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Comparison of Serum Digoxin Level and Clinical Response in Patients with Chronic Atrial Fibrillation in Two Different Ways of Continuous and Interrupted Use

Ebrahim Nematipour, MD, Fahimeh Sabour, MD and Soha Namazi, PharmD

Abstract

Background- Digoxin prescription with an interruption of one or two days a week is frequently used in Iran. We compared this kind of digoxin prescription with an uninterrupted one through the determination of serum digoxin level and clinical response in Iranian patients.

Methods- This study was designed as a crossover clinical trial on 28 patients suffering from chronic atrial fibrillation (AF), and the two different methods of digoxin prescription were compared through achieving therapeutic range of serum digoxin level and clinical response as control of heart rate in patients with chronic AF.

Results- The serum digoxin concentration in interrupted consumption, the day before (O.885 ± 0.29 ng/ml) and after (0.614 ± 0.35 ng/ml) interruption was significantly lower than the continuous form (1.157 ± 0.3 ng/ml), $p < 0.05$. About 35% of the patients in the interrupted schedule of digoxin had plasma levels lower than 0.8 ng/ml (minimum therapeutic range), compared with no one in the continuous schedule. Also none of the patients in the continuous consumption group showed clinical and/or electrocardiographic signs of digoxin toxicity. The mean heart rate in interrupted use on the day before (84.82 ± 7.2 beats/min) and after (86.5 ± 3.8 beats/min) interruption was significantly higher than that in the continuous form (75.9 ± 5.2 beats/ min), $p < 0.05$.

Conclusion- This study showed that the continuous use of digoxin has the advantage of achieving the therapeutic range and better controlling the heart rate in patients with AF rhythm and could be the preferred form of prescription in the majority of our patients, as it is in nearly all the countries around the world ***(Iranian Heart Journal 2003; 4 (4):63-67).***

Keywords: Digoxin ■ Arrhythmia ■ Atrial fibrillation ■ Prescription

Digoxin is a cardiac glycoside with positive inotropic effect. It decreases the ventricular rate, especially in atrial fibrillation (AF), which allows better ventricular filling.[1] Making use of this drug is a standard therapy in the treatment of congestive heart failure (CHF) with atrial fibrillation. It also decreases the sympathetic drive generated by the failing circulation, which provides a rational using of the drug in CHF with sinus rhythm.[2] However, dose adjustment in this drug is difficult because of a lack of good relationship between the dose and the desired effect,[3] its narrow therapeutic range and the variation in the pharmacokinetic characteristics of the drug.[4] Knowledge of the pharmacokinetics of digoxin is essential in optimizing its safety and efficacy. The variability in digoxin clearance creates difficulty for clinicians to choose the appropriate dosage

From the Department of Cardiology, Imam Khomeini Medical Center, Tehran University of Medical Sciences, Tehran, Iran.
Correspondence to: Department of Cardiology, Imam Khomeini Medical Center, Tehran University of Medical Sciences, Tehran, Iran.
Tel: (+9821) 6939537 , 6931999
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of the drug.[5] Serum concentration monitoring is a suitable guideline for the selection of digoxin regimen. [6]

In our country, serum concentration monitoring is not always possible, so it is likely to drop the medication for one or two days a week to avoid the risk of toxicity. This is contrary to the routine use of the drug in nearly all other countries. Therefore, it seems logical to compare these two ways of prescription by considering appropriate clinical effects and finding the minimum optimal therapeutic dose with the fewest complications. To this end, we designed a prospective study to compare the continuous and interrupted forms of drug prescription in Iranian patients.

Methods

This prospective study was carried out at our department from July 2000 to July 2001 and was a one-year crossover clinical trial. Patients suffering from chronic atrial fibrillation (AF) and taking digoxin tablet as a holiday regimen were included. The patients consist of out-patients and admitted patients of the cardiology ward. All the patients signed the written informed consent. The exclusion criteria are shown in Table I.

Table I . Exclusion criteria

Renal dysfunction (serum Cr >1 mg / dl)
Consumption of drugs that affect heart rate
Consumption of drugs that affect serum digoxin concentration
Hypo - or hyperthyroidism
Electrolyte imbalance
COPD

Twenty-eight patients, 5 men and 23 women, were included in the study. Table II shows the distribution of sex and age of the patients. Laboratory data consisted of BUN, creatinine, Na, K, Ca and Mg. The symptoms of digoxin toxicity (GI, CNS and cardiovascular) were described for each patient. The patients received 0.25mg digoxin tablet daily after at least 3.5 half lives to ensure that the serum steady state had been reached.

The patients were divided into two groups; A and B. Group A took the drug on an interrupted (holiday) schedule. Group B took the drug initially in the interrupted form and then in the continuous form.

First, all the patients received the drug as an interrupted regimen, i.e. digoxin was not taken on two days of the week: Mondays and Fridays. Blood samples were taken from each patient at pre-holiday and post-holiday intervals. Electrocardiogram (EKG) was taken at least after ten minutes' rest in a supine position from lead II in all the patients, and the mean heart rate was measured.

Next, group A continued the holiday (interrupted) regimen, but group B took the drug in the continuous form (0.25 mg digoxin daily) at least for one week.

Blood samples were taken again and frozen under - 20°C and assayed with Orion Diagnostica Digoxin Kit (I^{125}) radioimmunoassay technique with a sensitivity of 0.1 ng/ml.

All the data were collected and analyzed with SPSS program.

Table II: Distribution of age and sex of patients.

	Numbers of patients	Female %	male%	mean age ± SD (years)
group A	14	93%	7%	44.78 ± 12.17
group B	14	73%	27%	42.14 ±10.74
All	28	82%	18%	43.46 ± 11.34

Results

In the first blood sample, electrolytes were measured in all the 28 patients (Table III). The selected patients had no electrolyte imbalance.

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Table III. Serum electrolytes level

	Group A mean ± SD	Group B mean ± SD
Na meq/L	143.07 ± 3.0	141.78 ± 171
K meq/L	4.37 ± 0.28	4.21 ± 0.22
Cr mg/dL	0.9 ± 0.1	0.87 ± 012
Mg mg/dL	2 ± 0.1	1.9 ± 0.2
Ca mg/dL	9.35 ± 0.45	9.58 ± 0.51

Serum digoxin level and the mean heart rate in pre-holiday and post-holiday times in both groups are shown in Tables IV and V. There was no significant difference of serum digoxin level and heart rate between the two groups.

Table IV: Pre-holiday serum digoxin level and heart rate in the 2 groups.

		Group B	Group A
Serum digoxin level (ng/ml)	mean ± SD	0.885± 0.391	0.828 ± 0.307
	max	1.7	1.3
	min	0.4	0.4
	mode	0.4	0.7
Heart rate (beats/ min)	mean ± SD	84.85± 7.24	81.7 ± 4.58
	Max	105	90
	min	75	75
	mode	80	80

Table V: Post-holiday serum digoxin level and heart rate in the 2 groups.

		Group B	Group A
Serum digoxin level (ng / ml)	mean ± SD	0.614 ± 0.357	0.721 ± 0.269
	max	1.5	1
	min	0.3	0.2
	mode	0.3	1
heart rate beat/min	mean ± SD	86.5 ± 3.89	86.35 ± 6.53
	max	92	100
	min	80	75
	mode	90	90

After that, group A continued the interrupted form of digoxin consumption, whereas group B used the drug as continuous regimen (without interruption). Serum digoxin level and heart rate were compared in the 2 groups as shown in Table VI. There was a significant difference between them (P value < 0.01). Moreover, there was a significant difference of serum digoxin level and heart rate in group B when the patients used the drug as interrupted (stage1) and continuous regimen (stage 2), P value < 0.01 (Table VII).

About 35% of the patients in the interrupted regimen group had plasma level digoxin lower than 0.8 ng/ml as opposed to no one in the continuous regimen group. About 60% of the patients in interrupted regimen group had a heart rate higher than 80 beats/min, but this frequency in the continuous regimen was about 20%.

Table VI. Comparison of serum digoxin level and heart rate in the 2 groups in stage 2.

		Group B (continuous regimen)	Group A (interrupted regimen)
Serum digoxin level (ng / ml)	mean ± SD	0.614 ± 0.357	0.721 ± 0.269
	max	1.5	1
	min	0.3	0.2
	mode	0.3	1
heart rate (beat / min)	mean ± SD	86.5 ± 3.89	86.35 ± 6.53
	max	92	100
	min	80	75
	mode	90	90

None of the patients in the continuous regimen group showed clinical and/or electrocardiographic signs of digoxin toxicity.

Table VII. Comparison of serum digoxin level and heart rate in 2 different methods of interrupted and continuous drug prescription in group B.

	continuous	Post-holiday	Pre-holiday
Serum digoxin level (ng / ml)	1.157± 0. 303 *	0.614 ± 0.357 *	0.885 ± 0.291*
heart rate beat / min)	75.92 ± 5.26 *	86.5 ± 3.89*	84.85 ± 7.24*

*mean ± SD

Discussion

The narrow therapeutic range of digoxin and the limited availability of serum digoxin measurement have led to the cautious prescription of this drug by Iranian physicians, who are concerned about digoxin toxicity in their patients. For

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this reason, our physicians usually prescribe digoxin for 5 or 6 days a week, and if some physicians prescribe the drug according to a continuous regimen, pharmacists always warn the patient to avoid continuous use of the drug!

We know of just a few countries around the world using the holiday regimen for digoxin prescription, and we will discuss their studies later.

A knowledge of pharamacokinetic variability of drugs is mandatory in clinical practice. The kidneys have the most important role in digoxin clearance[2], thus in our study we excluded patients who had serum creatinine more than 1 mg/dL.

This study showed that an interrupted regimen for digoxin prescription leads to an insufficient serum concentration. The therapeutic level of digoxin is about 0.8 - 2 ng/ml,[7] but in this study about 35% of the patients using the holiday regimen had pre-holiday or post-holiday serum digoxin concentration below the therapeutic range. None of the patients in the continuous regimen method had this situation. Wide fluctuations and differences between pre-holiday and post-holiday digoxin level lead to an ineffective clinical response.

Patients who are digitalized via the holiday regimen reach the holiday period before reaching the steady state level of digoxin; therefore, either they will never reach the steady state level or if they do, it will take a long time, which may lead to a lack of control of clinical signs or symptoms.

Changing the holiday regimen to the continuous form led to a better control of resting heart rate. Mean heart rate at rest is used for monitoring the clinical response of patients.[8]

Controlled resting heart rate in patients with AF rhythm is in the range of 60 to 80 beats/min.[9] In this study, about 60% of the patients on holiday regimen had heart rates more than 80 beats/min, while this figure stands at 20% in the continuous regimen method.

A few comparable studies have been done in other countries. A study in Spain showed that 25% of interrupted group patients and 8.3% of continuous group patients had serum digoxin levels below 0.8 ng/dL: the minimum therapeutic level, and the mean heart rate was 83 beats/min and 72.9 beats/min, respectively. They concluded that the interrupted method was not a proper way to prescribe digoxin.[10]

Jnocchi et al.[11] in a single blind randomized prospective study of 36 patients, examined the effects of interrupted digoxin administration versus the continuous method and noted that the interruption of medication for two days a week decreased the serum level below the therapeutic range.

Our findings are in accordance with the afore-mentioned studies. No one in our study had clinical signs or symptoms of digoxin toxicity. Therefore, in patients with no renal dysfunction or other risk factors for digoxin toxicity, the continuous regimen is safe and useful for a better clinical response.

From an economic point of view, the cost difference between the two methods is only 500 Rials per month ($ 0.20), which is not significant.

Conclusion

Although digoxin toxicity is a real concern, justified prescription of the drug in the continuous form for patients with chronic AF and no renal dysfunction or other risk factors for digoxin toxicity is safe and has the advantage of achieving the therapeutic range and better controlling the heart rate. This could be the preferred form of prescription in the majority of our patients, as it is in nearly all the countries around the world.

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