DIGOXIN COMPLIANCE: A PHARMACOKINETIC QUANTIFICATION

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SUMMARY: To quantify extent of compliance in patients receiving digoxin by implementing an applied pharmacokinetic approach and to determine the percentage of patients with levels within therapeutic range.

One hundred-nineteen patients, whom met the required criteria, were enrolled in this study. Based on their digoxin doses, they were divided into 4 groups. Group A took 1 tablet (0.25 mg) per day, group B received half a tablet (0.125 mg) each day, group C used 6 tablets per week, and group D took 5 tablets per week and two days were off the drug. A pharmacokinetic approach was used to predict the serum digoxin concentrations of patients and the expected levels were compared with the actual concentrations.

52.29% of patients were compliant. There was no significant difference between the compliant and non-compliant groups with regard to gender, age, and number of concurrent medications or duration of digoxin intake. However, with respect to their doses, a significant difference existed between 2 groups ($p<0.01$). Patients in group D were more compliant (80.56%). In addition, their serum digoxin concentrations were relatively more within the therapeutic range (89.66%). Therefore, patients with the lowest frequency of digoxin intake were more compliant.

The results of this study indicate that a considerable number of patients do not take digoxin as directed. Patients with the least frequency of digoxin intake were relatively more compliant.

Key Words: Digoxin, concentration, compliance, pharmacokinetics.

INTRODUCTION

Digoxin, an oral inotropic drug, is an important therapeutic option in the management of congestive heart failure (CHF). Even though it is known as a drug with a narrow therapeutic index, due to several factors, its use has increased in recent years (1). Routine monitoring of digoxin levels has an undeniable role in this regard. In addition, monitoring is helpful in the evaluation of compliance. In the last three decades, clinicians and clinical research scientists have become more aware of the fact that patients do not always comply with prescribed drug therapy (2). In fact, patients with chronic illnesses are more liable to non-compliance, which can have a decisive influence on the outcome of their therapeutic regimens and the cost of their health care.

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The primary goal of this study was to quantify extent of compliance in patients receiving digoxin by implementing an applied pharmacokinetic approach and to determine the percentage of patients with concentrations within the therapeutic range.

MATERIALS AND METHODS

This prospective study was carried out from October 2002 to May 2003. After approval by human ethical committee of the Shahid Sadoughi Medical University, a written informed consent was obtained from each patient. All patients attending Sayedoshohada, an ambulatory cardiac clinic in the province of Yazd, and who fulfilled the following criteria were enrolled in this study. They had to have been taking the same brand of digoxin tablet (0.25 mg) for at least one month prior to ensure that steady state levels had been reached. In addition, they were not taking drugs that could affect digoxin concentration. Patients were excluded if they were under 15 years of age, pregnant, suffered from hepatic or renal failure, or had thyroid diseases (3–5). Patients were not enrolled if they were taking drugs known to affect the digoxin concentration such as amiodarone, tetracycline, erythromycin, verapamil, and metoclopramide. All of the patients claimed to be taking their drugs as directed.

The attending cardiologist recorded demographic characteristics, history of disease(s) of patients, results of EKG's, and clinical signs and symptoms. A pharmacist recorded a detailed digoxin dosage history including dose, frequency of dosage, time of the last dose, and concurrent medications. Symptoms of probable toxicity were checked by either the physician or the pharmacist.

Patients were classified into 4 groups based on their digoxin dosages. Group A received one tablet per day, group B took half a tablet per day, group C used 6 tablets per week and 1 day was (Friday) off the drug, and group D took 5 tablets per week and 2 days were (Monday and Friday) off the drug. It should be pointed out that dosing was based on the severity of CHF and age of each patient.

Blood was collected 22 to 24 hours after the last dose and patients had an hour of rest before blood collection because physical activity can decrease digoxin levels (5, 6). Serum digoxin concentration was determined by the AMERLEX Digoxin RIA Kit with the sensitivity of 0.06 ng/ml. Levels of creatinine, sodium, potassium, calcium, and magnesium were also measured.

Since digoxin is not distributed in the adipose tissue, lean body weight (LBW) was used in the calculation (6). The actual body weight was used when the LBW was greater than the actual one.

Equation 1:

$LBW_{(male)} = 50\ kg + 2.3$ x (height in inches above 5 feet)

$LBW_{(female)} = 45.5\ kg + 2.3$ x (height in inches above 5 feet)

To calculate the expected serum digoxin concentration (C_{ss} (exp)) creatinine clearance (Cl_{Cr}) and total body clearance (CL_T) were determined. Cl_{Cr} was estimated using the Cockcroft-Gault formula (8):

Equation 2

$$Cl_{Cr}\ (ml/min) = \frac{(140 - age) \times LBW}{72 \times Sr_{Cr}}$$ (For women, multiplied by 0.86)

Since it has been shown that Sheiner's method was the least biased and most precise for predicting observed serum levels, this method was used to calculate the CL_T (9):

Equation 3:

CL_T (ml/min/ 70 kg) = 23 + 0.88 Cl_{Cr} (ml/min/ 70 kg)

Finally, Equation 4 was employed to calculate C_{ss} (exp):

Equation 4:

$$C_{ss}\ (exp)\ (ng/ml) = \frac{FX_0}{CL_T \times \tau}$$

where F represents the bioavailability of digoxin tablets, X_0 is the maintenance dose, and τ denotes the dosing interval. For facilitation of calculation, the dosing interval was considered to be one day and the average dose of digoxin per day was substituted for X_0. Average daily dose was calculated by dividing the total digoxin taken per week by seven (6).

According to the digoxin package insert, its bioavailability ranged from 65% to 75%. In this study, 70% was accepted as F.

Non-compliance was defined similarly to Wiseman and Miller's study (10). They also used a pharmacokinetic approach to quantify noncompliance in patients receiving digoxin. In their study, patients whose predicted serum digoxin concentrations were more than 50% greater than the measured levels were considered as non-compliant. Nevertheless, in our study, overuse was also taken into account. Overall, non-compliance was assumed when the expected serum digoxin level was more than 50% greater or 50% lower than the measured level.

Table 1: Characteristics of patients.

Characteristics	Compliants (n=63)	Non-compliants (n=56)	p value
Female	31	29	0.92
Male	32	27	
Age (year)	54.67±14.75	51.45±14.78	0.24
Number of received drugs	3.64±1.14	3.78±1.36	0.59
Duration of digoxin use (year)	4.19±3.22	4.49±3.36	0.64
Dosing groups*			
A	6	19	<0.001
B	6	7	
C	22	23	
D	29	7	

*Average daily dose of each group: A=0.25 mg, B=0.125 mg, C=0.214 mg, D=0.179 mg

C_{ss}: Measured serum digoxin concentration

As some authors have stated, the possibility of digoxin toxicity increases at levels above 1.1 ng/ml or 1.5 ng/ml (11–15). In our earlier study, we also found that from 1.2 ng/ml, there was an increase in electrophysiological signs of toxicity, and it rose steeply with concentrations above 1.6 ng/ml (16). Therefore, the therapeutic range was considered to be between 0.5 and 1.5 ng/ml (12–15).

Statistical analysis was carried out by Chi-square (Yates corrected) and 2 tail t-test, using SPSS software. Differences were considered significant if the p value was less than 0.05.

RESULTS

One hundred-nineteen patients, including 58 men and 61 women, met the required conditions. Their age was 53.15±14.79 years, on average, where 25.2% of them were older than 65 years of age. The mean number of received drugs was 3.71±1.16, and 107 patients could recall the length of digoxin use (4.33±3.28 years).

The mean expected digoxin serum concentration was 1.22±0.81 ng/ml, which was 50.62% greater than the measured level (0.81±0.64 ng/ml).Twenty five patients were in group A, 13 in group B, 45 in group C, and 36 in group D. The mean serum digoxin levels of groups A, B, C, and D were 1.02±0.09, 0.54±0.30, 0.73±0.36, and 0.87±0.42 ng/ml, respectively. The serum concentrations of 35 patients were below 0.5 ng/ml, which was regarded as sub-therapeutic level. In fact, 32.0%, 53.8%, 31.11%, and 16.67% of the patients in groups A, B, C and D, respectively, had sub-therapeutic levels. Digoxin levels of 11 patients (9.24%) were above 1.5 ng/ml. Five of these patients were in group A, one in group B, two in group C, and three patients in group D. Thus, 48.0%, 38.46%, 64.44%, and 75.00% of patients in groups A, B, C, and D, respectively, fall in the therapeutic range. It should be mentioned that 3 patients (2.52%) were hospitalized for suspected digoxin toxicity. Two of them were taking one tablet daily and one was taking one tablet 6 days per week.

Based on the assumed definition for compliance, 63 (52.94%) patients were considered compliant and 56 (47.06%) were non-compliant. Twenty-nine women (48.33%) were non-compliant, while 27 men (45.76%) did not take digoxin as directed.

As shown in Table 1, 2 groups were not significantly different with regard to gender, age, number of concurrent medications, or duration of digoxin use. Nonetheless, with respect to their dosages, a significant difference was noticed between 2 groups ($p<0.001$). 24.0%, 46.15%, 48.89%, and 80.56% of patients in groups A, B, C, and D were compliant, respectively. Therefore, patients who were taking digoxin 5 days a week were comparatively more compliant. Conversely, non-compliance was most probable among those taking one tablet every day.

As illustrated in Table 2, there is a considerable difference between the predicted and the measured serum digoxin concentrations of the non-compliant patients. Overall, the expected concentrations were 101.56% greater than the measured levels. Indeed, the expected concentrations for groups A, B, C, and D were 63.33%, 152.50%, 134.55%, and 143.18% greater than the actual values, respectively. Thus, the least difference was noted among patients who were taking one tablet per day.

About 51.78% of the non-complaints had sub-therapeutic levels and 3.57% had levels above 1.5 ng/ml (Table 3). In other words, 44.65% of the non-compliants fall in the therapeutic range. By comparison, 76.19% of the compliant patients had acceptable levels. Serum digoxin

Table 2: Comparison of measured and expected serum digoxin concentrations.

Dosing groups	Compliants				Non-compliants			
	n	C_{ss} Mean±SD	C_{ss} (exp) (nmol/L)	p value	n	C_{ss} Mean±SD	C_{ss} (exp) (nmol/L)	p value
A	6	1.38±0.67	1.73±0.54	0.10	19	0.90±1.17	1.47±0.57	0.0015
B	6	0.66±0.28	0.74±0.25	0.43	7	0.40±0.10	0.96±0.22	<0.001
C	22	0.92±0.35	1.14±0.35	0.10	23	0.55±0.26	1.29±0.60	<0.001
D	29	0.97±0.39	1.12±0.49	0.10	7	0.44±0.15	0.07±0.21	<0.0001

*Average daily dose of each group: A=0.25 mg, B=0.125 mg, C=0.214 mg, D=0.174 mg

C_{ss}: Measured serum digoxin concentration

C_{ss} (exp): Expected serum digoxin concentration

concentrations of 33.33%, 50%, 77.27%, and 89.66% of the compliants in groups A, B, C and D were within the therapeutic range. The majority of the non-compliant patients used less than the prescribed dose, but 2 patients, both of them belonged to group A, overdosed and hospitalized. The electrolyte levels of these patients were within the normal range.

DISCUSSION

The results of this study indicate that a considerable number of patients (47.06%) do not take digoxin as directed. This could prove to be a great impediment to effective therapy, since several studies provide strong evidence of the efficacy of digoxin in patients with CHF (17, 18). In addition, this drug can reduce the rate of hospitalization (19).

In our study, 52.94% of patients were compliant. It is noteworthy that the rate of compliance among our patients was lower than some other studies. Wiseman and Miller (10) found that 59.58% of patients were compliant. However, in their study, overuse was not taken into account as non-compliance. Measurement of drug compliance by continuous electronic monitoring revealed that patients suffering from atrial fibrillation took 74±21% of the prescribed dose of digoxin during the monitoring period (20). On the other hand, a follow-up study done by Monane *et al.* (20) showed that only 10% of the patients filled enough prescriptions to have daily digoxin for the entire year.

In the current study, age, gender, number of concurrent medications, or length of digoxin use did not have any significant effect on the rate of compliance. However, another study reported a higher rate of compliance in women, patients over the age of 85, and those taking multiple medications (21). Nevertheless, Wiseman and Miller (10) observed a greater rate of non-compliance among women. The difference between our results and others could be attributed to cultural differences between our society and others.

Among the examined factors, only frequency of digoxin intake was found to have a considerable effect on the rate of compliance. In other words, patients taking 5 tablets per week were more compliant than other groups. On the other hand, those patients taking one tablet daily were the least compliant group.

Since only one physician prescribed digoxin for these patients, the effectiveness of the physician-patient relationship was not a source of difference in the rate of compliance. The only factor overlooked, due to some cultural problems, was the level of education.

It should be mentioned that this study was done by a population based equation and there are differences among individuals. However, for defining compliance, a wide range (±50%) has been taken into account. Therefore, individual differences could be overcome. Besides, when different prediction methods were examined and the Sheiner method was found to be the least biased and the most precise for predicting serum digoxin levels (9).

Table 3: Sub-therapeutic and high levels in the compliant and the non-compliant groups.

Dosing group*	Compliants	Non-compliants	Compliants	Non-compliants
	patients with C_{ss} <0.5 ng/ml		patients with C_{ss} >1.5 ng/ml	
A	1 (16.67%)	7 (36.84%)	3 (50%)	2 (10.52%)
B	2 (33.33%)	5 (71.43%)	1 (16.67%)	0
C	3 (13.64%)	11 (47.83%)	2 (9.09%)	0
D	0	6 (85.71%)	3 (10.34%)	0

*Average daily dose of each group: A=0.25 mg, B=0.125 mg, C=0.214 mg, D=0.179 mg

C_{ss}: Measured serum digoxin concentration

Overall, 61.35% of patients had levels within the therapeutic range and 76.19% of the compliant patients were in the desired range. However, patients with therapeutic levels were comparatively less than in the study done by the Digitalis Investigation Group (19). The mean serum digoxin concentration was similar to the DIG trial. Nevertheless, patients taking 0.25 mg daily had higher levels than the DIG trial, while those using 0.125 mg/day had relatively lower levels. Interestingly, the serum digoxin concentrations of individuals taking 5 or 6 tablets per week were more likely to be within the therapeutic range.

Sub-therapeutic levels were most often observed among the patients taking 0.125 mg per day, and levels above 1.5 ng/ml were more prevalent among the patients taking 0.25 mg per day.

Hospital admission for digoxin toxicity was 2.52%, which is higher than the results of the DIG trial (2%) (19) and the study done by Mahdyoon *et al.* (22) (1%). Nonetheless, Kernan *et al.* (23) found a higher incidence of hospitalization (4.2%) for digoxin toxicity among the elderly.

In conclusion, the results of this study indicate that patients taking 5 tablets of digoxin per week are more compliant, and the probability of their digoxin levels being within the therapeutic window is higher than others. Since some data suggest that a low dose can provide both a beneficial hemodynamic and neurohumoral effect (24), a dose of 0.25 mg 5 days per week could provide therapeutic results with a higher rate of compliance. Considering probable cultural and socio-economical differences, more studies are needed to confirm and generalize these results.

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