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Determination of digoxin serum level in patients with heart failure

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ABSTRACT

Heart failure is one of the common cardiovascular diseases, and digoxin is required in the list of drug treatments. Considering the positive effect of this drug on heart failure, unfortunately, its therapeutic and toxic serum levels are different and very close to each other in different people. This study aimed to investigate the digoxin serum level in heart failure patients. For this purpose, we examined 32 patients with heart failure and digoxin users in this cross-sectional descriptive study. Some important factors involved in determining digoxin toxicity, such as age, gender, creatinine, creatinine clearance, cardiac output, urea, potassium, calcium, and digoxin levels, were measured. Statistical analysis showed that digoxin serum level increases with age ($p<0.01$). The increase in digoxin serum level was related to urea, creatinine, and potassium serum levels ($p<0.01$). In general, it seems that to prevent the increase of digoxin serum level and poisoning with it, it is necessary to continuously control the serum level of this drug in the form of serum measurement or according to its clearance.

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Introduction

Heart failure is the inability to meet the body's metabolic needs (1). It is referred to as a condition in which the ventricles fail due to myocardial damage, insufficient coronary blood flow, or any condition that directly disrupts the mechanical function of the heart muscle (2). In other words, it is a clinical syndrome with different causes, which indicates the primary defect in the practical mechanical function of the heart. As a result, the cardiac output is insufficient to meet the body's needs. At first, it only manifests itself during activity (1). Still, with the progress of the disease, the contraction power of the heart also worsens, and the low cardiac output even while resting is associated with signs and symptoms of congestion and fatigue (3). Disruption in the systolic activity of the left ventricle and its failure causes a decrease in the emptying capacity or the emptying fraction up to 45%, which increases the end-diastolic volume (4). In the Malik *et al*. study (5), the prevalence of heart failure in the age range of 45-54 years is estimated to be 2 per thousand in men and 1 per thousand in women, and in the age range of 65-74 years, it is estimated to be about 7 per thousand, in both men and women.

In the list of necessary treatments for this disease, digoxin (digitalis glycosides) is included, which has a strengthening effect on myocardial contraction (3). Digitalis glycosides increase intracellular calcium by inhibiting Na-K ATPase membrane surface pump and increase cardiac output. This drug (digoxin) is absorbed 50-75% orally, its half-life is 38-40 hours, and 85% is excreted through the kidneys and 15% through bile and feces (6). Unfortunately, the therapeutic and toxic serum level of digoxin differs in different people, and the distance between the digoxin serum level and its toxin level is minimal (7). On the other hand, its serum level depends on various factors, such as the state of the kidneys, hepatic excretion (to a small extent), and the effect of other drugs. Since elderly patients are more susceptible to digoxin poisoning, therefore, to prevent poisoning with it, they stop taking medicine for 1-2 days a week (7, 8). For this purpose, taking medication based on digoxin serum concentration, symptoms, and clinical findings is better and the laboratory to be adjusted (8). The present study aimed to investigate the digoxin serum level in heart failure patients.

Materials and Methods

This research is a cross-sectional study. All patients with heart failure were selected by convenient sampling if they had the necessary conditions, including taking digoxin. The number of patients was 32 (13 women, 19 men). First, a questionnaire containing questions about age, gender, weight, and duration of the disease was completed by the patients. Then, 10 ml of blood was taken to measure serum levels of creatinine, urea, calcium, potassium, and digoxin for 24 hours, and creatinine clearance was measured using the patient's 24-hour urine.

If the patient was receiving digoxin for the first time, one week must have passed since the start of digoxin treatment, and blood sampling was done 6 hours after the last dose. They have received digoxin correctly. Blood was drawn 6 hours after the previous dose. Patients who did not comply with the medication dose prescribed by the attending physician for any reason or who left the hospital at least one week after starting digoxin intake were excluded from the study. In each patient's case, the administrator

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completed a questionnaire that included demographic characteristics, clinical conditions, and medications he received. Blood was collected from each sample from the hand's vein in 1-2 ml. The blood prepared in predetermined and coded vials was imported and transported to the health school laboratory to determine the digoxin serum level. Determining the digoxin serum level: The plasma of the sent samples was separated, and after the sample preparation steps, it was centrifuged with Ethinyl estradiol solution, dichloromethane, and vortex for 5 minutes, after drying under nitrogen flow and mixing with 200 microliters of the mobile phase containing dichloromethane, propanol-methanol and water (0.047-0.040-0.09-0.04) in the amount of 50 microliters of it to the HPLC device. (Model 2600-kColum [C18.5µm (4.6*250)] (Knauer-Germany) was injected with a flow rate of 1 min/ml, and its absorbance was read at a wavelength of 220 nm and calculated through the corresponding concentration calibration curve.

In this study, digoxin serum level of less than 0.8ng/dl is defined as insufficient, between 0.8-2 ng/dl therapeutic, 2.5-2.2ng/dl intermediate, and more than 2.5 ng/dl toxic. Is. For therapeutic amounts of potassium, calcium, and creatinine, potassium mEq/l 5-5-3, hypokalemia less than 5.3 mmol/l, hyperkalemia more than five mmol/l, calcium 5-10.9 mg/dl, creatinine less than It is defined as 1/5 dl/mg.

It should be mentioned that in the case of calcium and creatinine, the amounts lower and higher than the mentioned numbers are defined as hypo and hyper and no specific limit has been defined for it. They were considering the non-normal distribution of quantitative data of digoxin, potassium, calcium, creatinine, and BMI.

After the data was collected, it was subjected to statistical analysis. The results were presented as mean and standard error. Also, the data were analyzed with Pearson's correlation coefficient tests, and a p-value smaller than 0.05 was considered a significant difference. The statistical software used was SPSS version 5.11.

Results

The correlation coefficient (r=0.57) showed a positive relationship between the digoxin serum level and the age of the patients, in such a way that the digoxin serum level also increased with the age of the patients ($p<0.01$). The mean serum urea in both sexes was 59.37+17.18 mg/dl, in the normal range of 50-10 mg/dl. But in terms of the correlation coefficient (r=0.46) with the increase in digoxin serum level, urea serum level also increased significantly ($p<0.01$). The average serum creatinine level in both sexes was 0.5±0.09 mg/dl, almost within the normal range of 0.6-1.4 mg/dl. However, with the increase in the digoxin serum level, the serum creatinine level also increased significantly ($p<0.01$) (r=0.49). The mean serum level of potassium in both sexes was 4.13±0.41mEq/l, within the normal range of 3.5-5 mEq/l. In this case, with the increase in the digoxin serum level, the potassium serum level also showed a significant increase (r=0.47)($p<0.01$). The mean of the emptying fraction in both sexes was 81.17±16.31%, which was less than the normal range (70%), and the creatinine clearance in both sexes with an average of 86.46±05.26 ml/min was lower than the normal range of 88 It was 137 ml/min. With increasing digoxin serum levels, creatinine clearance decreased (r=-0.32), but it was not statistically significant. In other cases, no significant difference was observed. The information can be seen in Table 1.

Discussion

There is an increase in digoxin toxicity with age, especially in patients with congestive heart failure and atrial fibrillation. Older adults are more prone to digoxin toxicity, which can be due to a decrease in kidney activity and a decrease in digoxin distribution volume. In the present study, there was a positive relationship between the digoxin serum level and the age of the patients, so as the age of the patients increased, the digoxin serum level also increased, and it seems that increasing age is a risk factor for digoxin poisoning. In terms of the correlation coefficient with the increase of serum urea and serum creatinine levels in both sexes, which indicates kidney efficiency, the average digoxin serum level also increased significantly.

In a study by Dimant *et al*. (9), they investigated the clinical value of continuous measurement and continuous monitoring of serum digoxin levels in 51 elderly patients with heart disease. They found that determining the appropriate serum digoxin level can be influenced by medical supervision, including taking an electrocardiogram, determination of serum electrolytes, and renal function tests (renal clearance, serum creatinine, and urea). Also, clearance of digoxin may be influenced by serum creatinine

Table 1. The mean of variables affecting digoxin consumption in patients with heart failure.

Factor	Female n=13	Male n=19	Both Gender n=32	Correlation coefficient (r)	Natural range
Digoxin (ng/ml)	1.11 ± 0.53	0.8 ± 0.34	0.92 ± 0.45		0.5-2
Urea (mg/dl)	36.46 ± 18.92	38.36 ± 16.38	37.59 ± 17.18	**r = 0.46	10-50
Creatinine (mg/dl)	1.09 ± 0.71	1.1 ± 0.31	1.09 ± 0.5	**r = 0.49	0.6-1.4
Clearance Creatinine (milt/min)	32.85 ± 19.01	56.44 ± 26.25	*46.6 ± 26.05	***r = -0.32	88-137 (Adult)
Calcium (mg/dl)	9.1 ± 0.45	8.9 ± 0.57	8.98 ± 0.53		8.8-10.2
Potassium (Meq/l)	4.2 ± 0.53	4.08 ± 0.31	4.13 ± 0.41	**r = 0.47	3.5-5
Age (year)	54.46 ± 18.48	56.42 ± 15.35	56.6 ± 16.1	**r = 0.57	-
Weight (Kg)	59.92 ± 10.87	73.21 ± 13.2	68.14 ± 13.58		-
Disease duration (year)	2.35 ± 1.73	2.31 ± 2.73	2.4 ± 2.21		-

*: Not being in the normal range; **: $P<0.01$ (Correlation coefficient compared to digoxin); ***: $P<0.07$ (Correlation coefficient compared to digoxin)

(10, 11).

Digoxin excretion in patients is 85% dependent on renal factors and 15% dependent on hepatic excretion. The amount of renal excretion depends on the patient's renal clearance (12) because the increase of serum urea and creatinine in this study showed a decrease in kidney function. Therefore, the risk of digoxin poisoning has increased. Also, using digoxin in kidney patients can increase the accumulation of internally secreted toxins, including urea (13). The mean potassium serum level also increased with the increase in the mean digoxin serum level. Previous studies on digoxin and its effect on increasing the heart's contractile strength by inhibiting the Na-K ATPase enzyme (14, 15) emphasize that this, by affecting the potassium sodium pump and inhibiting it, causes an increase in intracellular sodium and an increase in extracellular potassium. The result of this study also confirms this issue. Contrary to the result, hypokalemia in patients with heart failure who take digoxin may lead to aggravation of fatal arrhythmias (7). Therefore, patients using digoxin should be monitored regularly to prevent hypokalemia.

In a study conducted in Spain on patients with heart failure who were treated with digoxin, to reduce digoxin toxicity, adjusting the dose according to creatinine clearance had the best result, and to prevent the toxic effects of digoxin, determining the dose according to kidney function. (Creatinine clearance) was more effective than stopping the treatment two days a week (16). Also, digoxin clearance may be affected by age, body weight, serum creatinine, and the height of creatinine clearance (1). Digoxin level is about 0.7-1.5 ng/ml or 0.9-2 nMol/l and is considered normal. However, digoxin poisoning may occur under special conditions such as severe lung diseases or during specific metabolic or electronic disorders even at these levels. The appropriate maintenance dose of digoxin depends on the amount prepared or calculated by the Jelliffe equation, mostly based on the patient's creatinine clearance (17).

The study of Srinivasan *et al*. (18) showed that digoxin dose should be considered for each person separately. If possible, its serum level should be controlled, and to reduce digoxin toxicity, the dose should be adjusted according to creatinine clearance (3). Also, the daily administration of digoxin should be based on existing diseases and drugs, which can affect the volume of drug distribution, drug transfer, or renal secretion.

To wrap up the discussion, it can be finally concluded that digoxin is a very toxic drug with minimal safety margin; each patient has their safety margin. In this study, the increase in the digoxin serum level was related to the urea, creatinine, and potassium serum levels. Therefore, it is suggested to prevent the rise in serum digoxin level and to prevent digoxin poisoning, the continuous control of digoxin serum level, either by serum measurement or by taking into account creatinine clearance. Correcting the patient's dose for a long time in terms of positive effectiveness and incidence, Toxic effects should be monitored to determine the amount of medicinal preservative for that patient gradually.

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