine, S.K, Serum Potassium						
Number(%) of studied cases laboratory findings according to digoxin concentrations (n=217)						

Table 3B. Laboratory findings detected in relation to difference SDC (n=217)

Blood Urea nitrogen (mg/dl) (10-20 mg/dl)			
	Therapeutic SDC Group (n=88) (%)	**Sub therapeutic SDC Group (n=103) (%)**	**Toxic SDC Group (n=36) (%)**
Within normal range	50(56.8%)	77 (74.8%)	16 (61%)
Above normal range	32 (36.4%)	21 (20.4%)	6 (23.7%)
Triple normal range	6 (6.8%)	5 (4.8%)	4 (15.3%)
Serum creatinine (mg/dl) (0.5-1.1mg/dl)			
Within normal range	50(56.8%)	77 (74.8%)	16 (61%)
Above normal range	32 (36.4%)	21 (20.4%)	6 (23.7%)
Triple normal range	6 (6.8%)	5 (4.8%)	4 (15.3%)
Serum potassium (mEq/L) (3.5-5.5 mEq/L)			
Within normal range	17(19.3%)	13(14.7%)	5 (19.2%)
Above normal range	69 (78.4%)	85 (82.5%)	19 (73.2%)
Triple normal range	2 (2.3%)	5 (5.6%)	2 (7.6%)
Serum ALT (IU/L) (5-40 IU/L)			
Within normal range	72 (81.9%)	67 (65%)	16 (61.5%)
Above normal range	11 (12.5%)	15 (13.5%)	6 (23.5%)
Triple normal range	5 (5.6%)	21 (20.5%)	4 (15%)
Serum AST (IU/L) (5-40 IU/L)			
Within normal range	65 (73.8%)	67 (66%)	20 (77%)
Above normal range	14 (16%)	16 (15.5%)	3 (11.5%)
Triple normal range	9 (10.2%)	19 (18.5%)	3 (11.5%)

Cases required readjustment of dose or interval, 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 case 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% male and 64% female having mean age 63.18 ± 19years. 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 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 [17]. 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 intoxications [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 toxic cases [5]. It became the norm to check the patients for any arrhythmia occurring in a patient who has receive digoxin Premature ventricular beats and atrial fibrillation were the mostly encountered ECG changes found in the study conducted so far [5]. All studied cases called for SDCs, about 88 patients were found to be therapeutic 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 therapeutic 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 [18]. 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, [19], 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. [20] 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 70years or older should be redefined as 0.5-1.4ng/ml. According to [21] toxicity has risks that are likely to occur with serum concentrations >2ng/ml and is almost certain at >3ng/ml. As per another analysis, it was also seen that SDCs >1.2ng/ml could possibly be harmful [22]. The serum digoxin level for chronic heart failure is recommended at not >0.6-1.2 ng/ml [23]. 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 [24]. 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 52cases 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 [25]. 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 [26]. 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 [27] 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 show that the measurement of SDCs of digoxin in cardiac patients is an important step towards the optimization of TDM. Digoxin has narrow therapeutic window and it is very difficult to maintain the potassium homeostasis in digoxin therapy, particularly when cardiac patients are switched on many drugs. In these patients, cardiologists have to prescribe many drugs because these patients have co morbidity and mostly hypokalemia makes the situation more severe as also the LFT and KFT tests are mandatory in these situations. Digoxin level makes a physician aware about the diagnosis of chronic digoxin toxicity because CHF is a chronic disease. Clinical evaluation of drug toxicity of digoxin cannot be taken separately but it is a step that should be dealt in accordance with the monitoring of SDCs as a TDM programme where the laboratory work is facilitated with quality control measures. So the need is to make TDM mandatory in all patients receiving digoxin which has a narrow therapeutic index. Individualizations of treatment is also important as therapeutic range is a population study but the level of digoxin is not relative term but it is an absolute quantity required as per the patient and its biochemical and pathophysiological conditions.

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