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DIAZEPAM OVERDOSE AND LIVER DISEASE WITH FATAL OUTCOME - *Case report*

PREDOZIRANJE DIAZEPAMOM I OŠTEĆENJE JETRE SA LETALNIM ISHODOM – *Prikaz slučaja*

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Ključne reči
diazepam, predoziranje, oštećenje jetre, letalni ishod

Abstract

Diazepam is benzodiazepine anxiolytic with wide spectrum efficiency. It is one of the most prescribed medications for treatment of different disorders. Because of their wide availability diazepam become the most frequent cause of poisoning. Diazepam overdose occurs when someone accidentally or intentionally takes more than the normal or recommended amount of this medication. Death as a result of diazepam poisoning is uncommon but does occasionally happen.
However, combination of high doses of benzodiazepines with alcohol, barbiturates or tricyclic antidepressants is dangerous and may lead to severe complication such as coma or death. The paper describes case of fatal poisoning as the result of severe and prolonged deterioration of liver damage due to the effects of diazepam.

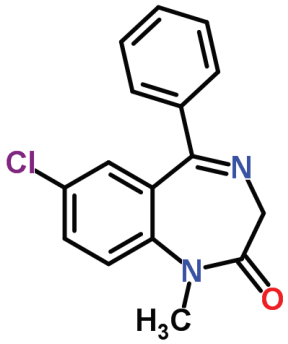
INTRODUCTION

Diazepam is a benzodiazepine derivative. The benzodiazepines are a class of drugs with hypnotic, anxiolytic, anticonvulsant and muscle relaxant properties.(1) They are the most commonly prescribed and used medicine in every section of medicine all around the world and obligatorily present in every home pharmacy. Because of their wide availability they become the most frequent cause of poisoning.(2)

In Serbia benzodiazepines are also the most frequent cause of poisoning. In the observed period of one year at the Clinic for Toxicology and Pharmacology (Poisoning Control Center at the Military Medical Academy) 272 patients poisoned by benzodiazepines have been treated. From all types of benzodiazepines, the most frequent poisonings were by bromazepam and diazepam. A literature data is similar: poisonings by benzodiazepines are the most frequent of all poisonings by medicaments. The most frequent are poisonings by diazepam, but poisonings by temazepam and nitrazepam are also common.(3)

Diazepam is a long-acting drug in the benzodiazepine class with wide spectrum efficiency. It deflects anxiety successfully, regulates autonomy functions, and has hypnosedative, miorelaxante and anticonvulsive effects.(4)

The chemical name of diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless to light yellow crystalline compound, insoluble in water and in hexane, soluble in alcohol, chloroform and ether. The structural formula is as follows: (5)



Picture 1. Structural formula of diazepam

The primary target of diazepam, like all benzodiazepines, is the GABA A receptor, a ligand-gated ion (chloride) channel, activated by gamma -aminobutyric acid (GABA), which is the major inhibitory neurotrans-

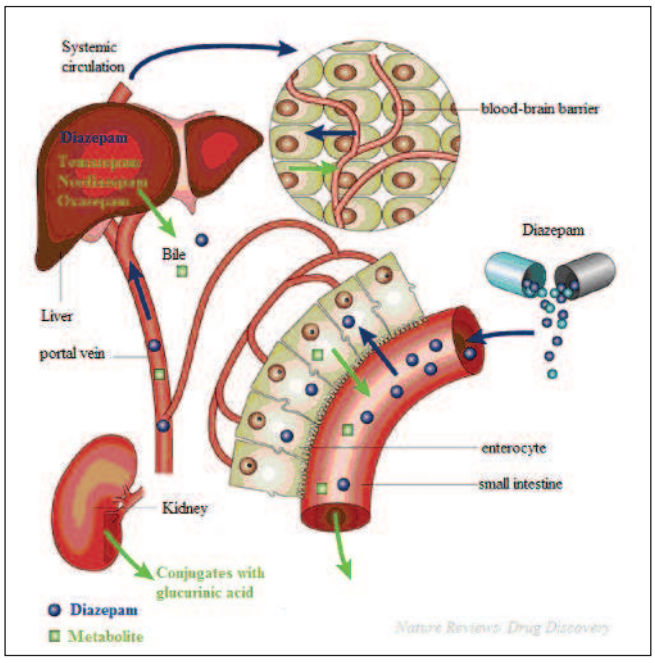
mitter in the central nervous system. Stimulation of the inhibitory GABAergic activity results in sedation, amnesia and ataxia. In CNS, there are specific receptors for benzodiazepines BZ1 and BZ2. Activation of these and GABA receptors leads to opens the chloride channel, causes the conduction of chloride ions across the neuronal cell membrane and begins inhibitory postsynaptic potential. The presence of multiple GABA A receptor subunits is responsible, for the pharmacological diversity in benzodiazepine effects. Binding of diazepam on one subtype could cause the sedation, and the binding on another could cause the anxiolytic.(6,7)

After oral administration diazepam is rapidly and competely absorbed and distributed in all organs with peak plasma levels occurring within 30-90 min. It is highly lypophilic and cross the blood-brain barrier. Plasma proteins bounding is about 98%, which limits effiency of dialysis in cases of poisoning.(8)

Metabolism of diazepam takes place in liver in two phases. In the first phase, diazepam is demethylated by enzyme CYP2C19 and N-desmethyldiazepam (nordiazepam) is generated. After hydroxylation by CYP3A4 nordiazepam generates oxazepam. Minor part of diazepam generate temazepam by C-3 hydroxylation, which transforms in oxazepam by N-1 demethylation. N-desmethyldiazepam, temazepam and oxazepam are pharmacologically active metabolites. In second phase of metabolism, oxazepam is conjugated with glucuronic acid, by glucuronyl transferasa, into inactive conjugates, which are eliminated by urine.(9-10)

Diazepam has a biphasic half-life of about one to three days, and two to seven days for the active metabolite desmethyldiazepam. The half life of diazepam is 20-40 hours, nordiazepam 40-100 hours, oxazepam 6-12 hours and temazepam 6-13 hours. (11)

Because of these active metabolites, the serum values of diazepam alone are not useful in predicting the effects of the drug. For a total consideration and monitoring of drug effect it is necessary to determinate concentrations of diazepam and its metabolites in serum. (12)



Picture 2. Schematic view of pharmacokinetic of diazepam

Therapeutic concentration of diazepam is in the range of 0,1-2 (2,5) mg/L. After discontinuation of chronic therapy, concetration of desmethyldiazepam may be substantially higher than diazepam and both unchanged drug and metabolite are still detectable 7 days after cessation of dosing. (13)

Symptoms of diazepam overdose can include: somnolence, ataxia, dysarthria, nystagmus, slurred speech, mental confusion, hypotension, impaired motor function, reflexes, coordination and balance, dizziness, respiratory arest, vasomotor collapse, coma and death.(14)

A diazepam poisonings require a medical treatment. The antidote for an overdose of diazepam (or any other benzodiazepine) is *flumazenil*. It is competitive antagonist of benzodiazepine receptors. Applying of flumazenil leads to inhibition of binding of benzodiazepines to receptor places.(15)

The therapeutic index of benzodiazepines is high, therefore fatal poisonings are rare. Some cases of fatal diazepam overdose have been described. The most of the cases were diazepam poisonings in combination with alcohol or other psychotropic drugs.

The aim of the paper is to present a case of diazepam overdose with a lethal result.

MATERIAL AND METHODS

Department of Toxicological Chemistry (Poison Control Center at the Military Medical Academy) received the blood, urine, gastric contents and body tissues of dead men 62 years old, with a request to carry out toxicological and chemical analysis for the presence of alcohol and drugs. Plastic bottle with an unknown fluid milky-white color also has been received.

Gas chromatography (GC) with flame ionization detector (FID) - head space technique is used for determination of alcohol in blood.

For the purpose of identification of drugs abusing immunochromatographic test is used as a screening method. It detect presence of five most abused drugs (opiates, cannabinoids, methamphetamines, cocaine and benzodiazepines)

Liquid chromatography with photo-diode array detection (HPLC-PDA) is used for toxicology screening and identification of diazepam in samples.

Determination of diazepam in samples is performed by applying of method described by Djordjevic et al (17).

RESULTS:

In the received samples of blood and urine has not proved the presence of ethanol and methanol.

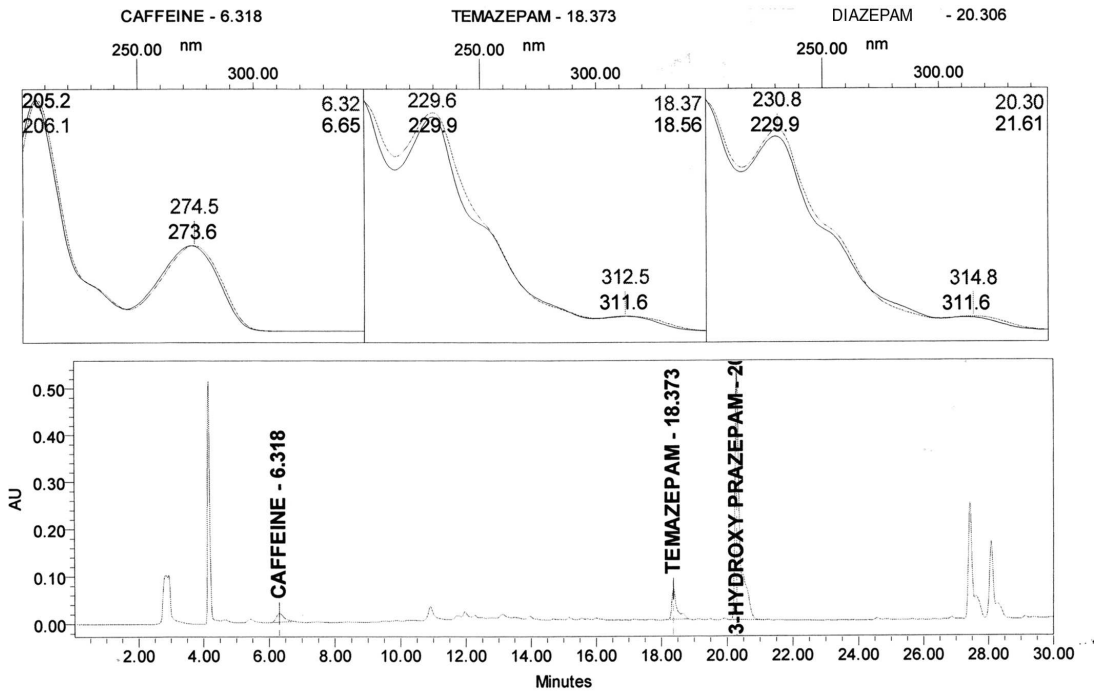
Immunochromatographic screening test of urine was positive on benzodiazepines.

Applying of HPLC-PDA method, in the unknown liquid was detected diazepam. In the analyzed biological samples were obtained the following results:

At autopsy, the most striking findings were in the liver. Histopathologically, there were necrosis focalis hepatis and metamorfosis adipoza hepatis.

SAMPLE	DIAZEPAM	TEMAZEPAM	CAFFEINE
Blood	2,94 µg/ml	0,20 µg/ml	1,88 µg/ml
Urine	0,12 µg/ml	0,04 µg/ml	1,3 µg/ml
Gastric content	1092,4 µg/ml	not proved	not proved
Brain	188,12 µg/kg	18,92 µg/kg	76,64 µg/kg
Liver	4090,2 µg/kg	469,6 µg/kg	825,6 µg/kg
Kidney	356,2 µg/kg	33,8 µg/kg	92,48 µg/kg

Synergistic effects of CNS depression is observed when diazepam is ingested together with ethanol and other CNS depressant drugs [22]. In a fatality due to diazepam an alcohol ingestion, post-mortem tissue diazepam concentration were: blood 1,3 mg/L, bile 4,5 mg/L, brain 2,4 µg/g, kidney 11,7 mg/kg, liver 11,4 mg/kg, urine 6,6 mg/L [23].



Picture 3. HPLC hromatogram of blood sample

DISCUSSION

Benzodiazepines are relatively safe drugs even in overdose. According to the great study done by Serfaty and Masterton (1993) in Britain, in the period from 1980 to 1989, 1576 cases in which benzodiazepines were included ended with a lethal result. The most toxic anxiolytic were diazepam, and lorazepam, and much less chlordiazepoxid, oxazepam and chlorazepat. It was noted that fatal poisonings with hypnotics increased with patient's age[18].

There is no specific dose associated with death. Toxic effects may produced by blood concetration greater than 1,5 mg/L. Fatalities caused by diazepam alone are rare, but may occur at blood concentrations greater than 5 mg/L [13,19].

In the few documented fatal cases doses have not been known with certainty and other factors complicated the clinical presentation[20]. In a survey of 914 benzodiazepine related deaths, in which diazepam was involved, it was found to be the sole cause of death in only two cases. Postmortem concentration of diazepam were 5 mg/L and 19 mg/L in blood. Concentration of diazepam in the first case liver was 13 mg/kg.

Only two cases were associated with diazepam alone, in the remainder other drugs were present which either contributed to or caused death [21].

In the article "Sudden Death and Benzodiazepines", Drumer and Ranson reported data on about 16 lethal cases after poisoning with bezodiazepines. The facts show that many of fatal poisonings have arisen in persons' mid age and in cases in which almost obligatorily existed some chronical disease that could deteriorate with poisonings, and that to be taken into account for death cause estimation. That is why it was very important to know history of disease and have a detailed autopsy report to know if benzodiazepines contribute to lethal result. It is impossible to determine a cause of death in cases in which some disease existed previously. Therefore, it is necessary to do a post mortem toxicological analysis and report on a suicide [24].

Kilibarda has described 3 fatal cases of diazepam overdose in Clinic of toxicology and pharmacology. One of them was 79 years old women. She was died 10 days after diazepam poisoning because of complications in poisoning included bronchopneumonia and cardiomyopathia. This case confirmed the fact that slow metabolism of old persons can lead to complications that have a lethal results. The other two cases were lethal poisoning by amitriptyline in combination with diazepam. Death has occurred as a consequence in inhibition of metabolism of antidepressant. Amitriptyline in combination with

benzodiazepines also increases the activity of GABA.

Patients with liver disease are unusually sensitive to certain sedatives and hepatic coma may follow their administration [25]. The major involvement of the liver in the metabolism of diazepam would suggest that hepatic dysfunction might alter the drug's disposition and elimination. That would be contrary to the general clinical impression that diazepam is a safe therapeutic agent and a sedative of choice in patients with liver disease, a concept based on the observations that there is no prolongation of the sedative effect or abnormality in the electroencephalographic pattern in such individuals after the administration of a single dose of the drug. The reduced clearance of diazepam in patients with acute and chronic parenchymal liver disease suggests that this drug should be used with caution, especially on a prolonged basis, in such individuals [26].

With chronic dosing, steady state concentrations of diazepam are achieved between 5 days to 2 weeks. The half-life is prolonged in the elderly and in patients with cirrhosis or hepatitis. Patients with cirrhosis showed a more than two fold prolongation in the half-life of diazepam. The active metabolite desmethyldiazepam has a longer half-life than diazepam, and takes longer to reach steady state concentrations [27].

Our results are in compliance with literature. Total concentration of diazepam and metabolites was more then 2.5 mg/L, which is in the toxic range. Due to the fact that patients was 62 year old, and that the histopathological result showed alterations in liver, can be assumed that the ingestion of high doses of diazepam led to a severe and prolonged deterioration of liver damage wich resulting in death.

CONCLUSION

Fatal poisonings by diazepam alone are rarely. But intoxication by diazepam in elderly with liver damage could provide slowing-down of metabolism and expression of sever toxic effect. In described case, on the basis of autopsy findings and toxicological chemical analysis, death has occurred as a result of severe and prolonged deterioration of liver damage due to the effects of diazepam and its active metabolites.

Apstrakt

Diazepam je benzodiazepinski anksiolitik sa širokim spektrom delovanja. On je jedan od najviše propisivanih lekova za lečenje različitih oboljenja. Zahvaljujući širokoj primeni i dostupnosti, on je jedan od najčešćih uzročnika trovanja. Do predoziranja diazepamom dolazi nakon slučajnog ili namernog uzimanja doze veću od preporučene. Smrt kao rezultat trovanja diazepamom je retka, mada se može dogoditi.

Kombinacija visokih doza diazepama sa alkoholom, barbituratima ili tricikličnim antidepresivima je opasna i može da dovede do ozbiljnih komplikacija kao što su koma i smrt. U ovom radu je prikazan slučaj letalnog trovanja koje je rezultat ozbiljnog i produženog oštećenja jetre kao posledica efekata diazepama.

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