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Research Paper

Acute Poisoning of Benzodiazepines Among Patients Admitted to Loghman Hakim Hospital

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ABSTRACT

Background: Benzodiazepines have been highly prescribed by physicians and have attracted public attention due to their high safety. These drugs have sedative, hypnotic, anti-anxiety, and anti-seizure properties. However, these drugs are also widely used for suicide. The present study was designed and implemented to determine the distribution of patients poisoned with benzodiazepines in terms of clinical and demographic characteristics.

Methods: Investigation of poisoning with benzodiazepines in one year in the poisoning department of Loghman Medical Center in Tehran City, Iran, was carried out as a descriptive-prospective study. In this research, 458 poisoned patients were studied to collect data on their age, gender, drug dosage, type of drug, duration of hospitalization, blood analysis results, and mortality.

Results: The majority of patients poisoned with benzodiazepines were women (62.2%). The mean age of people was 31.67 years. The most frequently used drugs were clonazepam and alprazolam. Other drugs used with benzodiazepines were propranolol, methadone, and acetaminophen. The death rate was 1.7%. The incidence of hypoglycemia and creatinine above 1.3 was 8.53% and 11.3%, respectively. Hyperglycemia was 10.6%. There were 11, 80, and 178 cases of elevated alanine transaminase, aspartate aminotransferase, and alkaline phosphatase, respectively.

Conclusion: Benzodiazepines have the potential to cause liver and kidney damage and changes in insulin secretion and blood sugar. This issue should be considered when dealing with a poisoned patient to prevent serious injuries.

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Introduction

Benzodiazepines are used to treat anxiety, seizures, withdrawal states, insomnia, and restlessness. Benzodiazepines have been widely prescribed and abused due to their various uses and addictive properties [1, 2]. Between 1996 and 2013, benzodiazepine prescriptions increased by about 2.5% each year. Substance abuse disorder treatment centers reported that admissions for benzodiazepine abuse increased by about 109% between 2003 and 2013 [3].

Benzodiazepines are organic bases with a benzene ring. Benzodiazepines exert their effect by modulating the gamma-aminobutyric acid A ($GABA_A$) receptor, an inhibitory neurotransmitter in the central nervous system (CNS). Benzodiazepines bind to the $GABA_A$ receptor site and keep the receptor in a conformation that increases its affinity for GABA. This binding ultimately increases the flow of chloride ions through the GABA ion channel, which reduces the ability of the neuron to generate an action potential [3-5].

Benzodiazepines taken in toxic doses without other concomitant medications rarely cause significant toxicity. The classic presentation in patients with benzodiazepine overdose CNS depression with normal or near-normal vital signs. Many patients become alert and even give a reliable history. Symptoms of poisoning include slurred speech, ataxia, and altered mental status. Respiratory depression is uncommon with benzodiazepines alone, but respiratory depression can be noted if taken with concomitant medications such as ethanol or other drugs or substances. Patients with severe intoxication appear in a state of anesthesia or coma [1, 3, 6-8].

Poisoning with benzodiazepines is one of the most common cases of poisoning, especially intentional poisoning [9-12]. This study was designed to investigate cases of poisoning with benzodiazepines in Loghman Hakim Hospital in Tehran City, which is one of the largest poisoning centers in Iran.

Materials and Methods

This prospective study was conducted on benzodiazepine-poisoned patients referred to Loghman Hakim Hospital in 2020. Every patient who had benzodiazepines his or her intoxication was included in the study. The exclusion criteria were as follows: 1) Patients who did not sign the consent form to participate in the study, 2) Non-cooperative patients in answering, and 3) Patients below 12 years old.

Patients or their companions completed the consent form and provided blood samples. Various information such as age, gender, type of poisoning, history of abuse, underlying diseases, and levels of different blood parameters like creatinine (Cr), blood sugar (BS), the international normalized ratio (INR), red blood cells (RBC), white blood cells (WBC), platelets (PLT), hematocrit (HCT), hemoglobin (Hgb), alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were recorded. Additionally, the number of days spent in the hospital and the final status of the patient (death or recovery) were also documented.

Data were analyzed by SPSS software, version 22. Dispersion indices were measured. Qualitative data were analyzed by chi-square test and quantitative data by independent t-test. A significance level of $P<0.05$ was considered.

Results

Demographic and basic information of the patients are given in Table 1. One hundred seventy-three (173) men and 285(62.2%) women were investigated in this study. The lowest age of the patients was 13 years and the highest was 82 years, the mean age of the patients was 31.67±12.45 years (Mean±SD). Ninety-eight (21.4%) patients had a history of drug abuse, which was significantly more in men. The most substances used by the patients were methadone (18 cases), alcohol (17 cases), opium (15 cases), and stimulants (14 cases). The history of benzodiazepine use included clonazepam (3 cases), diazepam (1 case), and alprazolam (1 case). Fifteen patients (3.3%) had an underlying disease in which diabetes (9 cases, 60%) was significantly more common. Three patients (20%) had high blood pressure, two patients (13.33%) had gout, and one patient (6.67%) had rheumatism.

The minimum interval between taking medicine and going to the hospital was 9 minutes and the maximum interval was 72 hours with a mean of 6.4±8.3 hours. The most benzodiazepine drugs used by patients were clonazepam and alprazolam (201 and 169 cases). Significantly, cases of poisoning with alprazolam, diazepam, and chlordiazepoxide were higher in women than in men. The mean dose of diazepam and chlordiazepoxide in women and clonazepam in men was significantly higher.

Table 1. Important demographic and laboratory variables in studied patients

Variables	Mean±SD/No. (%)		P
	Male (n=173)	Female (n=285)	
Age (y)	30.72±12.96	32.26±12.11	0.631
Consumption time (h)	6.75±9.85	6.18±7.3	0.166
History of abuse (No.)	66(67.34)	32(32.66)	0.001
Hospitalization (d)	2.15±2.5	1.56±1.34	0.001
Death rate	5(62.5)	3(37.5)	0.465
Alprazolam cases	53(31.36)	116(68.64)	0.001*
Clonazepam cases	90(44.78)	111(55.22)	0.139
Diazepam cases	14(34.15)	27(65.85)	0.042*
Lorazepam cases	12(44.44)	1555.56)	0.564
Chlordiazepoxide cases	12(19.67)	49(80.33)	0.001*
Alprazolam dose (mg)	6.62±23.4	8.47±22.7	0.377
Clonazepam dose (mg)	22.61±46.1	11.73±23.6	0.001*
Diazepam dose (mg)	7.95±35.6	21.44±98.6	0.001*
Lorazepam dose (mg)	2.57±11.9	1.67±8.6	0.059
Chlordiazepoxide dose (mg)	10.47±52.8	28.3±161.8	0.021*
Cr (mg/dL)	1.19±0.35	1.35±5.4	0.239
BS (mg/dL)	106.7±59.4	99.5±39.4	0.062
ALT (U/L)	42.97±126.96	18.7±9.31	0.001*
AST (U/L)	54.22±182.5	26.32±10.6	0.001*
ALP (U/L)	186.06±78.4	152.5±48.9	0.199

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Abbreviations: Cr: Creatinine; BS: Blood sugar; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase.

*P<0.05

Other drugs used together with benzodiazepines are shown in Figure 1. The most drugs included propranolol (27 cases), methadone (26 cases), acetaminophen (21 cases), zolpidem (18 cases), methanol (18 cases), and opium (17 cases). The results of simultaneous use of two benzodiazepines are shown in Figure 2. The highest frequency was related to the simultaneous use of alprazolam with clonazepam (21.7%) and alprazolam with chlordiazepoxide (16.9%).

The death rate was 1.7% (8 cases), of which 3 were men and 5 were women. Alprazolam was responsible for the majority of deaths (5 cases, 62.5%), with clonazepam (3 cases, 37.5%) being the next most common cause. The mean time of hospitalization was 1.78±1.9 days, which was significantly higher in men. Twenty-five people (7.3%) had anemia, which was significantly more in women (12 vs 4) (P=0.018). Forty-five people (13.12%) had polycythemia. The prevalence of thrombocytopenia, leukopenia, and leukocytosis was 12.5%, 5.6%, and 16.3%, respectively. The prevalence of hy-

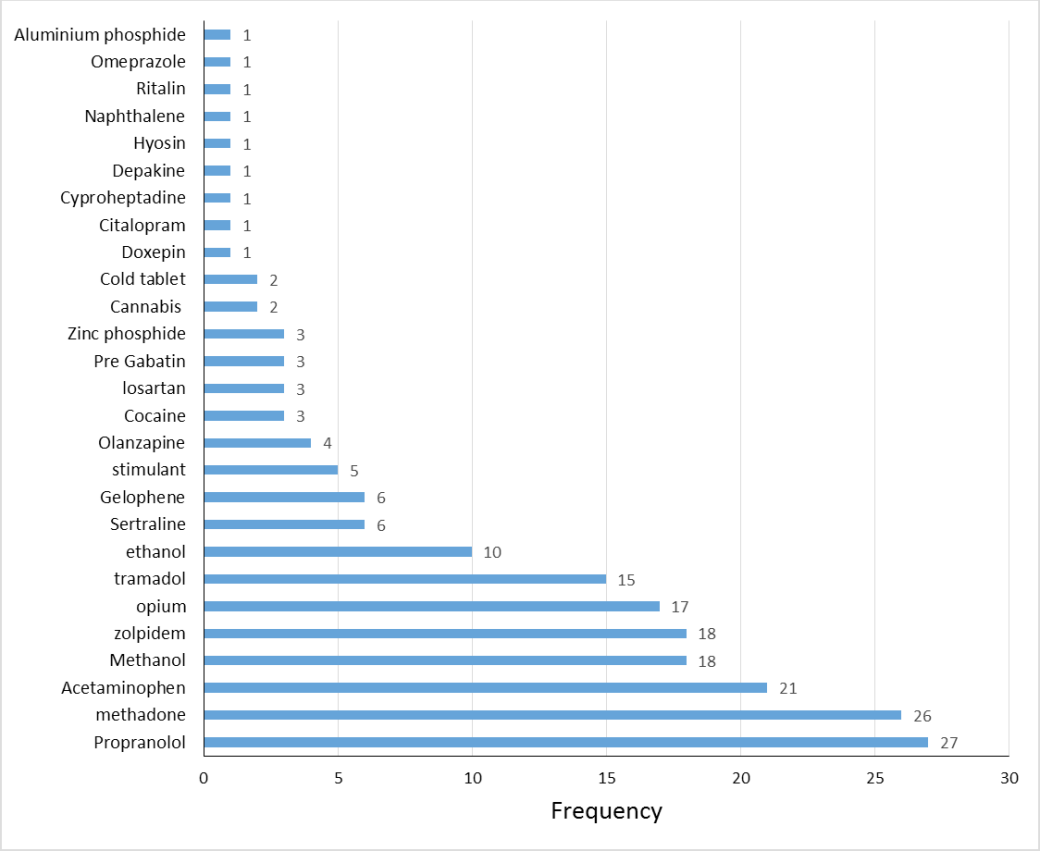

Figure 1. The frequency of drugs used together with benzodiazepines

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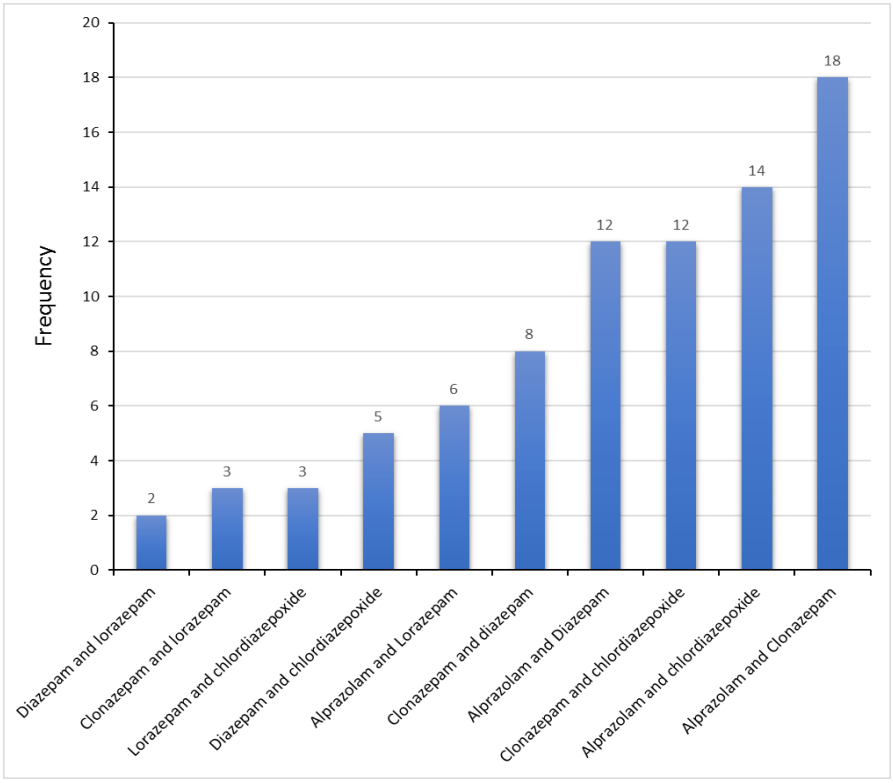

Figure 2. Frequency of simultaneous use of two benzodiazepines

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pochromic anemia (MCH below 27) was significantly higher in women than in men, with 28 cases (75.7%) versus 9 cases (24.3%) (P=0.01).

Cases of creatinine above 1.3 (indicating kidney damage or dehydration) were 39 patients (11.3%), which were significantly more in men compared to women (30 vs 9) (P=0.0001). The prevalence of hypoglycemia among patients was 8.53% (29 cases). Hyperglycemia was 10.6% (36 cases). The increase in liver enzymes was as follows: ALT above 56 U/L in 11 people (3.61%). AST above 33 U/L in 80 people (26.14%) and ALP above 147 U/L in 178 people (59.14%). Significantly, the number of cases of ALT above 56 U/L was higher in men (10 cases) (P=0.001). The mean level of ALT and AST enzymes was significantly higher in men. The mean level of creatinine was significantly higher in women (Table 1).

Discussion

Our study revealed that most people poisoned with benzodiazepines were women (62.2%). The mean age of people was 31.67 years. The most used drugs were clonazepam and alprazolam. The other drugs used with benzodiazepines were propranolol, methadone, and acetaminophen. The death rate was 1.7%. The incidence of hypoglycemia and creatinine above 1.3 was 8.53% and 11.3%, respectively. Hyperglycemia was 10.6%. There were 11, 80, and 178 cases of elevated ALT, AST, and ALP, respectively (3.61%, 26.14%, and 59.14%).

Similar to other studies, it was demonstrated that poisoning incidents were more frequent in women than in men [13-16]. These results could be occurred because women have more suicidal behaviors than men [17-19]. Research on cases of poisoning due to suicide attempts has shown that the rate of intentional poisoning is higher in women [20]. Studies have shown that most poisonings occur between the ages of 20-35 years [21-26]. Our results are in line with the findings of these studies. On average, patients were 31.67 years old.

The frequency of use of benzodiazepine group drugs was different, for example, in a study on the elderly, poisoning was more with bromazepam and diazepam [2]. In another study, the frequency of clonazepam and lorazepam use was higher [27]. Clonazepam and alprazolam were the drugs that were most frequently utilized in our research.

The effect of benzodiazepines on insulin secretion and blood glucose has been extensively evaluated [28-30]. Chevassus et al. stated that benzodiazepines, especially clonazepam, could change insulin secretion and insulin sensitivity in healthy patients [31]. Goudarzi et al. found that the prevalence of hypoglycemia in people poisoned with benzodiazepines is 31% [32]. On the other hand, some studies such as Salice's study showed that benzodiazepines, especially diazepam, can cause hyperglycemia [33]. Our study found that 8.53% of participants experienced hypoglycemia and 10.6% experienced hyperglycemia.

Benzodiazepines are among the drugs that could cause renal toxicity. Rhabdomyolysis occurs in benzodiazepines [7, 34]. Nzor et al. showed that benzodiazepines can increase plasma creatinine levels in albino rats [30]. In our study, 11.3% of the participants had a creatinine level that exceeded 1.3.

Benzodiazepines underwent liver metabolism and formed active metabolites. Benzodiazepines were not considered hepatotoxic, but in a few cases, they can cause liver damage [35, 36]. Mahdavinejad et al.'s study on poisoned patients showed that the increase of liver enzymes up to 4 times was seen in 4.6% of cases of benzodiazepine poisoning [37]. Roy-Byrne and Judd reported cases of hepatotoxicity with alprazolam [38, 39]. Anber et al. found that diazepam in large amounts for a long time can increase liver aminotransferases [40]. Clonazepam also can increase liver AST and ALT [41].

Conclusion

Benzodiazepine poisoning typically results in CNS symptoms, respiratory depression, and cardiovascular alterations. Nonetheless, this class of drugs can also lead to liver and kidney impairment, as well as modifications in insulin secretion and blood glucose levels. It is crucial to take into account these effects when managing a poisoned patient to avoid severe harm. There is a chance that an overdose of alprazolam could increase the likelihood of death. The prevalence of poisoning with benzodiazepines was higher in women.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1402.279).

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Authors' contributions

Conceptualization and study design: Farshad H Shirazi and Shahin Shadnia; Data collection and writing–original draft: Arezou Mahdavinejad; Review, editing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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