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Benzodiazepine poisoning in elderly

Akutna trovanja benzodiazepinima kod starijih bolesnika

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Abstract

Background/Aim. Benzodiazepines are among the most frequently ingested drugs in self-poisonings. Elderly may be at greater risk compared with younger individuals due to impaired metabolism and increased sensitivity to benzodiazepines. The aim of this study was to assess toxicity of benzodiazepines in elderly attempted suicide. **Methods.** A retrospective study of consecutive presentations to hospital after self-poisoning with benzodiazepines was done. Collected data consisted of patient's characteristics (age, gender), benzodiazepine ingested with its blood concentrations at admission, clinical findings including vital signs and Glasgow coma score, routine blood chemistry, complications of poisoning, details of management, length of hospital stay and outcome. According the age, patients are classified as young (15-40-year old), middle aged (41–65-year old) and elderly (older than 65). **Results.** During a 2-year observational period 387 patients were admitted because of pure benzodiazepine poisoning. The most frequently ingested drug was bromazepam, the second was diazepam. The incidence of coma was significantly higher, and the length of hospital stay significantly longer in elderly. Respiratory failure and aspiration pneumonia occurred more frequently in old age. Also, flumazenil was more frequently required in the group of elderly patients. **Conclusion.** Massive benzodiazepines overdose in elderly may be associated with a significant morbidity, including deep coma with aspiration pneumonia, respiratory failure, and even death. Flumazenil is indicated more often to reduce CNS depression and prevent complications of prolonged unconsciousness, but supportive treatment and proper airway management of comatose patients is the mainstay of the treatment of acute benzodiazepine poisoning.

Key words:
poisoning; benzodiazepines; overdose; flumazenil; aged.

Apstrakt

Uvod/Cilj. Benzodiazepini su najčešće korišćeni lekovi u slučaju akutnih samotrovanja. Zbog izmenjenog metabolizma i povećane osetljivosti na benzodiazepine, starije osobe su pod većim rizikom u odnosu na mlađe. Cilj ove studije bio je procena toksičnosti benzodiazepina u slučaju suicidalnih trovanja starijih osoba. **Metode.** Retrospektivno su analizirani podaci bolesnika primljenih na hospitalno lečenje zbog samotrovanja benzodiazepinima. Prikupljeni podaci obuhvatili su karakteristike bolesnika (pol, starost), vrstu ingestiranog benzodiazepina i koncentracije u krvi na prijemu, klinički nalaz uključujući vitalne parametre i Glazgov koma skor, osnovne laboratorijske analize, komplikacije trovanja, dužinu hospitalizacije i ishod. U odnosu na starost, bolesnici su grupisani u tri grupe: mlađe osobe (15–40 godina), osobe srednje dobi (41–65 godina) i starije osobe (stariji od 65). **Rezultati.** U posmatranom 2-godišnjem periodu zbog samotrovanja benzodiazepinima lečeno je 387 bolesnika. Najčešći uzročnik trovanja bio je bromazepam, a drugi po učestalosti bio je diazepam. U poređenju sa mlađim osobama, kod starijih osoba incidencija kome bila je statistički značajno veća, a trajanje hospitalizacije duže. Respiratorna insuficijencija i aspiraciona bronhopneumonija bile su češće kod starijih osoba. Takođe, starijim bolesnicima češće je bio potreban flumazenil. **Zaključak.** Akutna intoksikacija benzodiazepinima kod starijih osoba može biti udružena sa značajnim morbiditetom, dubokom komom, aspiracionom pneumonijom, respiratornom insuficijencijom, pa čak i smrtnim ishodom. Flumazenil je indikovan zbog reverzije depresije centralnog nervnog sistema i prevencije poremećaja nastalih kao posledica produženog poremećaja svesti, ali suportivna terapija i zaštita disajnog puta komatoznog bolesnika predstavljaju osnov terapije akutnog trovanja benzodiazepinima.

Ključne reči:
trovanje; benzodiazepini; predoziranost; flumazenil; stare osobe.

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Introduction

Benzodiazepines are widely used drugs, primarily as anxiolytics and hypnotics. Often prescribed on a long-term basis for the treatment of anxiety and insomnia in elderly patients [1], benzodiazepines are readily available for deliberate drug overdose, which is the commonest type of suicidal behaviour in the old age [2]. Benzodiazepines are generally thought to be among the safest psychoactive drugs in overdose [3]. Clinical picture of poisoning basically includes central nervous system (CNS) depression, usually manifested as mild to moderate sedation. Deep coma, with respiratory or circulatory failure is rare [4]. Aspiration, as well as certain level of respiratory depression may be a cause of death in benzodiazepine overdoses [5]. Though even a large overdoses taken alone rarely cause death, there is a concern about benzodiazepines adverse effects because of additive effects with other CNS depressants and alcohol. Also, elderly may be at greater risk compared with younger individuals, since the safety of therapeutic doses of benzodiazepines may be reduced due to impaired metabolism and increased sensitivity of this population [6]. Studies on benzodiazepine pharmacokinetics in old age imply some alterations, especially in distribution and elimination of certain compounds [7]. Though benzodiazepines are among the most frequently ingested drugs in self-poisonings, studies on benzodiazepines effects due to significant overdose in elderly are rare [8].

The aim of this study was to assess toxicity of benzodiazepines in elderly attempted suicide in comparison with younger patients.

Methods

This was a retrospective study of consecutive presentations to hospital after self poisoning with benzodiazepines during a 2-year period (2010–2012). Patients with co-ingestion of other drugs or alcohol were excluded from the study. Collected data consisted of patient's characteristics (age, gender), benzodiazepine ingested with its blood concentrations at admission, clinical findings including vital signs and Glasgow coma score (GCS), routine blood chemistry, complications of poisoning, details of management (mechanical ventilation and flumazenil administration), length of hospital stay (LOS) and outcome. According the age, patients are classified as young (15–40-year old), middle aged (41–65-year old) and elderly (older than 65).

Results

During the observational period 387 patients (284 females and 103 males) were admitted to our hospital because of pure benzodiazepine poisoning. Patients' age ranged from 15 to 93 (mean 45 ± 17.7 years for females and 42 ±1 5.5 for males).

Ingestion of single drug was recorded in 349 (90%) patients, while 38 patients (10%) ingested two or three different benzodiazepines. The most frequently ingested benzodiazepine was bromazepam. About 50% of the patients in all the age groups ingested this drug. There was no poisoning with clonazepam in the group of elderly patients. In this group short acting hypnotic midazolam was more frequently ingested than in younger patients. Types of benzodiazepine ingested in different age groups are listed in Table 1.

Table 1

Ingested benzodiazepines

Benzodiazepine	Patients' age (year)			Total (n)
	15–40 n (%)	41–65 n (%)	> 65 n (%)	
Bromazepam	102 (51)	79 (39.5)	19 (9.5)	200
Diazepam	33 (44)	32 8 (42.7)	10 (13.3)	75
Lorazepam	19 (40.4)	21 (44.7)	7 (14.9)	47
Clonazepam	22 (51.2)	21 (48.8)	0 (0.0)	43
Alprazolam	17 (50)	16 (47)	1 (3.0)	34
Midazolam	10 (38.5)	12 (46.1)	4 (15.4)	26

Level of sedation, according to GCS in different age groups is shown in Table 2. Among the patients with GCS of 13–15 there were 5 patients (1.29%) with episodes of paradoxal excitation. All of them were younger than 65. The incidence of coma (GCS of 3–8) was 12.4% (48/387 patients). Statistical analysis (χ^2 test) revealed significant differences in the level of sedation between the age groups, with more pronounced sedation with the increase in patients age.

Respiratory failure developed in 11 (2.8%) patients, 4 of them were older than 65. The incidence of respiratory failure in elderly patients was higher than in younger ones (10.5% *vs* 2%), but a statistically significant difference could not be proved because of a smal number of patients with this effect. Mechanical

Table 2

Level of sedation aceording to the Glasgow coma score (GCS)

Level of sedation (GCS)	Patients' age (years)			Total number of patients
	Group I (15–40) n (%)	Group II (41–65) n (%)	Group III (> 65) n (%)	
Mild (somnolence) GCS = 13–15	171 (92.43)	112 (68.29)	10 (26.32)	293
Moderate (sopor) GCS = 9–12	6 (3.25)	27 (16.47)	13 (34.21)	46
Severe (coma) GCS = 3–8	8 (4.32)	25 (15.24)	15 (39.47)	48
Total number of patients	185	164	38	387

Comparation:
Group I *vs* Group II: $\chi^2 = 33.27$; $p < 0.001$;
Group I *vs* Group III: $\chi^2 = 90.22$; $p < 0.001$;
Group II *vs* Group III: $\chi^2 = 23.05$; $p < 0.001$.

ventilation was necesary in three patients, two of them belonged into the group of elderly. About 1% of patients younger than 65 and 5% of elderly patients needed mechanical ventilation.

Hypotension with systolic blood pressure lower than 80 mmHg was recorded in 32 (8.26%) patients. There was no difference in the incidence of hypotension between elderly and younger patients (7.9% *vs* 8.3% respectively).

Biochemistry analyses included complete blood count (CBC), blood concentrations of glucose, urea nitrogen, creatinine, transaminases (AST, ALT) and creatine kinase (CK). Except for a single patient in the group II with chronic renal failure, there were no patients whose biochemistry indicated renal or liver disorders. Transient leukopenia with minimal white blood cells count of 1.78×10^9/L was revealed in a single patient with bromazepam overdose. Leucocytosis was registered in 34 patients. In 25 of them pneumonia was proved on chest radiography.

Major sedation was complicated with aspiration pneumonia and rhabdomyolysis. Elevated activity of CK accompanied with slight elevation of AST and ALT activities was noted in 21(5.42%) patients, probably due to rhabdomyolysis caused by pressure on muscles during severe sedation. Maximal value of CK in elderly was 8.464 U/L, and in patients under 65 was 13,000 U/L. The incidence of rhabdomyoliysis in comatose patients was 21.4%.

Aspiration pneumonia was noted in more than a half of patients in coma (52%). The incidence of pneumonia in comatose elderly, middle aged and young patients was 75%, 52%, and 25%, respectively.

Toxicological analyses were obtained for 376 patients. In 340 (90.42%) patients, concentrations of benzodiazepine in blood were in the range of toxic [9], and in the rest 36 (9.57%) were in therapeutic range. In the group of elderly, 4 of 5 patients with therapeutic concentration of benzodiazepines in blood had marked sedation (GCS score was even in the range of 3–8 in 2 patients). In groups of younger patients there were no comatose patients with therapeutic blood concentration of ingested drugs.

Maximal revealed concentrations for the two most frequently ingested drugs, bromazepam and diazepam were 8.52 mg/L and 11.84 mg/L, respectively. For diazepam, concentrations of its active metabolite, temazepam, are also obtained. Details on patients with maximal blood concentrations of these drugs are shown in Table 3.

Differences in severity of poisoning among the age groups may be the consequence of simply greater dose ingested. Therefore, to check this possibility, concentrations of drugs on admission were compared between the groups. Statistical analysis was possible for the most frequently ingested benzodiazepine, bromazepam, as blood concentrations were obtained for 192 patients poisoned only with this drug. Though the mean concentration of bromazepam was higher in elderly, the difference between the age groups was not significant (Table 4). Furthermore, there was no significant difference between the concentration of drugs among the groups with moderate and severe level of sedation (Table 5).

All the patients received intravenous solutions as supportive treatment. Gastric lavage was performed in 128 (33%) patients, admitted up to 2 hours after ingestion. Specific antidote, flumazenil was administered for diagnostic and/or therapeutic purposes to 64 patients. This drug was used as diagnostic tool given in single bolus dose to 38 (10%) patients with severe sedation. Flumazenil was given as an antidote in the cases of deep coma, with respiratory failure and hypotension, or in order to avoid intubation and prevent complications of prolonged unconsciousness. According the physician's estimation, flumazenil

Table 3

Characteristics of poisonings with the maximal concentration of bromazepam or diazepam

Parameters	Patients under 65		Elderly > 65	
Benzodiazepine	Bromazepam	Diazepam + Temazepam	Bromazepam	Diazepam + Temazepam
Blood concentration (mg/L)	8.52	5.22 + 3.46	7.22	11.84 + 7.46
Age (years), and sex	25, female	47, female	86, female	83, female
Level of sedation (GCS)	13	9	3	3
Complications	No	No	Pneumonia Respiratory failure	Pneumonia
Lenght of hospital stay (days)	3	5	42	14

GCS – Glasgow coma score.

Table 4

Comparation between the mean bromazepam concentrations on admission in relation to the age of patients

Age (year)	Bromazepam concentration (mg/L) mean ± SD	Kruskal-Wallis test
Group I (15 – 40)	0.87 ± 1.03	Group I *vs* Group II: n.s
Group II (41 – 65)	1.07 ± 1.04	Group II *vs* Group III: n.s
Group III (> 65)	1.28 ± 1.53	Group I *vs* Group III: n.s

Table 5

Comparation between mean bromazepam concentrations on admission in relation to the level of sedation

Level of sedation	Bromazepam concentration (mg/L) mean ± SD	Kruskal-Wallis test
Mild (somnolence): GCS = 13–15	0.86 ± 0.03	Mild *vs* Moderate: n.s
Moderate (sopor): GCS = 9–12	1.46 ± 1.82	Moderate *vs* Severe: n.s
Severe (coma): GCS = 3–8	1.45 ± 1.46	Mild *vs* Severe: n.s

GCS – Glasgow coma score.

was administered in repeated boluses or in continued intravenous infusion in 24 (6.26 %) patients. All the patients older than 65 years needed flumazenil for some of these reasons.

With the increase in age, the patents needed longer hospital treatment.

Hospital stay in the elderly was significantly longer than in the young and middle aged patients. There was also a significant difference between young and middle aged patients (Figure 1).

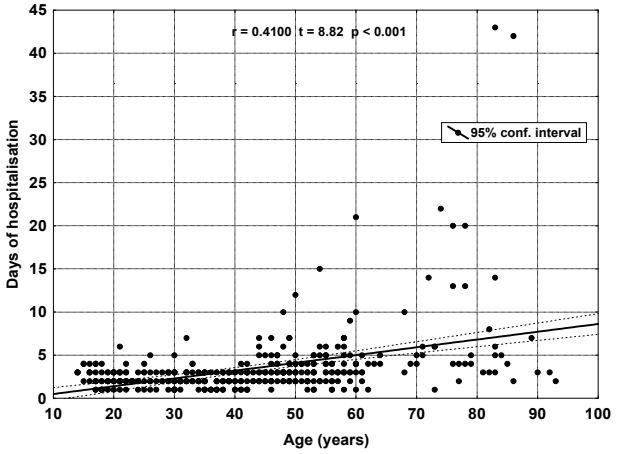

Fig. 1 – Correlation between age of the patients and the duration of hospital treatment.

In two female patients there was fatal outcome (0.5% of the total number); one belonged to the group of elderly (2.6%), and the other to the group of middle aged (0.6%). Both were without apparent biochemical findings suggesting liver or renal impairment on admission. However, the first was sick with ischemic heart and brain disease and the second had disseminated carcinoma.

Discussion

Our study suggests that clinical picture of benzodiazepine poisoning in elderly is more severe than in younger patients. It is primarily manifested as significantly greater level of CNS depression, with more frequent occurrence of coma. Consequently, the incidence of related complications is higher and the length of hospital stay is longer. We recorded more cases of respiratory failure among elderly patients, but because of overall infrequent occurrence of this disorder, there was no statistically significant difference between the groups.

Differences in severity of poisoning between elderly and younger patients may be caused by several reasons. Elderly patients may simply be more resolute to commit suicide taking higher doses of drugs. Reliable comparable data on ingested doses were not available in our patients. The most frequently ingested benzodiazepine was bromazepam. Bromazepam was often used for acute self-administered drug overdoses in other countries, for instance it was also ranked first in France [10], and second after diazepam in some Brazil states [11]. The obtained blood concentrations on admission in our 192 patients with bromazepam ingestion allowed comparison among the age groups. The mean concentration was over the therapeutic level of 0.08–0.2 mg/L [9] in all the age groups (Table 4), and was slightly, but not significantly higher in older patients. Study of bromazepam pharmacokinetics in volunteers divided into young (aged 21 to 29 years) and elderly (aged 60 to 81 years) groups who received single 6 mg oral doses revealed that elderly compared with young subjects had significantly higher peak serum bromazepam concentrations (132 *vs* 82 ng/mL respectively), smaller volume of distribution (0.88 *vs* 1.44 L/kg respectively), lower oral clearance (0.41 *vs* 0.76 mL/min/kg respectively), and increased serum free fraction (34.8% *vs* 28.8% unbound respectively) [12]. Accordingly, the difference in the obtained concentrations between the groups in our study may rather be age-related due to the changes in the pharmacokinetics than dose-related. In general, elderly have reduced muscle and fat mass, which may influence the volume of distribution of the drugs leading to higher plasma concentrations [13]. Other reason for higher susceptibility of elderly to benzodiazepines may be impaired metabolism due to subclinical deterioration in liver and renal function. In the case of benzodiazepines with active metabolites like diazepam, increases in the elimination half-life of both parent compound and metabolites may contribute to the more pronounced sedation [14].

Some pharmacodynamics changes in the elderly are commonly ascribed to alteration in the sensitivity to drugs, especially to those affecting central nervous system, irrespective of changes in drug disposition [15, 16]. Thus, the doses of midazolam needed to reach sedation in the elderly were 50% of those required in young subjects, though there were no differences in pharmacokinetics between the groups [17]. Comorbidity and possible interactions with drugs for treatment of these illnesses may also contribute to the vulnerability of elderly.

In our study the majority of cases could be managed with supportive care including adequate management of airway. Specific antidote flumazenil was administered in the selected cases. Coma in benzodiazepine poisoning is not commonly accompanied with respiratory depression, so ventilatory failure was rarely the indication for flumazenil administration. Decision to intubate or not was primarily based on physicians assessment of risk of aspiration and the majority of our patients received flumazenil to avoid intubation. Because sedation was more severe and prolonged in elderly flumazenil is used more often in this group of patients. Other studies also report on more frequent use of flumazenil with the increased age, severe poisoning and respiratory failure [18]. However, a high incidence of aspiration pneumonia in comatose patients suggests the obligation of proper airway management and intubation, despite the use of flumazenil.

Conclusion

Our study indicates that benzodiazepines massive overdose in elderly may be associated with significant morbidity, including deep coma with aspiration pneumonia, respiratory failure, and even death. Flumazenil is indicated more often to reduce central nervous system depression and prevent complications of prolonged unconsciousness. However, supportive treatment and proper airway management of comatose patients is the mainstay of treatment in these patients.

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