Research Article

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Features of Benzodiazepine Poisoning in the Elderly and Senile Patients

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AIM OF THE STUDY To study benzodiazepine poisoning in geriatric patients compared to patients of working age.

MATERIAL AND METHODS We examined 82 patients with benzodiazepine poisoning, hospitalized in the Department of Acute Poisoning and Somatopsychiatric Disorders of the N.V. Sklifosovsky Research Institute for Emergency Medicine in 2020–2021, which were divided into age categories: young (18–44 years old), middle (45–59 years old) and older (over 60 years old) age. The presence of benzodiazepines in urine was confirmed by immunochromatographic analysis and gas chromatography–mass spectrometry (GC-MS). The concentration of phenazepam in the blood and urine was determined in 45 patients by GC-MS. Statistical processing of the material was performed using the IBM program SPSS Statistics 27.0. The median (Me), 25th and 75th percentiles were determined. The comparison of quantitative data was performed using non-parametric criteria, the level of significance was taken as $p<0.05$.

RESULTS It was found that acute phenazepam poisoning prevailed in all age groups (90% of patients). Among young and middle-aged patients, moderate and deep stunning (GCS score 12–14) prevailed, and in older people moderate and severe poisoning prevailed (GCS score 3–12), with no statistically significant differences in blood concentrations of phenazepam between the groups. In patients of the older age group with benzodiazepine poisoning, compared to people of working age, the development of respiratory failure was statistically significantly more frequent — 13.8-fold, pneumonia — 12.6-fold, vein thrombosis of the lower extremities — 7.8-fold, trophic skin changes — 29-fold. The duration of treatment in older patients with benzodiazepine poisoning was 3.5-fold higher than in young and middle-aged patients, mortality in the older age group was 41%.

CONCLUSION The course of acute poisoning with benzodiazepines, including phenazepam, in the elderly and senile age differs in comparison with persons of working age with a high incidence of complications and adverse outcomes.

Keywords: acute poisoning, elderly patients, geriatric patients, benzodiazepines, phenazepam

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ALV - artificial lung ventilation
CNS - central nervous system
GABA - gamma-aminobutyric acid
GC-MA - gas chromatography mass-spectrometry
HTS - chemical-toxicological study
GCS - Glasgow Coma Scale
PFA - psychopharmacological action

INTRODUCTION

The leading place in the structure of acute exotoxemia in the world is occupied by drug poisoning (T36-T50 according to ICD-10), among them poisoning by psychopharmacological drugs (PPD) is in the lead [1-5]. This is due to their accumulation in everyday life and widespread use among the population. According to the literature, PPD are included in five classes of drugs, poisoning with which leads to the greatest number of deaths from drugs [1].

Drugs of the benzodiazepine group included in class T42 according to ICD-10 "Poisoning by anticonvulsants, sedatives, hypnotics and antiparkinsonian drugs" are most often used as anxiolytics and hypnotics [1, 5], in geriatric patients as well [6–8]. Despite the results of studies proving the occurrence of serious side effects when taking benzodiazepines in elderly patients, they are the most commonly prescribed PPD in this category of patients [9–13]. In this regard, PPD, including benzodiazepines, are the main cause of poisoning in people of gerontological age, in most cases taken by them for the purpose of suicide [14, 15]. Benzodiazepines act both on GABA receptors in the central nervous system (CNS) and on certain types of peripheral benzodiazepine receptors. Symptoms of poisoning are due to CNS depression. According to the literature, people of working age rarely experience depression of consciousness to coma with respiratory and circulatory disorders. However, in geriatric patients, the risk of severe course and death from PPD poisoning, including benzodiazepines, is high. This is associated with age-related changes in pharmacodynamics and pharmacokinetics that occur against the background of a decrease in the physiological functions of the body, the presence of concomitant diseases, polypharmacy, specific geriatric syndromes such as senile asthenia, sarcopenia and cachexia. The acute poisoning with PPD, including benzodiazepines, in elderly and senile patients at the present stage is an urgent medical problem due to a significant incidence and high mortality [2, 3, 14]. Despite the fact that drugs of the benzodiazepine group are most often taken in the elderly, at present there are practically no materials on the study of their toxic effects in people of this category.

Aim of study: to study the features of benzodiazepine poisoning in geriatric patients compared with their course in people of working age.

MATERIAL AND METHODS

A retrospective cohort study was conducted in 182 patients with benzodiazepine poisoning at the Department of Acute Poisoning and Somatopsychiatric Disorders of the N.V. Sklifosovsky Research Institute for Emergency Medicine in 2020–2021. There were 124 women (68.2%), and 58 men (31.8%). The median age of patients was 37.0 (24.0–59.0) years, *min* — 17 years, *max* — 95 years. Inclusion criteria for the study were: male and female patients with acute benzodiazepine poisoning, age 18 years and older. Exclusion criteria: concomitant poisoning with other drugs, detection of ethanol in the blood and urine during a chemical-toxicological study (CTI). The primary endpoints in this study were mortality and length of hospital stay. The following indicators were also evaluated: characteristics of patients (gender, age), level of consciousness according to the Glasgow Coma Scale (GCS), and the severity of poisoning according to the classification of E.A. Luzhnikov [5], frequency and characteristics of complications.

According to the classification of the World Health Organization (WHO), patients were divided into the following age groups: young age (18–44 years), middle age (45–59 years), persons over 60 years old, including the elderly (60–74 years), old age (75–89 years), long-livers (90 and more years) [5].

Upon admission to the hospital, the presence of benzodiazepines in the urine was determined by the methods of immunochromatographic analysis and confirmatory chromato-mass spectrometry in all patients. The concentration of phenazepam in the blood and urine was determined in 45 patients upon admission to the hospital by gas-liquid chromatography-mass spectrometry on an *Agilent* 7890 *B instrument* with a 5977 *B mass-selective detector* after extraction from the blood. The therapeutic range of phenazepam in the blood, according to WHO data, is from 20 to 80 ng/ml [16].

Statistical processing of the material was performed using the *IBM SPSS Statistics* 27.0 program. The normality of data distribution was assessed using the Shapiro–Wilk test ($n \leqslant 50$). Due to the fact that the data distribution was not normal, the median (*Me*), 25th and 75th percentiles were determined as *Me* (*Q* 25– *Q* 75). The comparison of quantitative data between groups was performed using the Mann–Whitney test (cr. *M–W*) for two independent groups, the Kruskal–Walliss test for three independent groups. Fisher's exact test was used to compare categorical data between groups. The level of significance was taken as $p < 0.05$.

RESULTS

According to the data obtained, 75.9% of patients were young and middle-aged persons, the share of patients of gerontological age accounted for 24.1% ($n = 44$). The figure shows the distribution of patients by age groups.

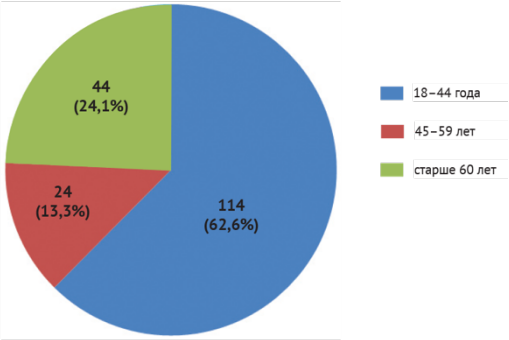

Figure. Distribution of patients by age group

All patients received one drug from the benzodiazepine group.

In 2020, 102 cases of benzodiazepine poisoning were registered, among them there were 90 (88.2%) vases of phenazepam poisoning. In 2021, the total number of benzodiazepine poisonings decreased to 80, while the proportion of phenazepam poisonings increased to 92.5%.

Table 1 shows that the most commonly used drug in all age groups of patients was phenazepam — 164 patients (90.2%), then in descending order: clonazepam, alprazolam, diazepam, tofisopam and bromazepam in one case. In all age groups, in more than 80% of cases, phenazepam became the etiological cause of acute poisoning.

Table 1

Distribution of drugs taken in different age groups

A drug from the benzodiazepine group	Age of patients, years			Total, *n* (%)
	18–44	45–59	60 and over	
Phenazepam, *n* (%)	102 (89.5)	20 (83.3)	42 (95.4)	164 (90.2)
Clonazepam, *n* (%)	4 (3.6)	2 (8.3)	1 (2.3)	7 (3.9)
Alprazolam, *n* (%)	5 (4.4)	1 (4.2)	–	6 (3.3)
Diazepam, *n* (%)	2 (1.7)		1 (2.3)	3 (1.6)
Tofisopam, *n* (%)	–	1 (4.2)	–	1 (0.5)
Bromazepam, *n* (%)	1 (0.8)	–	–	1 (0.5)
Total patients, *n*	114	24	44	182

Assessment of the level of consciousness in patients upon admission to the hospital showed that in the age categories of 18–44 years (young age) and 45–59 years (middle age), patients with moderate and deep stunning prevailed (12–14 points according to the GCS) — 77, 2% and 66.7%, respectively (Table 2). In the elderly and senile age, on the contrary, upon admission to the hospital, in most cases, moderate and severe poisoning (3-12 points according to the GCS) was observed, 63.6%. Statistical analysis revealed significant differences in indicators between age groups.

Table 2

Distribution of patients upon admission to the hospital according to the level of consciousness and severity in different age groups

Impaired level of consciousness on the Glasgow Coma Scale	Age of patients, years			Total patients *n*	*p-value*
	18–44	45–59	60 and over		
Score 13–14, *n* (%)	88 (77.2)	16 (66.7)	16 (36.3)	120	<0.001*
Score 9–12, *n* (%)	24 (21.1)	8 (33.3)	18 (41)	50	<0.001*
Score 3–8, *n* (%)	2 (1.7)	–	10 (22.7)	12	<0.001*
Total patients, *n*	114	24	44	182	

Note: * - differences between the indicators are statistically significant

Analysis of the data showed that the development of respiratory failure, which required tracheal intubation and mechanical ventilation (ALV), was noted in 14.8% of cases (*n* = 27) of the total number of patients (Table 3).

Table 3

Characteristics and incidence of complications in acute benzodiazepine poisoning in patients of different age groups

Complications	Age of patients, years		Total patients *n*	*p-value*
	Up to 60 (*n* =138)	Over 60 (*n* =44)		
Respiratory failure, *n* (%)	5 (3.6)	22 (50)	27	<0.001*
Pneumonia, *n* (%)	5 (3.6)	20 (45.4)	25	<0.001*
Thrombosis of the veins of the lower extremities, *n* (%)	4 (2.9)	10 (22.7)	19	<0.001*
Trophic disorders of the skin, *n* (%)	1 (0.7)	9 (20.4)	10	<0.001*

Note: * - differences between the indicators are statistically significant

The incidence of complications in patients over 60 years of age compared with people of working age was statistically significantly higher: acute respiratory failure,13.9-fold; pneumonia, 12.6-fold, thrombosis of the veins of the lower extremities, 7.8-fold, trophic disorders skin, 29.1-fold.

Due to the fact that a statistically significant difference in the severity of poisoning in patients aged 60 years and over, in contrast to people of working age, could be the result of taking a larger dose of the drug. We conducted a comparative analysis of the quantitative determination of phenazepam in the blood as a frequently used drug between age groups upon admission to a hospital. The concentration of phenazepam in the blood was determined in 45 patients (8 at the age of 18-44 years, 11 at the age of 45-59 years, 26 at the age of 60 and over).

The results presented in Table 4 show that at a young age the median concentration of phenazepam in the blood approached the therapeutic level, in middle-aged patients it was 1.5-fold higher than the upper limit of the therapeutic range, and in the older group it was only 10% higher than it. In all the studied groups, a wide range of concentrations from therapeutic to different values of the toxic level was revealed.

Table 4

Distribution of patients by age and concentration of phenazepam in the blood

	Age of patients, years			*p-value*
	18–44	45–59	60 and over	
Concentration phenazepam, ng/ml	88.3 (45.8–189)	126 (53.9–215)	92.2 (36.7–156.7)	0.356

Of the total number of patients, 7 (15.5%) had a therapeutic concentration, the remaining 38 (84.4%) had different levels of toxic concentrations. It should be noted that in 5 patients of the older age group (over 60 years) with a therapeutic level of phenazepam in the blood, depression of consciousness up to score 7–8 according to the GCS was noted. In the age category up to 60 years, on the contrary, there were no patients with a therapeutic concentration of phenazepam, who would have observed depression of consciousness to the point of stupor and coma.

All patients underwent a complex of therapeutic measures, including infusion therapy and intestinal lavage. Flumazenil was prescribed for diagnostic purposes in a single intravenous bolus dose in 23 patients (12.6%) with depression of consciousness to stupor. For therapeutic purposes, antidote therapy with flumazenil was performed in severe benzodiazepine poisoning (GCS scores 3–8) (n = 12). The drug was administered intravenously as a bolus of 0.1 mg/min to 1 mg, if necessary, repeatedly.

Clinical indicators associated with benzodiazepine poisoning in individuals of different age groups are reflected in Table 5.

Table 5

Comparative assessment of the length of hospital stay and mortality depending on the age of patients

	Age of patients, years			*p-value*
	18–44 (*n* =114)	45–59 (*n* =24)	60 or more (*n* =44)	
General term hospitalization, days	3.0 (2.0–4.0)	3.0 (2.0–5.25)	10.5 (4.25–21.0)	<0.001*
Lethality, *n* (%)	0	1 (4.1)	18 (41)	<0.001*

Note: * - the difference in this indicator is statistically significant for the totality of the groups represented

As can be seen from the Table, the median duration of hospital stay in patients older than 60 years was significantly, 3.5-fold higher than in young and middle-aged patients.

There were no statistically significant differences in the total duration of hospitalization between groups of young and middle-aged patients. It should be noted that in the group of patients younger than 60 years, a fatal outcome occurred in a 59-year-old patient with an initial blood concentration of phenazepam of 202 ng/ml and a severe degree of intoxication. In the group of elderly and senile patients, mortality was 41%, while in the group of young patients it was absent, and in the group of middle-aged patients it was almost 10-fold less. It is noteworthy that in the group of people of the older age group, in 6 cases, death occurred with an initial severity of poisoning of a moderate degree, followed by deterioration.

DISCUSSION

Our data indicate that in most cases (90%) among benzodiazepine poisonings, phenazepam was registered. Phenazepam is the first domestic anxiolytic, surpassing the well-known drugs of the benzodiazepine series in terms of tranquilizing, hypnotic and anticonvulsant effects. Phenazepam was synthesized at the Odessa Institute of Physics and Chemistry of the USSR Academy of Sciences and studied at the Scientific Research Institute of Physics of the USSR Academy of Medical Sciences in the late 1970s [17, 18]. Currently, it is produced in the Russian Federation and the CIS countries. Since March 22, 2021, phenazepam has been classified as a potent substance in the Russian Federation, it can only be purchased using prescription form No. 148 [19]. All other drugs in this group (lorazepam, diazepam, clonazepam) have long been on the list of potent substances, as well as psychotropic substances, the circulation of which is limited and for which some control measures are allowed to be excluded. In this regard, their leave and appointment are limited and difficult. In many European countries and the USA, phenazepam is not approved for sale by *the FDA* and *EMA* [17, 18].

It is known that phenazepam has a therapeutic effect similar to lorazepam, has the most significant anxiolytic effect compared to other drugs from the benzodiazepine group. The structure of phenazepam is close to that of clonazepam. A 1 mg dose of phenazepam is equivalent to 5 mg of diazepam [20]. Phenazepam enhances the inhibitory effects of gamma-aminobutyric acid due to interaction with GABAergic systems and, as a result, inhibits adreno- and cholinergic systems, changing the activity of norepinephrine and 5-hydroxytryptamine, which play an important role in the regulation of stress reactions [21]. The mechanism of the antihypoxic effect of phenazepam is still unknown, but it is probably multicomponent and includes the elimination of free radicals and enhancement

of GABA-mediated inhibition. Numerous studies using adequate methods have shown that phenazepam has a tranquilizing, sedative, anticonvulsant, hypnotic and muscle relaxant effect [20].

According to the literature, in recent years, despite the fact that in many countries phenazepam is banned as an anxiolytic drug due to its potent effect, it has been used for recreational purposes. Foreign literature presents clinical cases of phenazepam poisoning that ended in death [20]. This is of concern to a number of countries where phenazepam has become widely used for the purpose of drug intoxication. At present, phenazepam and other drugs of the benzodiazepine group are widely used in combination with narcotic and psychoactive substances, as well as designer drugs [22, 23].

The analysis of the data obtained shows that during the analyzed period, despite the introduction of restrictions on the sale of phenazepam, the number of poisonings by it in 2021 remained high, and phenazepam was the leading etiological cause of benzodiazepine poisoning (90%). This is probably due to its large accumulation in everyday life, especially in elderly and senile people and independent active use in order to relieve neurotic conditions, panic attacks, anxiety attacks and problems with falling asleep.

The research results show that benzodiazepine poisoning in elderly and senile people is characterized by a more severe course, the development of complications in the toxicogenic and somatogenic stages of poisoning, which cause prolonged treatment and a high level of mortality compared to its level in young and middle-aged people.

During the study, it was found that in patients of gerontological age, the range of phenazepam concentrations in the blood is lower than in the compared groups. However, the poisoning was more severe. This is probably due to age-related changes in pharmacokinetics and pharmacodynamics in geriatric patients. Previously, it was found that in this category of patients there is a sharp decrease in the values of critical and irreversible levels of toxic substances in the blood compared to those in young and middle-aged people [5]. According to M.V. Belova et al., for geriatric patients, a characteristic feature of the course of acute poisoning with psychotropic drugs is also a long-term elimination of the toxicant from the body (120–186 hours) [24]. The physiological decrease in the body's defenses in the older age group predisposes to the frequent occurrence of infectious complications, the severe course of the disease, and an unfavorable outcome [5].

CONCLUSION

Our data indicate that due to a decrease in the physiological reserves of the body and the associated age-related changes in pharmacokinetics and pharmacodynamics, a decrease in the concentration thresholds of toxicants that cause a toxic effect to a therapeutic level and a longer toxicogenic stage of poisoning in the elderly and senile age, the course of acute benzodiazepine poisoning, including phenazepam, in this group of patients, compared with those in people of working age, it has a significantly higher incidence of complications and, as a rule, the presence of adverse outcomes.

1. It has been established that the most common etiological cause among acute benzodiazepine poisoning is phenazepam (90%).

2. It was found that upon admission to the hospital in geriatric patients in 64% of cases, benzodiazepine poisoning of moderate and severe degree was diagnosed, and in patients under 60 years of age, predominantly (66.7–77.2%) mild degree. At the same time, there were no statistically significant differences in the concentrations of phenazepam in the blood upon admission to the hospital between the groups.

3. In patients of the older age group with benzodiazepine poisoning, compared with those of working age, statistically significant differences were found between the incidence of respiratory failure (50% vs. 3.6%), pneumonia (45.4% vs. 3.6%), thrombosis of lower limbs veins (22.7% versus 2.9%) and trophic skin changes (20.4% versus 0.7%).

4. For the totality of groups of patients of young, middle age and 60 years or more with the indicated poisonings, there is a statistically significant difference in the total duration of hospitalization and mortality (p <0.001). At the same time, in patients older than 60 years, the duration of treatment is 3.5-fold higher compared to that in young and middle-aged people. Mortality in the older age group was 41%, while in the group of middle-aged patients there was only one death, and in the group of young people there were no deaths.

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