Evaluation of cardiovascular manifestations in Benzodiazepine poisoning

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ABSTRACT

Background: Benzodiazepine (BZD) toxicity alone or with other drugs is common in poisoning emergency departments of Iran. The aim of this study was to evaluate the cardiovascular findings in patients with benzodiazepine poisoning upon admission to the emergency department.

Methods: In a prospective study which was followed by retrospective analysis, 267 patients poisoned with BZD were evaluated. ECG and initial vital signs and symptoms of poisoning were evaluated upon admission. To investigate the relationship between cardiovascular symptoms, changes in ECG, and the type of benzodiazepine consumption, Spearman correlation was utilized.

Results: Most patients had normal heart rate (92.88%), normal blood pressure (95.14%), and normal ECG (96.67%). Hypotension (2.99%), hypertension and bradycardia (1.87%), and tachycardia (5.25%) were also observed in the patients. There were not any significant relationships between cardiovascular symptoms, ECG changes, and the type of ingested BZD. All patients survived without any complications.

Conclusion: Cardiovascular toxicity with BZD alone is not common. Although few changes in cardiovascular or ECG are seen, the prognosis is considered good.

Keywords: Benzodiazepines, Bradycardia, ECG, Hypertension, Hypotension, Poisoning, Tachycardia

INTRODUCTION

Benzodiazepines (BZD) are a class of tranquilizers and sleeping medications. These drugs are largely prescribed and receive a lot of attention from physicians for various clinical applications because of their high safety, required effectiveness, low side effects, and low risk of addiction, and public demand for anti-anxiety drugs and sedatives (1-4). Due to ease of access, the incidence of suicide with these drugs is high so that the second common type of drug poisoning in poisoning emergency departments in Iran is BZD overdose (5, 6). The main target of oral toxicity with these drugs is the central nervous system (CNS) with symptoms such as ataxia, confusion, and decreased level of consciousness, from drowsiness to low grade coma (7). Respiratory depression can be seen with intravenous injections of BZDs. Although oral benzodiazepine poisoning is usually considered safe, mortality and morbidity have been reported in a few cases of poisoning (8-11). The negative intoropic effects of BZDs through peripheral receptors on the heart have been shown in animal studies (12, 13).

Noticing the high prevalence of BZD poisoning in emergency departments and metabolism differences in different communities (14), the cardiovascular findings in BZD poisoned patients upon their arrival to the emergency department were evaluated.

MATERIALS AND METHODS

This study involved prospective data collection followed by retrospective analysis and was conducted by the Anesthesiology Research Department of Noor University Hospital. The protocol was reviewed and approved by the Institutional Ethics Committee of Noor University. Considering Z (confidence coefficient of 0.95), P (an estimate of relative frequency of each of the studied factor that averagely considered 0.5), and D (the precession of the study considered 0.06), 267 patients were evaluated.

Inclusion criteria were:

1- Anesthesiology and Intensive Care Department, Isfahan University of Medical Sciences, Isfahan, Iran
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1- History of taking benzodiazepines, regardless of the type and dose of ingested benzodiazepine
2- Response to flumazenil (15)
3 - No history of cardiovascular diseases and hypertension
4 - No history of ingestion of cardiovascular drugs
5 - Lack of concomitant use of drugs other than benzodiazepines categories.

Discharge with self-fulfillment was intended as the exclusion criterion. Data collection was done using checklist and the questions were asked verbally with permission of the patient and his/her attendances (father, mother, wife/husband, and guardian) through interviews with him/her after resolving the signs and symptoms. Upon admission, vital signs (pulse rate, blood pressure, respiratory rate, and temperature) and electrocardiogram (ECG) were recorded for the patients.

Diagnosis of poisoning in suspected cases was confirmed using flumazenil, intravenous injection (0.1-0.5 mg) (16, 17). The variables included pulse rate (bradycardia, heart rate less than 60 and tachycardia, heart rate greater than 100 per minute), systolic blood pressure (hypertension, systolic blood pressure over 140 mmHg and hypotension, blood pressure less than 90 mmHg), wide-complex QRS (QRS duration more than 0.10 second), PR interval (normal PR, 0.12-0.20 sec), QTC duration (normally between 0.34-0.44 sec), ST segment changes (ST depression or elevation; rising or declining more than one mm was considered abnormal) (18), and T wave changes (invert T wave, flat T wave, or height of T wave more than 10mm considered abnormal) (18). Patients were evaluated during hospitalization until resolving the symptoms and the psychiatric consultation were done before discharge.

Data were analyzed using SPSS 13.0 statistical software ((SPSS Inc, Chicago, IL, USA). To investigate the relationship between cardiovascular symptoms, changes in ECG, and type of benzodiazepine consumption, Spearman correlation test was used. P value less than 0.05 was considered significant.

RESULTS

Most patients poisoned with benzodiazepines were in the age group 20-40 years (65.3%). Women formed 59.3% of the population and 68.2% of the patients were married. The majority of the patients poisoned with enzodiazepines upon arrival at the emergency department had normal heart rate (92.88%) and blood pressure (95.14%). Hypotension and hypertension were observed in 2.99% and 1.87% of the patients, respectively. ECG of the patients showed that most patients had normal ECG. Wide QRS complex, long PR interval was observed in 1% of patients (Table 1). The most common ingested BZDs were clonazepam and lorazepam (Table 2).

Table 1: The frequency distribution of cardiovascular findings in patients with benzodiazepine poisoning

Variables	N (%)
Heart rate	248
Normal	(92.88)
Tachycardia	14 (1.87)
Bradycardia	5 (5.25)
Blood pressure	254
Normal	(95.14)
Hypotension	8 (2.99)
Hypertension	5 (1.87)
ECG	258
Normal	(96.67)
QRS duration > 0.10 ms	3 (1.12)
PR interval > 0.21 ms	3 (1.12)
T Changes	2 (0.74)
ST segment changes	1 (0.35)

N, number of patients

Table 2: Type of ingested benzodiazepine in poisoning cases

Type of Benzodiazepine	N (%)
Clonazepam	20 (16.6)
Lorazepam	19 (15.8)
Diazepam	13 (10.8)
Alprazolam	7 (5.8)
Chlorodiazepoxide	6 (5)
Oxazepam	3 (2.5)
Flurazepam	2 (1.6)
Mixed of benzodiazepines	197 (41.9)

There were no significant relationships between pulse rate, blood pressure, ECG changes, and type of benzodiazepines. All poisoned patients were completely recovered without any complications.

DISCUSSION

The findings of this study showed that the prevalence of benzodiazepine intoxication among 20 - 40 year old age group was more

common which is similar to those of other studies regarding the epidemiology of poisoning (5, 6). This might probably be due to the specific situation of spirituality and youth, employment problems, education, etc. Toxicity was found to be more in women than men which might be due to the psychological structure of women against the spiritual problems of life and being sensitive and stressful. Other studies also reported similar results (5, 6).

In terms of marital status, intentional poisoning was more common in married patients. More problems, conflicts, and responsibilities in life compared to single people may be the reason for more susceptibility to the emotional stress.

Examination of the patients affected by the homodynamic effects of BZDs showed that the majority of the patients had normal heart rate. Overall, 1.87% of the patients had developed bradycardia and one patient was in severe bradycardia (heart rate less than 45 minutes). Atropine 0.5 mg was injected only to one patient with severe bradycardia which was resolved. This effect may be related to sedative effects of BZD (19), although the weak effect of benzodiazepines on calcium channels in addition to their central effects has been reported previously (18).

In this study, 5.25% of patients poisoned with benzodiazepines had tachycardia.

Although the tachycardia has not been reported in benzodiazepine intoxication so far, in one animal study, tachycardia was indicated (13). Also, the negative inotropic effects of diazepam dose dependent on the heart in animal studies indicated that the basis may cause reflex tachycardia 18). On discharge, all patients had normal heart rate. Other reasons for initial tachycardia, such as stress due to psychological problems, might be considered as well.

The findings showed that in 2.99% of the patients, systolic blood pressure was less than 90 mmHg which was treated with infusion of normal saline. None of the patients needed inotrope or vasopressor drugs for hypotension management.

Benzodiazepine intoxication due to its depressant effect on the central nervous system can cause mild hypotension. The negative inotropic effects of benzodiazepines on cardiac contractility should not be also hidden (12). On the other hand, hypertension was observed in 1.87% of the patients. None of these patients had a previous history of hypertension.

However, the issue of abnormality in patients with hypertension needs further studies.

PR interval in ECG was prolonged in 1.05% of the patients. In a study by Molin, a severe first degree AV block was observed in alprazolam overdose reversed by flumazenil (20).

The results showed no significant relationships between cardiovascular symptoms, changes in ECG, and the type of ingested benzodiazepine. All of the patients recovered completely without any complications. Mortality in oral toxicity is minimal with benzodiazepines poisoning. In a few of the reported cases, the synchronization with other drugs has been considered (7).

CONCLUSION

In conclusion, it can be stated that benzodiazepine poisoning is safe and imposes no significant risks of cardiovascular toxicity.

None of the patients with cardiovascular toxicity required specific treatment except for patients with hypotension who received normal saline infusion. Atropine 0.5 mg was injected only to one patient with severe bradycardia.

More studies evaluating the cardiovascular effects of BZD poisoning with a special focus on the specific type of BZD are recommended.

Limitations of the study

Noticing the sample size and the specific type of BZD, a significant relationship between cardiovascular changes and the specific BZD drugs could not be observed. However, the possibility of cardiovascular changes associated with the type of benzodiazepine consumption can not be rejected. More particularly, the toxicity of some benzodiazepines such as alprazolam has been reported previously (10).

The possibility of cardiovascular changes in BZD poisoned patients with sub-clinical cardiovascular problems can not be ruled out.

Our information on patients' history regarding cardiovascular diseases was just limited to the history obtained upon admission.

None of our patients had medical records in our hospital computer. Therefore, comparison of cardiovascular manifestations in BZD poisoning cases with or without definite medical record regarding cardiovascular disorders is recommended.

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