Original Article

The Applicability of International Reports on Digoxin Toxicity to Iranian Patients

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Background: The striking similarities between signs and symptoms of digoxin intoxication and clinical picture of primary congestive heart failure (CHF) make their diagnosis relatively difficult. Narrow therapeutic window of digoxin and increasing mortality and morbidity due to its intoxication make serum digoxin measurements an essential point of concern.
Objectives: The aims of present investigation were to study digoxin therapeutic and toxic levels in Iranian patients and to evaluate the applicability of most clinical findings in relation to digoxin toxic levels.
Patients and Methods: Serum digoxin levels of 195 patients with heart failure, who used digoxin for at least 10 days, were evaluated by radioimmunoassay. Patients' clinical and electrocardiographic (ECG) manifestations of digoxin toxicity were evaluated and compared with serum digoxin level. Therapeutic range of digoxin in patients to be used as a reference was 0.9 to 2.3 ng/ml.
Results: Twenty-one patients showed both clinical and ECG signs of digoxin toxicity, 19 patients had only a single manifestation and 155 did not present with any of these manifestations. Although the serum digoxin level in patients was of great importance, our results showed that clinical manifestation was not completely related to serum digoxin level.
Conclusion: Considering the narrow therapeutic window of digoxin, periodical monitoring of serum digoxin levels must be conducted in all patients receiving digoxin. Nevertheless, clinical manifestation of digoxin toxicity was not sufficient to be used for evaluation of drug toxicity.

Keywords: Heart Failure, Iran, Digoxin toxicity.

Introduction

The prevalence of chronic heart failure has been rising in recent years, despite advances in the management of cardiovascular diseases. In 1997, it was estimated that four to five million individuals in the United States were diagnosed with chronic heart failure [1], and its six-year mortality rate was reported to be 80 percent for men and 56 percent for women[2].

Digitalis glycosides, which have been used for over 200 years for the treatment of heart failure[3], provided better circulation in tissues in patients with congestive heart failure (CHF) by increasing cardiac contractility on one hand while diminishing ventricular contraction rate in patients with atrial flutter and fibrillation on the other[3-5]. Digoxin is a cardiac glycoside most widely used in the treatment of CHF[6,7], and is extracted from the leaves of Digitalis lanata and Digitalis orientalis[8,9]. Digoxin has very variable bioavailability due to variations in its

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absorption from gastrointestinal, distribution and excretion[3]. These differences, in addition to its narrow therapeutic window[6,10], cause a relatively high incidence of toxicity in the patients undergoing digoxin therapy[6,10,11], with a ratio of 5 to 35 percent in hospitalized patients[11,12]. According to the previous studies, therapeutic range for digoxin in patients was 0.9 to 2.3 ng/ml[19]. Serum digoxin levels below and above this range were considered as ineffective and toxic respectively. Serum digoxin levels between 2.0 to 2.3 ng/ml were regarded as borderline. Acute digoxin intoxication can cause a wide variety of arrhythmias [5,13] and many other extra cardiac side effects ranging from headache, nausea and vomiting to death[4].

Differentiating digoxin intoxication from the clinical picture of primary CHF is difficult to achieve because of their overlapping signs and symptoms[3]. Even the electrocardiographic data are not completely diagnostic. Generally, whenever in doub about digoxin intoxication, its usage must be discontinued[5]. Nowadays, the recommended method for the diagnosis of digoxin intoxication is radioimmunoassay (RIA)[5,14]. Calculating serum digoxin level by RIA can be useful in validating dosage, access compliance, bioavailability, effects of renal function and other pharmacological agents on eliminating, preventing and diagnosis of digoxin toxicity[15].

In practice, clinical manifestations of the patients and data from their electrocardiogram are the key points for diagnosing digoxin toxicity. Nevertheless, this diagnosis becomes more complicated because of the non-intoxicated patients with suspected electrocardiograms similar to intoxication, and intoxicated patients without major clinical manifestations. The primary objective of present investigation was to evaluate different therapeutic, toxic, and borderline digoxin levels in patients receiving digoxin, drawing the attention of internists to the importance of checking serum digoxin and improving the patient's management.

Patients and Methods

The present descriptive-analytical study was performed as a cross sectional study on 195 patients from January 1999 to January 2000. Because of using digoxin, these patients were referred to the hospitals of Shiraz University of Medical Sciences for follow-up.

The data obtained from ECG, included supraventricular and ventricular tachycardia, atrial fibrillation, atrio-ventricular block[16], and bradycardia[17]. Clinical manifestations consisted of gastrointestinal symptoms such as loss of appetite, nausea and vomiting, abdominal pain, and diarrhea,as well as neurological disorders namely dizziness, insomnia, irritability, and hallucinations, and visual problems such as difficulty in reading, color vision disturbances, and blurred vision[18]. Patients exhibiting both electrocardiographic and clinical symptoms of intoxication were regarded as intoxicated. On the other hand, cases with one of these manifestations were suspected of being intoxicated. Patients who had used digoxin for less than 10 days, or their blood sample had been obtained longer than 3 hours after admission, were excluded from this study.

Patients' ECG and clinical manifestations of digoxin toxicity were evaluated immediately upon admission. Blood samples obtained 6 to 8 hours after the last dose of digoxin were centrifuged at 3000 rpm for 5 minute.

The sera were collected and stored at -20°C until used. The sera were used for measuring digoxin, blood urea nitrogen (BUN), creatinine, sodium, and potassium levels. Serum digoxin levels were measured by RIA using a commercial kit (Amerlex Company, England). Sodium and potassium levels were determined by flame photometer, whereas BUN and creatinine determined by Autoanalyzer RA-1000.

The data thus obtained, were analyzed by SPSSWIN version. 9 software using statistical tests of simple regression, student t-test, ANOVA, Chi-square and Duncan tests, with $P<0.05$ considered as significant.

Results

Of 195 patients studied, 91 males and 104 females, 21 subjects exhibited ECG and clinical signs of intoxication, 19 patients were suspected of being intoxicated based on only one of the above-mentioned manifestations whereas 155 showed no SIGN of intoxication. Of 21 cases being clinically intoxicated, in 15, 2, and 4 patients the corresponding serum digoxin levels were above 2.3 ng/ml, between 2.0 to 2.3 ng/ml, and below 2.0 ng/ml. Among 19 patients clinically suspected of being intoxicated , the respective serum digoxin levels above 2.3 ng/ml, between 2.0 to 2.3 ng/ml and below 2.0 ng/ml were found in 2, 2 and 15 patients (Fig. 1). Out of 155 patients with no sign of intoxication, 5 patients had serum digoxin level above 2.3 ng/ml, 7 patients had a level between 2.0 to 2.3 ng/ml, and in 143 patients this level was below 2.0 ng/ml. A statistically significant difference was found between serum digoxin levels in patients with intoxication, those suspected of and cases with no intoxication (P value < 0.001).

There was also a statistically significant relationship between weekly-prescribed dosage of digoxin and possibility of toxicity. In other words, in patients intoxicated with digoxin, weekly dosages of the drug were significantly higher ($P < 0.001$) than other groups.

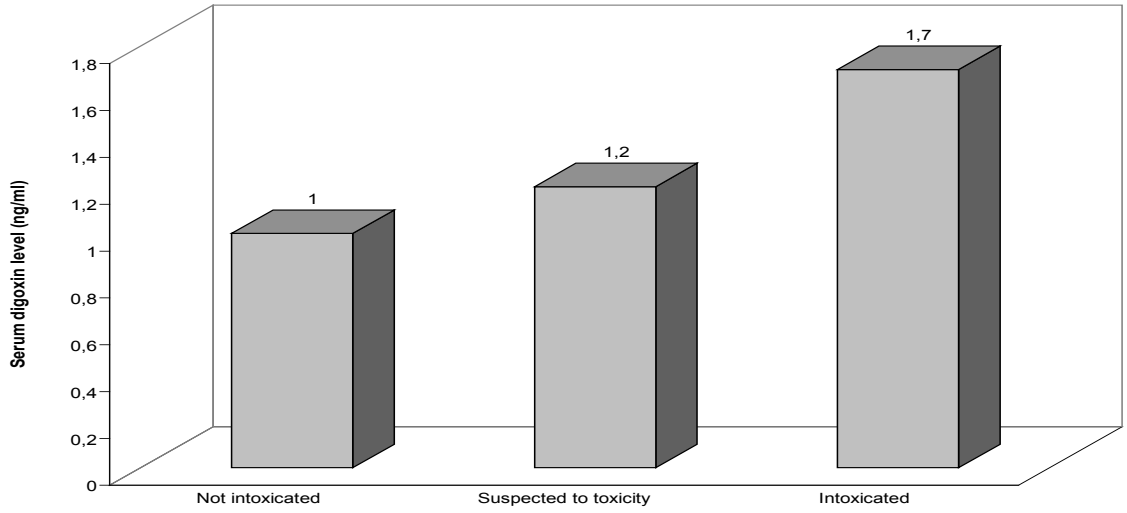

Figure 1. Mean serum digoxin levels in patients who were intoxicated, suspected for toxicity and not intoxicated with digoxin,CLINICALLY

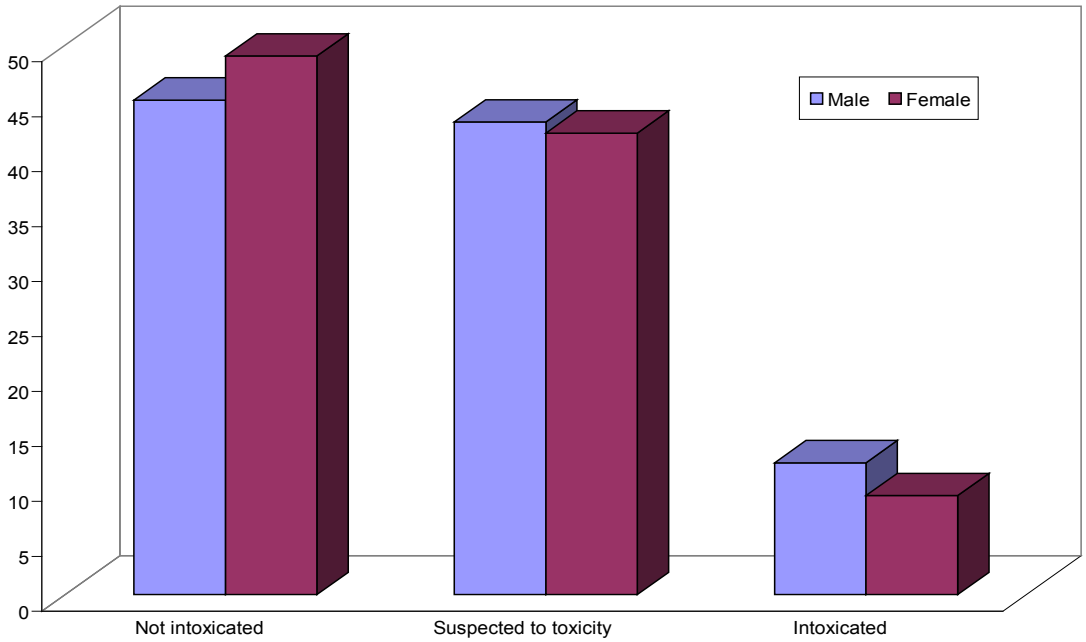

Figure 2. Frequency of digitalis toxicity, being suspected for intoxication and not intoxicated CLINICALLY in both males and females.

Among the male patients, the rates of intoxication and suspected toxicity were 13.6 and 4.5 respectively. However, no statistically significant difference was found in regard to gender (Fig.2).

There was a statistically significant correlation between age and serum digoxin levels in patients receiving a constant dosage of the drug. This is evidenced by rising serum digoxin level with increasing age which is exemplified by P = 0.037 and R = 0.33 in patients taking a weekly dosage of of 0.8 mg of digoxin.

Discussion

Digoxin is an important drug in the treatment of heart failure[5]. It has a very narrow therapeutic range beyond which it causes intoxication in 21 to 25 percent of patients receiving this drug before reaching the time for measuring serum digoxin[15,20,21]. The measurement of serum digoxin level is useful not only for the diagnosis of digoxin toxicity, but also for establishing digoxin therapeutic levels[15] as well as a significant reduction in the incidence of digoxin intoxication[22]. RIA for the measurement of serum digoxin toxicity is a simple, rapid, accurate[7,16], sensitive, and specific[23]. Blood samples were obtained 6 to 8 hours after the last dosage of digoxin, a time necessary to achieve equilibrium between tissue and drug concentration in plasma[14,24]. There were linear correlations between the age and serum digoxin level in patients receiving constant doses of digoxin. This can be due to a decrease in metabolic rate with increasing age.

There was also a correlation between renal failure and serum digoxin level. This could be ascribed to several factors including

decreasing drug excretion in patients with renal failure ,causing in vivo accumulation of digoxin ,rising its serum level and half-life[24,25].

There were no statistically significant correlation between serum sodium and potassium concentrations and serum digoxin levels. This was in accord with the reports of Beller et al. and Evered et al[7,20]. Finally, for verification of the therapeutic effects of digoxin and subsequent prevention of in toxicity, a regular monitoring of serum digoxin level seems to be necessary.

Acknowledgements: The authors acknowledge the financial support by the Office of Vice Chancellor for Research , Shiraz University of Medical Sciences.

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