

ORIGINAL ARTICLE

Investigation of factors affecting outcome of patients with acute digoxin intoxication in two academic emergency departments during 2004-2016

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Received: December 24, 2018

Revised: October 21, 2018

Accepted: October 21, 2018

Abstract

Introduction: Acute digoxin intoxication is a relatively common cause of poisoning. It might be fatal especially in patients with cardiovascular underlying diseases or the cases ingesting a large dose of digoxin intentionally or accidentally. The aim of this study was to investigate the outcome of the patients admitted to Emergency Department with digoxin intoxication. Moreover, the prognostic factors were studied.

Methods: This observational cross-sectional study investigated the outcome of patients with acute digoxin intoxication during 2004 to 2016. All the patients were admitted to emergency department, with acute or acute on chronic poisoning entered the study within 13 years. The documents of emergency departments, ordinary wards, and intensive care units (ICUs) were studied. The outcome and mortality of the patients was investigated. The collected data were analyzed using SPSS software (version 18). Significance level was considered less than 0.05. The chi-squared test and Fisher's exact test were applied to compare the qualitative variables. Furthermore, binary logistic regression was used to find out the factors predicting the outcome of patients with acute digoxin poisoning.

Results: Totally, 81 patients with acute digoxin intoxication were enrolled in the study. Out of the 81 patients, nine patients (11.11%) were admitted to the ICUs. Four cases (4.9%) were intubated and underwent mechanical ventilation, and four subjects (4.9%) died. All the patients that were intubated or died had serum potassium level above normal ranges at the time of admission. In the logistic regression model (admission to ICU or ordinary wards), age, and high potassium level were found to be as an independent factor for adverse outcome (odd ratio=3.11, confidence interval=95%, 2.22-4.5 and odd ratio=12.2; confidence interval=95%, 10.1-14, respectively).

Conclusions: In the present study, it was found that acute digoxin intoxication could result in worse outcomes. Moreover, it was noticed that in patients with higher age and abnormal potassium level, the incidence of morbidity and mortality is higher and requires more careful treatment.

Key Words: Digoxin, Patient outcome, Poisoning, Prognosis



Introduction

Acute intoxication with digoxin can be fatal, especially in patients with underlying cardiac diseases or high doses of digoxin by accident or intentional use. The signs and symptoms of acute poisoning with digoxin include hyperkalemia, cardiac block in the atrioventricular node and fatal ventricular tachyarrhythmias. Although hemodialysis and hemopoietic anesthetics is effective in the treatment of acute poisoning with digoxin (1, 2), it is inadequate due to high distribution of digoxin. To achieve this, there are some cases requiring more effective treatments, such as digoxin-specific antibodies with a high potential for linkage with digoxin. (3) It was first used (1976) to treat patients with digoxin poisoned (4). Currently, indications of digoxin consumption are limited to advanced heart failure; however, acute and chronic toxicity with digoxin is still common (5, 6).

Digoxin has an inotropic positive and chronotropic effects on the heart. Digoxin has a slim treatment window; therefore, the symptoms of poisoning easily appear in patients. Nausea, vomiting, various types of heart block, and ventricular and supraventricular tachyarrhythmias are common symptoms (2, 6, 7). Due to the fact that Fab-specific anti-inflammatory is not available in many countries and has a high price, the improved protective treatments, including heart rate control and electrolyte correction in patients have also acceptable results (7, 8). One of the problems in digoxin poisoning is that in the absence of a clear bias record of digoxin poisoning, the symptoms of poisoning with this drug can be misleading. The clinical manifestations of dioxin poisoning are wide-ranging, and cardiac findings are not specific to digoxin poisoning (9). The deaths from digoxin poisoning have been decreasing, with the rate of 20-30% in the early 1990s (10, 11) reaching to less than 10% in recent years (5, 12). A review of published articles about digoxin poisoning shows that limited number of studies have been conducted in Iran (13, 14), and further studies are needed, especially on the acute toxicity of digoxin. Therefore, the aim of the present study was to investigate the outcome of patients with acute dioxin poisoning referred to the emergency departments of the two teaching hospitals, namely Rasoul and Firoozgar, in Tehran, Iran. Furthermore, the factors affecting their prognosis have been studied.

Methods

This observational cross-sectional study was

conducted from the beginning of March 2004 to the end of March 2016. This study was aimed to investigate the outcome of the patients with acute dioxin poisoning. This study was approved by the University of Medical Sciences with the ethics code of 1783/129/d/93. The information obtained from the patients was confidential to the researchers and the names of the individuals were not mentioned in the publication of the results.

After the research approval at the university, it was referred to the medical record sections of Rasoul and Firoozgar hospitals in Tehran and then the cases of emergency and general (special) patients were examined. All the subjects studied included indexed cases with a diagnosis of acute poisoning or acute and chronic diseases during 13 years. The information was extracted from patients' records. The dose, serum levels of digoxin, serum electrolytes, age, sex, and cause of poisoning with digoxin, along with symptoms and symptoms, were recorded. Furthermore, the outcomes of the patients were found in the special section, intubation, death, and discharge with appropriate general condition.

The inclusion criteria were the ages over 18 years old and acute poisoning with non-toxic digoxin. In addition, the withdrawal criteria were considered the lack of information in patients' records to complete the data, the need for the patients' follow-up for any reasons, and co-ingestion with the other drugs. The outcome of the patients with acute digoxin poisoning was determined as the main objective, as well as the factors affecting the outcomes of the cases as a secondary objective.

The data were analyzed by SPSS software (version 18). Descriptive analysis was performed for quantitative variables with standard deviation and frequency of qualitative variables. In analytical analysis, logistic regression model was utilized to determine the relations between qualitative variables from chi-square or Fisher's exact tests and the factors independent from the outcome of the patients. Moreover, the significance level was considered less than 5%. In the present study, due to the low number of people's deaths, patients' states of health, and admission or denial in the intensive care units (ICU) are considered as the outcome.

Results

A total of 81 patients suffering from acute poisoning with digoxin were enrolled in this study. The mean age of the subjects was 60.4±15.8 years. The patients consisted of 53 (65.34%) females and

Table 1: Specifications of patients based on admission to intensive care unit or general unit

P-value		General units	Intensive care units
		Number (percent)	Number (percent)
0/04	Gender (female)	48 (0.66%)	5 (55.5%)
0/12	(Concentration of digoxin>2 ng / L)	69 (95.3%)	8 (88.9%)
0/45	Heart rate indicators		
	Atrial fibrillation	43(59/7%)	5(55/5%)
	Junctional	12(16/6%)	2(22/2%)
	Sinus tachycardia	9(12/5%)	1(11/1%)
	Others	8(11/1%)	1(11/1%)

Table 2: Multivariate analysis of the outcome of patients in terms of admission to special sections

	Odds Ratio	Confidence interval (95%)	P-value
Age	≥65 years	3.11	2.22-4.5
	<65 years		
Potassium (K)	>5 meq/l	12.2	10.1-14
	<3.5-5 meq/l		

28 (34.66%) males. The reasons for the acute intoxication with digoxin were suicide attempts (51 patients, 62.96%), drug misuse (20 cases, 24.69%), and drug administration with therapeutic dose (10 subjects, 12.23%). The clinical symptoms of the patients at the time of admission were nausea (45 patients, 55.5%), decreased consciousness (29 patients, 35.8%), dizziness (19 patients, 23.4%), headache (14 patients, diarrhea (8 cases, 9.8%), visual disturbances (6 cases, 7.4%) and dyspnea (6 cases, 7.4%). Out Of 81 patients, 9 patients (11.11%) were admitted to the intensive care unit, 4 cases (4.9%) were diagnosed with mechanical ventilation, and 4 subjects (4.9%) died. Out of four cases that were implanted three patients died.

The serum level of the patients was divided into two groups, including 77 patients (95.1%) with a serum level of digoxin higher than 2 ng/dL and 4 patients (4.9%) with serum levels below 2. It was reported that 59.25% of the cases (48 patients), had cardiac artery of atrial fibrillation, 17.28% of the subjects junctional rhythm (14 patients), 34.12% of the patients sinus tachycardia (10 patients), 6.6% of the cases heart block (5 patients), and 4.93% of the subjects (4 patients) had other dysrhythmias, such as ventricular tachycardia. Table 1 tabulates the characteristics of the patients in terms of admission to the general and special sections. The patients were divided into two groups consisted of the cases under 65 years and 65 years or older and the probability of admission to the intensive care unit was significantly higher in the higher age group ($P<0.001$).

Out of 4 deaths, 3 patients were in ≥65-year-old and group. Moreover, the patients were divided into two groups of normal range (5 mg/dL) and >normal range. Among the patients admitted to the

intensive care unit, the level of potassium was significantly higher than 5 ($P=0.002$). In 7 out of 9 cases admitted to the intensive care unit (78%), the level of potassium was higher than normal. In fact, all the patients that died or died initially, the level of potassium was higher than normal.

In the logistic regression analysis (admission to the special department or non-hospitalization), factors entered that were meaningful in the primary analysis (gender, age, and potassium level). Based on the results, the cases over the age of 65 had 11.3 times more chance of being hospitalized in the special department, and the subjects with higher levels of potassium than normal had 12.2 times more chance of being hospitalized in special sectors (Table 2).

Discussion

In this study, 81 patients were enrolled with acute intoxication of digoxin. Higher age and potassium levels above normal range were the factors that independently predicted poor prognosis in the patients. In a study carried out by Kirilmaz et al. (2012), 71 patients with digoxin poisoning were investigated. In this study, 5-year time series has been selected for sampling. The common symptoms of digoxin poisoning in these patients were atrial fibrillation, hypertension, and gastrointestinal complaints. The rate of death was 7%; meanwhile, based on the results of the present study, it was noticed that the mortality rate was 4.9% lower than the study by Kirilmaz. The majority of deaths were in the recent study due to cardiac complications (5). Furthermore, Aarnoudse et al. reported a lower mortality rate (0.7%) compared to that in this study (12).

In a study performed by Lapostolle et al., all the

patients received digoxin-specific Fab. The percentage of death in patients was 6.7%, which was higher than that the present study. The median age in the mentioned study was 74 years, which was higher than that in this study (60 years). It could be one of the reasons for a higher mortality rate (15). In another study, 75-93 year-old patients with digoxin poisoning were included in the study and the mortality rate was 22.9%. Of course, in this study, serum potassium levels did not correlate with death outcome, and serum levels of digoxin had no direct relation with the patients (16).

In a study carried out by See et al. during 2005 to 2010, all referrals to emergency rooms in the United States were investigated due to digoxin poisoning. With the analysis of databases, there were 5,165 annual visits. In 95.8% of cases, the serum level was ≥ 2 ng/dL. In this study, there was a significant increase in gingival toxin toxicity at the older age and female gender (6). Aarnoudse et al. reported a higher incidence of poisoning in women in Netherlands in an investigation of 1286 poisoning with digoxin (12).

In another study conducted during five years from 2003 to 1998, 83 patients were examined. In this study, the factors, such as renal failure, hypoproteinemia, dehydration, hypoxia, and electrolyte disturbances had an adverse effect on the outcome of patients (17). In the present study, electrolyte disturbances (high potassium) were the most important predictive factors.

In the present study, digoxin was found to be a drug, which despite the therapeutic uses can be fatal or severe if poisoning occurs. According to the findings of this study, the two independent factors that increased the risk of drug leakage included the patient's age and serum potassium levels. Since the age of the patients was higher than 65 and the potassium level was more than 5, the likelihood of death was higher and other factors were related to these two independent factors. In addition, according to the literature, the patients should be monitored for a long time after the symptoms of poisoning were resolved due to the risk of relapse (2).

Another important issue is the effects of the onset of cardio, pulmonary, and renal diseases on the deaths of patients with acute digoxin intoxication. Clearing the cardiac glycosylated drugs requires a healthy kidney function, because in patients with renal insufficiency, due to reduced volume of distribution and drug binding to the carrier protein, it is necessary to reduce the maintenance dose, and in the absence of kidney disease during prescription, the probability of poisoning will increase (18). One of the problems

of older patients, in addition to the age-old nature of the disease, is a risk factor for the digoxin toxicity and its complications (19), such as multiple underlying diseases in the elderly patients. Therefore, in this group, patients need to be more precise diagnostic and therapeutic strategy and any deterioration in their health status should be considered in the intoxication of older patients taking digoxin (18, 20).

Changes in the electrocardiography and atrial and ventricular dysrhythmias are among the main symptoms of patients and reported as important causes of death (2, 3). In this study, atrial fibrillation was observed in more than half of the patients. In a study carried out by Kirilmaz, atrial fibrillation was the most common disorientation (5).

In the present study, the prevalence of acute poisoning was higher in women (65%). In other studies, the prevalence of poisoning in women was higher than men (15, 21, 22). In addition, according to the comparison of patients' deaths, gender was effective in the spread of poisoning (suicide attempts were more common in women); however, it did not count risk factors in mortality rates (23, 24).

One of the limitations of this study was that the ultimate cause of the patient's death was not determined. Furthermore, in other countries, Fab can be used to reduce the mortality rate (15, 21, 25). However, due to the limitations in Iran, Fab was not injected to the patients, and therefore the cases were not analyzed. According to the results of a similar study in Iran, the treatment process of the subjects without Fab injection was successful (14).

Conclusions

The result of this study revealed that digoxin poisoning could be accompanied by adverse effects. In addition, it was observed that in patients with high age and potassium, more than five deaths were likely to occur and it requires more careful treatment. Moreover, gender was not considered a risk factor for mortality in patients.

Acknowledgments

The authors would like to thank the emergency staff and medical records of Firoozgh and Hazrat Rasool hospitals.

Author's contribution

Mehdi Rezaei conceived and designed the analysis and study monitoring. Dr. Faeze Delpasand collected the data and wrote the paper. Dr. Kiana Shirsavar performed data collection and edited the

article text. Dr. Khosrow Amiri designed the analysis and registration at university. Dr. Reza Mosaddegh collected the data and edited the article. Dr. Neda Ashayeri monitored the plan, edited the article, and performed the paper's amendments. Manijeh Nasirizadeh (responsible author) translated the article translation and carried out the final edition.

Funding

No research institute was charged for the present study.

Conflict of Interest

The authors declare that there is no conflict of interests.

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