



Cross-sectional Study

Occurrence of hypoglycemia in patients with benzodiazepines poisoning: A cross-sectional study

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ABSTRACT

Background: Benzodiazepine (BZD) poisoning is a common medical condition often accompanied by respiratory arrest, aspiration pneumonitis, and may rarely result in death. Although it is not studied well, hypoglycemia is a real and life-threatening condition that may occur in BZD poisoning. Thus, the present study was shown to determine the prevalence of hypoglycemia among patients with BZD poisoning compared to toxicity with other drugs.

Patients and methods: In this study, patients with drug-induced poisoning referred to Vasei hospital, Sabzevar, eastern Iran, were registered and their blood glucose levels at presentation were collected during 2019.

Results: Overall, 300 poisoned patients were evaluated (17% with BZD poisoning). The prevalence of hypoglycemia was significantly higher in patients with BZD poisoning (11.8% vs. 2.8%, $p = 0.004$), especially in males ($P = 0.016$), aged >30 years old ($p = 0.006$). However, the prevalence of hypoglycemia was higher in patients with $GCS < 10$ ($p = 0.005$) and in patients referred later than 1 h to a medical center ($p = 0.015$).

Conclusion: Results were show that hypoglycemia is a frequent complication of BZD poisoning and should be considered in the initial evaluation of patients referred to the emergency department with this medical condition.

1. Introduction

Drug poisoning is one of the major health system difficulties. The pattern of occurrence of these intoxications is related to various factors, such as accessibility of medicine as well as the social culture of countries regarding drug preservation [1]. Nowadays, benzodiazepines (BZD) are one of the most widely available drug groups. Although BZDs are not over the counter drugs, because of the wide range of indications available for their use, and are prescribed in most clinical settings by physicians, this group of drugs is widely available and therefore has a high poisoning probability [2].

BZD intoxication affects various organs in the body, although the major effects of an excessive dose of these drugs are on the central nervous system, and an intoxicated person presents symptoms such as dizziness, confusion, anxiety, agitation, and decreased response to

environmental stimuli. Given the major effects of these drugs on GABAergic receptors, it is not out of question to observe these effects [3].

Rarely, changes in blood biochemistry occur due to direct effects of BZD poisoning. The association of hypoglycemia with BZD intoxication is one of the changes considered in previous studies, and some of which have been reported in case reports so far [4,5]. This is especially the case in patients with an increased risk of hypoglycemia [6]. Despite such evidence, to date, there has been no comprehensive study on the occurrence of hypoglycemia during BZD intoxication and its potential risk factors. Thus, this study was aimed at estimating the prevalence of hypoglycemia in BZD poisoning and determining the pattern of blood glucose checks in comparison with other drug-poisoned patients admitted to level 3 hospitals.

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2. Patients and methods

This study was a cross-sectional research in which patients drug-poisoned were referred to the tertiary level hospital in Sabzevar from 2018 to 2019. A census was used as a sampling method, during which all patients who met inclusion criteria, including confirmation of drug intoxication in urine test, and diagnosed with one substance toxicity at initial examination, and without exclusion criteria, including incomplete records and dissent for inclusion in the case study, were evaluated. This study was confirmed by the Ethics committee of Sabzevar University of Medical Sciences (IR.SBUMS.REC. 1397.021), and informed consent was achieved from all patients (or their legal guardians in case of low consciousness).

Patients' data, including age, sex, drug type, medication dose, consciousness level, admission time, admission time after drug consumption, whether or not pre-hospital procedures were done, blood sugar level, and hypoglycemia existence, was collected using a checklist based on the patient's history, examination, and tests. The degree of consciousness was assessed based on the Glasgow Coma Score. Pre-hospital procedures were defined as administration of remedies at Level 1 clinics in the form of active charcoal prescription, gastric lavage, and complete intestinal washing before referral to the emergency department of Vasei hospital (Sabzevar, Iran). Blood sugar (BS) less than 60 mg/dl is defined as hypoglycemia.

The mean (standard deviation) was used to define quantitative variables according to situations, and for qualitative variables, frequency (percentage) was used. The T-test, or its asymmetric test, the Mann-Whitney *U* test, was used to evaluate the mean quantitative outcomes between the two groups. The Chi-Square or Fisher Exact test was used to compare qualitative factors between the groups. The SPSS software version 21 was used for data analysis and a P-value of <0.05 was considered as statistically significant. The work has been reported in line with the STROCSS criteria [7]. This study is registered with the Research Registry, and the UIN is research registry 7019 (<https://www.researchregistry.com/register-now#home/addregistration/register-research-study-please-note-it-costs-99-to-register-payment/60d30450b5d71d0020bd1c32/>).

3. Results

In the present study, a total of 300 patients with different types of poisoning, 51 (17%) with BZD poisoning and 249 (83%) with other poisonings were studied, out of which 172 (57.3%) were male and 128 (42.7%) were female. The mean age of individuals was 31.15 ± 6.24 years old (with an age range of 4–78 years old).

Hypoglycemia was found to be significantly more frequent in patients with BZD poisoning compared to other poisonings ($P = 0.004$). The frequency of hypoglycemia occurrence in patients with BZD intoxication was significantly higher in males, with GCS less than 10, and those referred to the emergency department for longer than 1 h, and those who received no pre-hospital procedures compared to other drug poisonings ($P = 0.016$). But, no significant difference was found in female gender, with GCS greater than 10, and those referred to the emergency department for less than 1 h, and receiving pre-hospital procedures (Table 1). There was no considerable difference in the frequency of hypoglycemia occurrence in patients with BZD poisoning based on drug type ($P > 0.05$) (Table 2).

4. Discussion

This study was shown to determine the prevalence of hypoglycemia in BZD poisoning patients and determine the pattern of blood sugar checks in comparison with other drug toxicity admitted to Vasei hospital in Sabzevar, Iran during the 2018–2019 years. The results of this study showed that the frequency of hypoglycemia occurrence in patients with BZD poisoning was significantly higher than in patients poisoned with

Table 1

Hypoglycemia in patients with benzodiazepine intoxication.

		Group	Hypoglycemia		
			Hypoglycemia	BZD	Other drugs
Age	<30 years	Positive	29 (96.7%)	140 (99.3%)	169 (98.8%)
		Negative	1 (3.3%)	1 (0.7%)	2 (1.2%)
	>30 years	Negative	16 (76.2%)	102 (94.4%)	118 (91.5%)
		Positive	5 (23.8%)	6 (5.6%)	11 (8.5%)
	Test Result		Chi square test: P-value = 0.006		
	Test Result		Fisher exact test: P-value = 0.321		
Sex	Male	Negative	25 (86.2%)	140 (99.9%)	165 (95.9%)
		Positive	4 (9.1%)	4 (3.8%)	6 (4.7%)
	Female	Negative	20 (90.9%)	102 (96.2%)	122 (95.3%)
		Positive	2 (9.1%)	4 (3.8%)	6 (4.7%)
	Test Result		Fisher exact test: P-value = 0.274		
	GCS	10 and less	Negative	20 (80.0%)	130 (97.0%)
Positive			5 (20.0%)	4 (0.3%)	9 (5.7%)
More than 10		Negative	25 (96.2%)	112 (97.4%)	137 (97.2%)
		Positive	1 (3.8%)	3 (2.6%)	4 (2.8%)
Test Result		Fisher exact test: P-value = 0.562			
Admission time		1 Hour and less	Negative	30 (90.9%)	122 (96.1%)
	Positive		3 (9.1%)	5 (3.9%)	8 (5.0%)
	More than 1 h	Negative	15 (83.3%)	120 (98.4%)	135 (96.4%)
		Positive	3 (16.7%)	2 (1.6%)	5 (3.6%)
	Test Result		Fisher exact test: P-value = 0.015		
	Pre-hospital procedures	Done	Negative	37 (88.1%)	179 (96.8%)
Positive			5 (11.9%)	6 (3.2%)	11 (4.8%)
Not done		Negative	8 (88.9%)	63 (98.4%)	71 (97.3%)
		Positive	1 (11.1%)	1 (1.6%)	2 (2.7%)
Test Result		Fisher exact test: P-value = 0.233			

other substances, and hypoglycemia occurrence significantly increased in patients with BZD poisoning with older age, male sex, decreased GCS, increased admission time, and no pre-hospital procedures. The majority of studies showing the association of hypoglycemia occurrence in patients with BZD intoxication were case reports, case series, or evaluations of high-risk patients such as diabetic patients, and the current study was among the first studies to accurately assess the frequency of hypoglycemia occurrence and associated risk factors in this group of poisoned patients. The main aim of this study was the inclusion of patients with isolated drug intoxication, and thus, observed effects can be directly attributed to pathophysiology induced by BZD poisoning. Of course, this limits the generalizability of the results of this study to patients with multi-drug toxicity (such as BZD and opioid poisoning, which is nowadays considered as an eminent health problem).

Lustman et al. evaluated the effects of alprazolam on blood sugar regulation of Fifty-eight patients with poor glycemic control, 16 (27.6%) of whom had a symptomatic generalized anxiety disorder, were entered into a randomized, double-blind, placebo-controlled, 8-week trial using alprazolam (up to 2 mg/day) as the active agent. Generalized anxiety disorder was determined in accordance with Diagnostic and Statistical Manual of Mental Disorders criteria, and anxiety symptoms were

Table 2
Hypoglycemia in benzodiazepine intoxication based on causes.

Group	Alprazolam	Diazepam	Clonazepam	Zolpidem	Oxazepam	More than 1 h
Hypoglycemia						
Positive	9 (90.0%)	7 (87.5%)	3 (100.0%)	8 (88.9%)	4 (100.0%)	14 (82.4%)
Negative	1 (10.0%)	1 (12.5%)	0	1 (11.1%)	0	3 (17.6%)
Test Result	Fisher exact test: P-value = 0.909					

measured using the Hopkins Symptom Checklist. They showed that glycated hemoglobin levels were significantly lower in patients receiving alprazolam compared to those who did not receive alprazolam, indicating possible effects of benzodiazepines on lowering blood sugar levels in the long term, in addition to their acute effects during intoxication [8].

In 2018, Peng et al. reported a case of a patient with cocaine and benzodiazepine intoxication. The patient was a 45-year-old man whose blood sugar was equal to 55 mg/dl for several days. They found that blood insulin levels were significantly elevated (27 mIU/L) and that there was also a considerable increase in the level of proinsulin (50.1 pmol/L). HbA1c levels also dropped (5.8%). Finally, the treatment team focused on lowering blood glucose levels in the patient, and eventually they were able to relieve hypoglycemia. They suggested that the use of benzodiazepines in combination with other substances intoxication simultaneously increases the risk of hypoglycemia, which may increase prognosis in patients [9].

In our study, the frequency of hypoglycemia occurrence was found to be significantly higher in patients with BZD poisoning compared to other drugs (11.8% vs. 2.8%), which also significantly increased in older, male patients with decreased GCS, increased admission time, and those who received no pre-referral procedures.

In a cross-sectional study, Bottai T et al. investigated the effect of benzodiazepine administration on glucose tolerance; oral glucose tolerance test (GTT) in nine anxious patients (mean age 37 years) treated with alpidem (imidazopyridine-derived) before and after 1 week of drug administration. Compared to pre-treatment values, they observed significant changes in insulin response to glucose. They recommended that daily administration of alpidem at impressive doses for the management of anxiety may alter blood glucose and lead to an increase in blood sugar level and, in some cases, hyperglycemia in treated patients [10].

Chevassus et al. in a study double-blind, placebo-controlled, cross-over clinical trial evaluated the effects of benzodiazepine on beta-cell function, insulin sensitivity, and efficacy of intravenous dextrose administration for GTT on fifteen healthy male volunteers aged 20–29 years (mean 22.5 years). They showed that BZDs, especially clonazepam, may alter insulin secretion and insulin sensitivity after a single dose in healthy individuals. Therefore, the results of this study are in line with the findings of our study. Although, in our study, beta-cell function and insulin sensitivity were not evaluated, it was found that more than 12% of patients with BZD poisoning had hypoglycemia, indicating acute effects of BZDs on the body's hormone system. They suggested that benzodiazepines, in particular clonazepam, may alter insulin secretion and insulin sensitivity after a single administration in healthy volunteers [11].

Giordano et al. in a cross-sectional study of eight normal individuals [four women and four men, 22–34 years old, body mass index (BMI) of 20–25 kg/m²] were studied in two sessions for at least 10 days. It has been shown that alprazolam inhibits neuroendocrine response and also desensitizes adrenal medullar to hyperglycemia by activating the GABA pathway, so the effects of poisoning with these drugs on hypoglycemia are likely to result from this mechanism [12].

5. Conclusion

The results of the present study showed that the frequency of hypoglycemia occurrence was significantly higher in patients with BZD

poisoning compared to other drugs (11.8% vs. 2.8%), which also significantly increased in older, male patients with low GCS, increased admission time, and those who received no pre-referral procedure. According to the results of the present study, hypoglycemia may occur in patients with BZD poisoning and this is effective in improving the prognosis of patients. Therefore, it is suggested to estimate blood glucose levels routinely in patients taking BZD and other intoxicating drugs.

Availability of data and materials

The raw data belonged to the present study cannot be made publicly available, because the disclosure of personal data was not included in the research protocol of the present study.

Provenance and peer review

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Ethics approval and consent to participate

This research was reviewed and approved by the research ethics committee of Sabzevar University of Medical Sciences (IR.SBUMS.REC.1397.021).

Consent for publication

Written informed consent was obtained from the patients for publication of this research and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors' contributions

DS involved in the interpretation and collecting of data and editing of the manuscript. ZZ and HA involved in writing, editing, and preparing the final version of the manuscript. ESB is involved in critically revising the whole manuscript. RT is responsible for collecting data and submitting the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

Registration of research studies

This study is registered with the Research Registry, and the UIN is research registry 7019 (<https://www.researchregistry.com/register-now#home/addregistration/register-research-study-please-note-it-costs-99-to-register-payment/60d30450b5d71d0020bd1c32/>)

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102772>.

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