ASSESSMENT OF DIGOXIN SERUM CONCENTRATION IN CONTINUOUS AND INTERRUPTED DIGOXIN REGIMENS

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ABSTRACT

Since digoxin possesses a narrow therapeutic index and shows a large interpatient pharmacokinetic variability, serum digoxin monitoring is a suitable guideline for optimization of digoxin therapy. However, digoxin concentration monitoring is not always accessible; and as result sometimes in order to prevent digoxin toxicity a drug holiday is performed (the drug is off for 1 or 2 days a week). In this investigation a prospective cohort study was designed to evaluate drug regimen. One hundred and twenty three inpatients receiving digoxin for heart failure or atrial were included in this study. In the group with a drug holiday regimen, 3 samples of serum were taken from each patient. (Preholiday trough, 6-8 hrs after the last dose in steady state, post holiday trough). In other groups 2 samples were collected (trough and 6-8 hrs after the last dose in steady state) and samples were assayed by radioimmunoassay. The results showed that 73.33% of patients receiving 0.125 mg/day had a level less than 0.8 ng/ml (sub therapeutic). While most patients had preholiday concentration within therapeutic range (0.8-2 ng/ml), due to the concentration fluctuation, clinical ineffectiveness of this drug regimen is questionable. In patients with 0.25 mg/day regimen, 62.5% of had therapeutic level and an appropriate clinical response. While a population pharmacokinetic analysis must be designed for a proper decision about the dosage adjustment in patients of this study in future, it seems that 1 tablet/day regimen is preferred.

Key words: Digoxin, Pharmacokinetic, Congestive heart failure, Holiday regimen, Interrupted regimen.

INTRODUCTION

Digoxin is widely prescribed for the treatment of congestive heart failure and atrial fibrillation. However, it is a difficult drug regarding adjustment of dosage because of a lack of a good relationship between the dose and the desired effect, its narrow therapeutic range, and variation in the pharmacokinetic characteristics of the drug. Knowledge of the pharmacokinetics of digoxin is essential in order to optimize its safety and efficacy. The variation in digoxin clearance creates difficulties for clinicians in choosing the drug dosage (1). Therefore, serum concentration monitoring as a suitable guideline for selection of digoxin regimen and the pharmacokinetics of digoxin is well known. When dosage of the drug is adjusted on the basis of the body weight and kidney function, interrupted digoxin administration is not required. However since in this country serum concentration monitoring is not always available, usually a drug holiday is performed conventionally (the patient is off drug for 1 or 2 days a week).In order to prevent digoxin toxicity, a prospective cohort study was designed to evaluate this drug regimen. With this approach it is possible to determine the best digoxin regimen considering serum concentration of the drug and clinical effectiveness. In support of this idea results of a Spanish clinical research was shown that the daily digoxin regimen was more effective than the interrupted regimen in control of atrial fibrillation (2)

MATERIALS AND METHODS

This prospective study was carried out at the following hospitals in Tehran, Iran: Imam Khomieny, Shahid Rajaii, and Bahgiatallah. Patients suffering from congestive heart failure

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(CHF) and/or atrial fibrillation (AF) taking digoxin tablets with or without holiday regimen were included. They received the same brand of digoxin tablet (0.25mg) for at least 3-5 half-lives to ensure that steady state was achieved (or ten doses were administered before the last dose). Patients were excluded if they were under 18 years old. A careful history of all patients including demographic characteristics, physical examination, chief complain, past medical history, drug history, familial history, social history, disease(s), digoxin dosage, Para clinical data (ECG, Echocardiography, engiography, chest–X-ray), laboratory data (BUN, serum creatinine, Na^{+}, K^{+}, Ca^{++}, Mg^{++}, CBC, ALT, AST, thyroid function test, ABG) and signs and symptoms usually associated with digoxin toxicity (GI, CNS, Cardiovascular) were recorded. Blood samples were collected on the basis of digoxin dosage. In a group with a drug holiday regimen, 3 samples of serum was taken from each patient. (Preholiday trough, 6-8 hrs after the last dose in steady state, post holiday trough). In the other two group (daily or every other day) 2 samples were collected (trough and 6-8 hrs after the last dose in steady state). These samples were frozen under –20°C (3) and assayed with Orion Diagnostica Digoxin Kit (^{125}I) (Radioimmunoassay technique) with sensitivity of 0.1 ng/ml in which inter/intra-assay precision was 4.2% and 2.4% respectively. All patients had an hour of rest before blood collection since physical activity could decrease digoxin level (4). Since digoxin is mainly excreted by kidneys, (3, 5), creatinine clearance (Cl_{cr}) was calculated by four methods to quantify renal functions:

1) Cockroft – Gault formula (based on lean the body weight) (6)

2) Cockroft – Gault formula (based on the total body weight) (7, 8)

3) Cockroft – Gault formula adjusted by body surface area (9)

4) Modified Diet in Renal Diseases (MDRD) (7) and MDRD were selected with the formula:

$Cl_{cr} = (age)^{-0.203} \times (S_{cr})^{-1.154} \times 186$ (for women it was multiplied to 0.742)

Statistical data analysis was carried out using logistic regression and chi-square tests.

RESULTS

One hundreds and twenty three patients including sixty eight women and fifty five men were included in this study. These patients on the basis of Cl_{cr} were divided in two groups:

Table1. Demographic data of patients

Variable	Range	Mean ± SD
No. =123 Female, n=68 Male, n=55		
Age (year)	18-88	54.5 ± 16
Weight (kg)	35-96	62.5 ± 12
Body surface area(m^2)	1.24-2.14	1.66± 0.18
Height (cm)	101-180	160 ± 12
Creatinine Clearance: (ml/min/1.73 m^2)*		
Female:		
≥ 50, n = 46		
< 50, n = 15		
Male:		
≥ 60, n = 35		
< 60, n = 10		
Dose(mg):	0.0625-0.25	0.1964 ±0.0631
0.0625 mg, n = 1		
0.125 mg, n =53		
0.25 mg, n = 69		
*CHF**:* n =97		
Grade 0, n = 28		
Grade 1, n = 16		
Grade 2, n =12		
Grade 3, n = 41		
AF***, n = 40		
AF + CHF, n = 18		
Others, n=3		
Social Habit:		
Smocking, n=15		
Alcoholism, n = 1		
Opium, n = 3		
Diseases :		
Cardiac, n = 7		
Pulmonary, n = 5		
Liver, n = 0		
Hypothyroid, n = 1		

*GFR was calculated by MDRD formula, ** CHF= Congestive Heart Failure, ***AF= Atrial Fibrillation

eighty one patients had normal renal function (Cl_{cr} > 60 ml/min for males and Cl_{cr} > 50 ml/min for females) and twenty five patients had renal failure (for seventeen patient S_{cr} was not recorded) (Table.1).

In this study digoxin was administered for AF and/or CHF. Severity of the heart failure was an important factor for determination of the clinical effects of digoxin. Patients based on their left ventricular ejection fractions (LVEF) were divided into four groups (5): (Table.1)

1) LVEF >50% (grade 0; normal)

2) LVEF = 45-50% (grade 1; mild heart failure)

3) LVEF = 35 – 45% (grade 2; moderate heart failure)

4) LVEF = 35% (grade 3; severe heart failure)

Table 2.Relationship between digoxin peak concentration and digoxin regimens in two therapeutic ranges (0.8-2 ng/ml and 0.5-1.5 ng/ml)

Regimen	<0.8 (ng/ml)	0.8-2 (ng/ml)	>2 (ng/ml)	<0.5 (ng/ml)	0.5-1.5 (ng/ml)	>1.5 (ng/ml)	No.	Miss
0.125mg (5/7) [1]	1	2	0	1	2	0	8	5
0.25mg (5/7)	7	16	0	4	17	2	29	6
0.25mg(5/7T,F) [2]	0	1	0	0	1	0	3	2
0.125mg (6/7) [3]	0	2	2	0	2	2	4	0
0.25mg (6/7)	0	9	0	0	7	2	10	1
0.0625mg (day)	1	0	0	1	0	0	1	0
0.125mg (day)	19	7	1	12	12	3	33	6
0.25mg (day)	2	15	6	2	11	10	26	3
0.125mg(e.o.d)	3	4	1	3	2	3	8	0
0.25mg (e.o.d)[4]	1	0	0	1	0	0	1	0
SUM	34	56	10	24	54	22	123	23

1-Holiday was Monday and Friday.

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2- Holiday was Thursday and Friday.

3- Holiday was Friday.

4-Every other day.

Table3. Comparison between digoxin peak, trough, preholiday and post holiday concentration in digoxin regimen in two therapeutic ranges (0.8-2 and 0.5-1.5ng/ml)

Sampling time	<0.8 (ng/ml)	0.8-2 (ng/ml)	>2 (ng/ml)	<0.5 (ng/ml)	0.5-1.5 (ng/ml)	>1.5 (ng/ml)	Range (ng/ml)	Mean (ng/ml)	SD
Trough	24	27	8	23	21	15	0.09-3.3	0.99	0.91
Preholiday	17	28	1	14	21	11	0.09-2.2	0.94	0.65
Post holiday	24	15	1	15	22	3	0.09-2.2	0.75	0.51
Peak	34	56	10	24	47	29	0.09-5.8	1.12	0.87

Table 4.Relationship between digoxin peak level and clinical response in continuous and interrupted regimen

Clinical Response	<0.5 (ng/ml)	0.5-0.8 (ng/ml)	0.8-1.5 (ng/ml)	1.5-2 (ng/ml)	>2 (ng/ml)	Miss	No.
Not Responsive	8	5	10	2	-	7	32
Responsive	9	3	16	12	7	3	50
Not possible toJudge	5	4	8	2	3	5	25

*Clinical signs and symptoms were not reliable to evaluate effects of digoxin.

Table 5. Relationship between digoxin trough/preholiday level and clinical response in continuous and interrupted regimen.

Clinical Response	<0.5 (ng/ml)	0.5-0.8 (ng/ml)	0.8-1.5 (ng/ml)	1.5-2 (ng/ml)	>2 (ng/ml)	Miss	No.
Not Responsive	17	3	5	4	-	3	32
Responsive	9	1	21	6	6	7	50
Not possible to judge	5	1	5	7	1	6	25

Table 6. Comparison between peak, trough, clinical response and creatinine clearance in 0.25 mg (daily) and 0.25 mg (5/7) digoxin regimen.

Regimen	Peak (ng/ml)	Trough (ng/ml)	Post holiday Trough (ng/ml)	Clinical Response (+ /- /unknown**)	Toxic Effects	Creatinine Clearance (ml/min)	No.
0.25mg(daily)	1.70 ±1.23	1.28 ±0.98	-	16 / 1 / 9	1	74.21 ±26.44	26
0.25mg(5/7)*	1.03 ±0.53	0.91 ±1.69	0.71 ±0.5	8 / 10 / 11	1	64.31 ±23.36	29
P-value	0.02	0.13	-	0.009	-	0.2	

*Holiday is Monday and Friday.
** Clinical signs and symptoms were not reliable to evaluate effects of digoxin

Since digoxin regimen is one of the several factors that affect digoxin serum concentration, this important parameter was evaluated in this study. On the whole, ten dosage regimens of which 60 cases had daily regimen, 54 cases had holiday and 9 cases had every other day regimen were included in this study (Table2). Since peak serum concentration is an important concentra-ation for digoxin monitoring, two serum peak concentration limits: 0.8-2 ng/ml and 0.5-1.5 ng/ml were evaluated. According to table 2, 56% of patients had peak serum level within therapeutic range. 34% had sub-therapeutic level and 10% had level above 2ng/ml. According to table 2, 54% of the patients had serum concentration of 0.5-1.5 ng/ml, 24% of patients had sub therapeutic range and 22 % had level above 1.5 ng/ml.

Trough level was evaluated for patients who had daily or every other day regimen. In these groups most of the patients had therapeutic trough level with mean concentration of 0.99±.0.91ng/ml. (Table 3)

Preholiday and post holiday concentrations are essential to evaluate the effectiveness of drug holiday regimen, and on the basis of table 3 most of patients had preholiday level at therapeutic range with mean concentration 0.94±0.65 ng/ml and post holiday level mostly was sub- therapeutic in 0.8-2 ng/ml and therapeutic in 0.5-1.5 ng/ml with mean concentration of 0.75±0.51 ng/ml.

Table 4 and 5 summarizes the relationship between serum concentration ranges of digoxin and clinical responses. The best therapeutic range of digoxin was found 0.8-1.5 ng/ml for both peak and trough levels.

In 0.25mg dosage regimen with and without holiday, there were 29 and 26 patients, respectively, and data were proper for two sub-groups regarding their peak concentrations, trough levels, clinical responses, toxic effects and creatinine clearances. Results are shown in table 6

DISCUSSION

The kidneys have the most important role in digoxin clearance; therefore in this study renal function of each patient has to be evaluated. Creatinine clearance was calculated by four methods and then considering age, sex, serum creatinine, total body weight and ideal body weight MDRD formula was selected. In general, creatinine clearances about 120 ± 15 for male and 110 ± 15 for females are normal (7). In patients of this study, because of a fall in LVEF, kidney tissue perfusion and as a result creatinine clearance was decreased. Cl_{cr} above 60 ml/min for males and above 50 ml/min for females were considered normal.

Digoxin is administered for severe or class III to IV heart failure (5, 10, 11, 12). Classification of heart failure is based on: left ventricular ejection fraction or clinical symptoms (NYHA classification) (5, 10).

Several factors such as: demographic, physiologic and pathologic parameters affect serum digoxin concentration. One of the most important factors is drug regimen and the time of sampling. Ten different digoxin regimens were used in this investigation (Table 2), and in order to determine the most effective one; serum drug monitoring and clinical signs and symptoms (such as: S3 heart sound, radiological evidence of pulmonary congestion, rales, orthopnoea, dyspnoea on exertion, enlarged heart, sacral oedema, tibial oedema and LVEF for CHF and heart rate and EKG for AF rhythm) had to be evaluated.

There are debates about the optimal time for monitoring digoxin level. Some authors suggest that trough level is appropriate, while others

believe that peak level (13,14,15) (6-8 hrs after the last dose when distribution phase will be complete.) and/or maximum concentration time (about 100 minutes after the dose) are proper (16). The type of study determines the optimal time, and it has been reported that trough levels by themselves are not useful in making an individual Bayesian pharmacokinetic model for the behavior of digoxin in patients (16). In this clinical research both peak and trough were studied to evaluate the best predictor for therapeutic outcome. Statistical analyses by logistic regression showed that the clinical response was significantly related to both peak and trough levels (p=0.012 for coefficient of peak in logistic equation and p=0.0003 for that of trough), but relation to the trough level was much stronger. (Pearson's χ^2 associated with 68 degree of freedom were 67.7 for peak levels and 69.3 for trough levels, respectively and McFadden- R^2 was 0.19 for trough and 0.08 for peak levels, respectively).

There are different reports about the appropriate therapeutic range for digoxin. Some authors suggest the range of 0.8-2.0 ng/ml (3,13,14,15,16,17), while others believe that serum digoxin concentration between0.5-1.5 ng/ml is optimal (14,15,18,19,20,21). In the present study both ranges were considered. The number of patients responding to digoxin was greater in the range of 0.8-1.5 ng/ml (Tables 4,5) and much stronger correlation was observed for trough levels (for peak: χ^2=9.726 associated with p=0.045 for 4 degree of freedom and for trough: χ^2=18.402 associated with p=0.001 for 4 degree of freedom). Out of 50 patients who showed good responses to digoxin, 19 of them had digoxin peak levels greater than 1.5 ng/ml and only one patient with a digoxin peak concentration greater than 2 ng/ml toxicity was observed. From these results it might be concluded that increase in digoxin concentration to 2 ng/ml is also acceptable. However, for better judgment a larger number of patients are required for future studies.

In evaluation of serum concentration of patients with different drug regimens, it was recognized that most of patients had peak serum concentrations in therapeutic range (except for ½ tab/day regimen) (tables 2, 3), but in interruption regimen, there was many fluctuations in the serum concentration. For example, peak concentration between holidays was different from peak concentration of post holiday periods. There were even patients with peak levels less than trough preholiday levels (20.83%) and in patients who had pre-holiday levels within therapeutic range, their post-holiday concentrations were sub-therapeutic (27.77%). However, there were no significant statistical differences between interruption and continuous regimens in the pool data. (χ^2 = 4.32 associated with p=0.116 for 2 degree of freedom), but changing the regimen in patients who were on drug holiday to one in a day regimen led to a better clinical responses and more appropriate digoxin concentration.

Results of comparison of two groups who had the same number of patients and received the same dose (0.25 mg) in different regimen, namely every day of the week or five days of a week, are shown in Table 6. The peak concentrations and the clinical response were significantly different, with p-values of 0.02 and 0.009, respectively. Since creatinine clearances of patients were not significantly different (p=0.2), differences in results might be attributed to the kind of regimen. From results of Table 6 it may be concluded that daily per week regimen is better.

Of patients receiving ½ tab/day, 73.33% had peak or through levels less than 0.8 ng/ml and 44.44% even had very low concentration (0.1-0.3ng/ml). It is of interest to mention due to digoxin-like immunoreactive substances, a low level of digoxin may be detected in the serum of a person who has not taken digoxin at all. (22,23,24). These patients also received drugs such as amiodarone, verapamil, quinidine and captopril concomitantly that does not have any negative impact on serum digoxin level. Most of patients receiving ½ tablet /day were not in good control (table 4,5) on the basis clinical signs and symptoms and serial LVEF.

The index for determination of the renal function in all hospital departments were creatinine clearance, except in the nephrology department, in which for ease serum creatinine was used and as a result only patients having serum creatinine higher than normal, were considered having renal failure. These patients were taking ½ tab of digoxin every other day without considering their creatinine clearances. In this study by determination of creatinine clearance by the MDRD method it was shown that some of patients who had serum creatinine in the normal range had creatinine clearance less than 50 or 60 ml/min. This was the reason why

these patients showed toxic serum levels, or when they used ½ tab / day, their serum digoxin levels were in the therapeutic range.

Only four of patients showed signs of digoxin toxicity that led to drug discontinuation. (These patients had normal level of the serum electrolytes, normal thyroid function tests and other states that make cardiac tissue sensitive to digoxin) (19, 21). The signs of toxicity were abnormal EKG signs in 3 patients (two AF rhythms and one junctional rhythm), and GI complications in one patient. Only one of the patients had a serum level higher than the therapeutic range (2.7 ng/ml), and digoxin levels in the other 3 were: 1.2, 1.25, 1.6 ng/ml .It is interesting to note that 7.32% of patients with serum level higher than 2 ng/ml showed no signs or symptoms of toxicity while 13.4% of patients showed P-R prolongation but drug discontinuation was not necessary. In these patients there were not any correlation between signs and symptoms of digoxin toxicity and serum digoxin concentration.

From these results it is concluded that variability in digoxin serum concentration makes it difficult to predict the optimal dosing regimen for individual subjects and understanding the effects of a variety of demographic factors on pharmacokinetic parameters seems beneficial. Therefore, a method that would provide precise predictions about whether a drug concentration is sub therapeutic, therapeutic, or toxic from a given dosage regimen is required and population pharmacokinetic analysis for a proper decision about the dosage adjustment in patients would be valuable.

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