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Review Article

Hypnosedative Drugs and Alcohol Consumption: Case Report and Literature Review

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Abstract

Besides of abuse alcohol consumption, abuse of hypnosedative drugs is unsettingly common. As a result of concomitant consumption of these substances together, undesirable side effects such as decreased reasoning ability, blurred consciousness, decreased reflexes and death appear in the clinic. In this review, when alcohol and benzodiazepine are used together, the physiological absorption processes of these chemicals and the factors affecting their distribution in body tissues are discussed.

Key words: *Alcohol, Hypnosedative drugs, Abuse, Concomitant consumption.*

1. Introduction

Alcohol is one of the most commonly abused substances in the world. The sedative effect of alcohol on the central nervous system may vary according to the type and amount of alcohol consumed, drugs taken at the same time with or just before or after alcohol consumption, foods and individual factors. In contrast to limited alcohol consumption, increasing doses of alcohol are associated with numerous adverse effects on physiological and neuropsychological mechanisms.

Benzodiazepines are an important type of hypnosedative drug with the potential for abuse. Among the clinical indications of benzodiazepines are anxiety disorders, convulsions, muscular rigidity, insomnia, and preoperative medication. Benzodiazepines have now begun to replace barbiturates, another group of hypnosedative drugs often used in the past. Because benzodiazepines do not have an addictive effect as barbiturates, but they can cause sedation at least as much as they do. They show their effects through gamma-aminobutyric acid – A channel (GABA – A) which transmits anions after binding GABA, an effective inhibitory neurotransmitter in the central nervous system (CNS).

Any concomitant use of benzodiazepines and alcohol, which have sedative properties on the CNS, carries risks of overdose, a more severe reduction in cognition and reflexes, a greater potential for side effects, and increased potential for unpredictable outcomes that may accompany acute states or long-term results.

In this article, chemical analyses reports of body samples obtained from individuals who died after a fall from height accident were investigated. Those reports which

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have been providing information about probability of having been used alcohol before death, in which way the substances detected in blood samples had been taken into the body, the observable effects of the substances on human body, how the fatality influences transformation of the substances, factors that may affect the distribution in various tissues where the samples had been obtained from, and possible effects of end products at determined doses, were discussed in this article.

Case Report

A 37-year-old patient was reached after getting trapped under a roble for 34 hours due to falling from height. Various body fluid samples were taken and sent to laboratory for analyses. In chemical analyses, 10 g of liver tissue, 10 g of kidney tissue and10 ml of stomach content were examined. Accordingto the final report, blood sample was found to contain (91 mg/dl) ethanol, (143 mg/dl) methanol, no formic acid, vitreous humor neither ethanol nor methanol, and liver and stomach contents nordiazepam (14 ng/ml) and diazepem (<1 ng/ml). Also, it is stated that there was some food residue, but no other substances could be detectable with the relevant laboratory systematics.

2. Discussion

Ethanol (ethyl alcohol) belongs to the group of chemical compounds known as alcohols. These compounds consist of carbon, hydrogen, and oxygen molecules arranged in specific configurations, giving them specific properties such as solubility in water and lipid (oil) and volatility (ease of evaporation). Ethanol (C2H5OH), one of the flammable organic compounds, is the only type of alcohol found alcoholic beverages. During manufacture of alcoholic beverages, microorganisms called yeast are added to the sugar–containing medium, and alcohol is produced by the fermentation method.

Blood alcohol concentration (BAC) is measured in humans for medicolegal and forensic purposes. It is widely known that the higher level of ethanol in circulation the more deteriorated physical and cognitive performance. In daily practice, blood alcohol level and blood ethanol level are used synonymously. The use of ethyl alcohol as a drink creates important forensic problems. Beer obtained by fermentation contains 4-8% of alcohol by volume, wine 9-14%, and beverages such as raki, vodka, gin, rum, brandy, whiskey obtained by distillation method contain 35-45% of alcohol (1).

Positive ethanol in body samples taken after death can be interpreted as important evidence that the person consumed alcohol exogenously (externally) before death. It should not be overlooked that after death, there are factors that can lower the level of alcohol consumed before death (false miscarriage). In addition, there are situations that may cause high alcohol levels in tissue samples taken after death, even without alcohol consumption before death.

The equilibrium concentration of alcohol in a tissue depends on the water content of that tissue. The stabilization of alcohol in a tissue depends on its water content, blood flow rate, and tissue mass size. Ethanol has properties similar to water, insoluble in fats and oils, but can pass through biological membranes. Ethanol is distributed from the blood to all tissues and fluids in proportion to the amount of water they contain. Based on this information, the same amount of alcohol consumed per body weight may cause different levels of blood alcohol

concentration values to be measured in different individuals. These differences are due to the changes in the fat and water ratios in body composition of people. The most obvious example of this situation is higher blood alcohol levels are encountered in women compared to men, despite consuming the same amount of alcohol. In addition, due to the faster first–pass metabolism of alcohol through stomach of men, the blood alcohol level may be lower during absorption (2-3). In other words, if there was an early death in the absorption phase after drinking alcohol, the alcohol level, which is likely to reach higher levels, may have been determined relatively low.

Many factors have been identified that affect alcohol absorption. Absorption of alcohol in the duedonum and jejunum (regions of the small intestine) is faster than in the stomach. Thus, the rate of gastric emptying is an important determinant of the rate of absorption of orally ingested alcohol. The various factors that affect alcohol absorption and therefore the level of ethanol measured in the blood are as follows; 1) Alcohol crosses biological membranes by passive diffusion. Therefore, the higher amount of alcohol consumed, the faster it is absorbed into the body. 2) If the blood flow in the intestinal region through where alcohol is absorbed is sufficient, it will increase the absorption of alcohol. In case of premature death, alcohol absorption will stop. 3) Alcohol is an irritating molecule. If taken in high concentrations, it can cause bleeding and superficial erosion (destruction) in the smooth muscle layer of the stomach. This may reduce alcohol absorption. 4) If the ethanol consumed is taken at once rather than in many small doses, the level of blood alcohol level may be higher. 5) Presence of food in the stomach delays gastric emptying and therefore reduces the absorption of alcohol, which is associated with the concept of “should not be consumed on an empty stomach”. The most important factor determining the rate of alcohol absorption is whether the beverage is taken on an empty stomach, with meals, or after meals.

10-20% of the alcohol consumed orally is absorbed from the stomach and mixes into the blood. The remaining (80-90%) part is absorbed from the small intestines and mixes with the blood. The majority of alcohol absorption occurs in the small intestines because of the large absorption surface and high blood flow velocity of this region. For this reason, the rate of alcohol absorption may vary depending on the rate of gastric emptying and adequate blood supply to the intestines. The time elapsed after alcohol consumption is one of the most important determinants of the amount of alcohol consumed, which can be absorbed from the intestines and cause a significant difference in the level of alcohol mixed into the blood. The absorption phase continues as long as alcohol is consumed. The blood alcohol concentration (BCC) continues to increase until the maximum blood alcohol concentration (Cmax) is reached. According to the results of many controlled drinking experiments, the Cmax level is usually reached within 10-60 minutes after the last alcohol consumption. However, the factors described above show that the time to reach the Cmax level (tmax) in individuals consuming alcohol can shrink to 10 minutes if the stomach is empty, or extend up to 120 minutes in the presence of retarding factors (4). Some factors affecting the blood–alcohol concentration (BCC) or Cmax reached

after consumption of a certain dose of ethanol and their possible mechanisms are given in Table 1. In the light of this information, the blood alcohol concentration varies (lower or higher than it should be) depending on the amount of alcohol consumed, the oxidation (breakdown) rate of alcohol, drugs that affect the gastric emptying rate, and whether or not they are taken with food. The fact that there was food residue in the stomach contents in the autopsy report of the person supports that he ate recently.

Table 1: Some factors and possible mechanisms affecting blood–alcohol concentration (BAC) or Cmax.

Various variables or Alcohol consumption factors	Possible mechanism and/or explanation	Expected effect on BAC Level
Low body weight	Low body water	Higher BAC
Body fat level, high BMI*	Excess fat and decreased body water	Higher BAC
Female gender	Decreased body water	Higher BAC
Fast consuming	Fast absorption	Higher BAC
Consumption on an empty stomach	Rapid gastric emptying	Higher BAC
Consumption with/after meals	Delayed gastric emptying	Lower BAC
Alcohol consumption with high ethanol content	Fast absorption	Higher BAC
Low or decreased liver blood flow	Slow metabolism	Higher BAC
Smoking	Delayed gastric emtying	Higher BAC
Drugs that contract the pylorosphincter	Rapid ghastric emptying and absorption	Higher BAC
Drugs that delay gastric emptying	Slow absorption	Lower BAC
Gastric bypass surgery	Fast absorption	Higher BAC

Ethanol absorbed after the intestines reaches the liver via the portal vein system. Not all ethanol reaching the liver can be metabolized at once. Some ethanol continues to circulate in the blood without being metabolized. Because the alcohol dehydrogenase enzyme reaches saturation and ethanol is maximally metabolized at this saturation level. Ethanol is formed mainly by the effect of various biochemical processes and enzymatic activity in the liver (5). Some of the alcohol taken orally does not enter the systemic circulation, but can be oxidized by alcohol dehydrogenase (Types I and III) in the stomach. The efficiency of this first pass metabolism can regulate alcohol toxicity by determining alcohol bioavailability (intestinal absorption). Medications such as histamine receptor agonists such as cimetidine and ranitidine or drugs such as aspirin inhibit ADH activity in the stomach. This effect will also decrease the stomach's first–pass metabolism and therefore increase ethanol concentrations in the blood. The overall clinical impact of first–pass metabolism in the stomach is controversial. The rate of gastric emptying regulates the gastric and hepatic first–pass metabolism of alcohol. Considering the higher levels of alcohol metabolizing enzymes in the liver, it suggests that the liver plays the main role in alcohol metabolism (6-8) The enzyme mainly responsible for ethanol metabolism is alcohol dehydrogenase (Type I ADH),

which is found in the cytosol of hepatocytes and converts ethanol to a more toxic product, acetaldehyde. Fortunately, in mitochondria, acetaldehyde is rapidly oxidized to acetic acid. Acetate produced during the metabolism of ethanol leaves the liver and enters the Krebs cycle and turns into carbon dioxide and water in tissues outside the liver (9). As a result; 1) About 90% of the alcohol is removed by oxidation. 2) Most of this alcohol oxidation occurs in the liver. 3) Alcohol cannot be stored in the liver and is broken down into its metabolites. After the liver, it reaches the heart via the hepatic veins. After ethanol is transported from the right heart cavities to the lungs via the pulmonary artery, it returns to the heart. After the left heart cavities, it is pumped to the tissues through the arterial blood flow. The equilibration of ethanol between extravascular tissues and between tissues and blood depends on regional capillaries and blood flow per gram of tissue (10). Organs and tissues with a high blood flow per gram of tissue, such as the brain, liver, and kidney, are rapidly stabilized by the ethanol concentration in the arterial blood. This contrasts with equilibration in skeletal muscle tissues, and during the ethanol absorption phase (in the case of sudden death without equilibration) ethanol concentrations in arterial blood are expected to be approximately 40% higher than in venous blood. The reason for this is that when alcohol is absorbed from the stomach, it first goes to the arterial blood (11-13). It is not known where the blood sample was taken from in the case. In cases of delayed autopsy, it is known that in practice, samples are taken from the pooled blood in the abdominal cavity, intracardiac and intrathoracic regions. In the concrete case, if the person drank alcohol and a venous blood sample was taken while it was still in the absorption phase, the alcohol value might have been found to be approximately 40% lower.

In forensic toxicology, samples are taken from various body fluids to be examined during autopsy in order to determine whether alcohol and various drugs have been used. These are blood, urine, saliva, vitreous humor (intraocular fluid), cerebrospinal fluid, bile fluid and gastric contents. Vitreous humor (intraocular fluid) is a fluid located within the eyeball between the retina and the lens. This liquid does not contain cellular elements, has a gel–like consistency, is colorless, and consists of a large amount of water (over 90%), hyaluronic acid, collagen fibers (type II), inorganic salts and ascorbic acid. Since vitreous fluid is an isolated tissue that is relatively affected by post–mortem changes such as redistribution of chemicals in the body and increase in blood density, it is used in post–mortem examinations. However, although it is not a common situation, it should be kept in mind that in the case of structural disorders or diseases in the eye structure, the vitreous fluid results may be affected when interpreting. Alcohol metabolism in vitreous fluid is minimal. Therefore, although it is popular in the detection of alcohol use in forensic toxicology, the ethanol content of other body fluids should also be examined and interpreted together. If alcohol is detected in the vitreous fluid, it may be evidence that the person may have used alcohol before death. However, this transition requires a reasonable amount of time. It has been stated in various sources that ethanol may be positive in the vitreous fluid approximately 2 hours after oral (by mouth) alcohol intake (14). If ethanol is not detected in the vitreous fluid (that is,

during this period when the alcohol distribution in the tissues is not fully formed), it can not be said with certainty that the individual does not consume alcohol. When the literature is examined, there are many studies comparing the rates or levels of blood and vitreous liquid alcohol concentrations. However, the striking point in these studies is that the time between alcohol consumption and the moment of death in the examined corpses usually takes days. In a study of 295 people, alcohol was examined in vitreous fluid and blood analysis. In 27% of the cases (81 cases), blood alcohol concentrations were higher than the vitreous fluid concentration. In fact, in 24 of these 81 cases, alcohol was positive in the blood, while alcohol was negative in the vitreous fluid. The blood alcohol level of these cases in which alcohol was not detected in the vitreous fluid was also found to be in the range of 10-300 mg/dl (15). Although these data are rarely encountered in practice, it shows that in an individual who consumes alcohol before death, alcohol may not be positively detected in the vitreous fluid within the first 2 hours after the last alcohol intake.

Although 90% of ethanol is metabolized in the liver, 5-8% is excreted unchanged through respiration and in urine. Therefore, it is also possible to search for alcohol directly in the urine. However, in the present case, urine sample was not taken and the material content, which is an important evidence value, cannot be evaluated.

Alcohol can also be searched for in stomach content examination. In a person who has taken alcohol orally, there is a possibility that the stomach content sample will be positive only if it is sampled within the first few hours after alcohol intake (in the absorption phase). After death, the alcohol in the stomach quickly escapes from the stomach mucous membranes by diffusion method. As in the concrete case, it does not seem theoretically possible to detect alcohol positivity in the stomach content, when the delayed autopsy of a corpse found 33 hours after death and the time taken for the gastric content sample to be taken in this process are added.

In the concrete case, in the presence of many variable factors, it is necessary to examine the postmortem alcohol consumption markers that can concretely reveal the antemortem (pre-death) alcohol intake. About 1% of the alcohol consumed is metabolized in different ways. Ethyl glucuronide (EtG), ethyl sulfate (EtS), phosphatidylethanol and fatty acid ethyl esters (FAEE), which are minor metabolites of alcohol, are formed by these different metabolic pathways (16-20). Since forensic toxicology laboratories are not available in every city in our country, this opportunity cannot be applied in practice. Therefore, none of these markers were examined in the body fluids or tissues of the present case. If these parameters were examined and found to be negative, the claim that alcohol was not consumed before death could be supported. However, the fact that the aforementioned markers were not examined in this case cannot constitute a definitive judgment that the person did not consume alcohol before death.

It is also possible that the ethanol level decreases due to the consumption of microorganisms (In vitro alcohol consumption). Samples taken from body fluids should be kept in suitable conditions until the time they will be studied. Otherwise, the actual blood ethanol level can be measured lower. This can cause a

low blood ethanol level of someone who consumed alcohol before death. The cause of the described condition is usually contamination by microorganisms that metabolize ethanol in samples with other compounds. To minimize this problem, samples should be collected with suitable protective fluids and containers and stored at 4°C (21).

Alcohol can be detected in body samples by postmortem diffusion or contamination. Contamination occurs when the stomach or other hollow organ is disrupted, possibly by dispersal of ethanol-containing contents into other body cavities. If blood is taken from these cavities (for example, the chest cavity) during the autopsy procedure, a false elevation of the ethanol level may be detected. A peripheral vein, the femoral vein (inguinal vein), is a preferred site for the specimen as it is generally not affected by this condition.

Alcohol production after death is another challenging situation in forensic examinations. The ideal timing is to collect blood samples immediately after death for toxicological examination. Because after death, microorganisms both inside and outside the body can cause decay in tissues. They can produce alcohol from glucose (carbohydrate, sugar) by fermentation method by various bacteria and yeasts. This situation can be seen similarly in the human body. Glucose in the body is the raw material for these microorganisms to produce alcohol. A dead human body can create ideal conditions for these microorganisms. In general, it is known that corpses can produce alcohol within a few days of death under conditions of 20-25°C (22). Rapid decay may occur at temperatures above 20-25°C, but the highest and lowest temperatures were recorded as 20-8°C and 21-8°C within 48 hours encompassing the moment of the case we reported. Another point to be noted here is that these microorganisms do not only produce pure alcohol. Besides alcohol, butanol, 2-propanol, acetone and 1-propanol are produced (23-24). However, in the present case, the level of these molecules was not examined. According to the literature, the alcohol level produced by severe decay can reach 200 mg/dl. In the present case, the signs of decay are the larvae in the left eye and ear, and a slight discoloration of the liver, which can not be considered as signs of severe decay. In the experiences of the same authors, it has been explained that isolated post-mortem alcohol production may rarely increase the ethanol level above 60 mg/dl, and if the alcohol amount above 120 mg/dl is detected, this is due to antemortem (pre-death) alcohol consumption. (25-26). 91 mg/dl ethanol and 143 mg/dl methanol were detected in the blood of the concrete case, and a total of 234 mg/dl alcohol was detected.

Ethyl alcohol is a central nervous system depressant anesthetic. In alcohol poisoning, the frontal lobe of the brain is affected. This may cause decreased reasoning ability, coordination disorder in voluntary body movements and disorientation. Higher doses can cause drowsiness, followed by coma or death. Clinical findings are not always dependent on blood alcohol level. Tolerance to alcohol against high blood alcohol levels in chronic alcoholics may lead to the absence of an important clinical finding. People who do not have the habit of using alcohol and who do not develop tolerance to alcohol have more severe symptoms than normal. According to the data in the literature, motor coordination disorders (decrease/loss of voluntary control of the

musculoskeletal system) and judgment disorders, mood changes and deterioration in cognitive functions are expected due to the cerebellum (cerebellum) effect at a blood ethanol level of 80-200 mg/dl (27-30).

Another alcohol derivative that can be detected in postmortem analysis of body tissues and fluids is methanol. Methanol (CH3OH) is a simple alcohol and is obtained by distillation of sawdust. It is a colorless, volatile and toxic liquid. It is widely used in industry. For this purpose, it is used in the production of substances such as paint thinner, duplicator fluid, antifreeze, glass cleaner. Under normal conditions, it is not used in the production of alcoholic beverages, but methanol poisoning has been frequently encountered in our country recently.

Methanol is a highly toxic (poisonous) substance for the human body. While acute poisoning occurs mostly as a result of accidental use as a fake drink, chronic poisoning occurs as a result of inhalation (inhalation) of the vapor in the workplace. Apart from this, it is also possible to absorb methyl alcohol, which is abundantly contaminated with clothes, by absorption through the skin. The methyl alcohol that comes to the liver through the blood is first slowly converted to formaldehyde by the alcohol dehydrogenase enzyme and then to formic acid by the aldehyde dehydrogenase enzyme. However, this conversion takes place 5-10 times slower than the rate of conversion of ethyl alcohol. Therefore, if there had been fake alcohol consumption in the concrete case, the metabolite of methanol (formic acid), whose metabolism is much slower, might not have been at a level that could be measured in the blood because of the absorption phase. As mentioned in the previous sections, it will take 5-10 times longer than ethyl alcohol to mix with the blood, reach the liver, and be metabolized like ethyl alcohol in the absorption phase. It should not be expected to become positive in vitreous fluid. It is a situation that is frequently the subject of judicial cases where alcohol is used to reduce costs in bars or restaurants where alcohol is consumed or false alcohol is served by mistake. In this case, in addition to the presence of methanol detected in the blood of the case, the negative formic acid in the blood and vitreous fluid may be due to incomplete methyl alcohol absorption and insufficient metabolism due to the premature death of the case while still in the absorption phase of the fake alcohol (methyl alcohol), which may have been consumed orally may occur. In addition, except for methyl alcohol consumption, if blood samples are collected from outside the body with contaminated (contaminated) blood, this situation may also develop as a result of contact.

Benzodiazepines are a group of drugs that have sedation, hypnotic (sleeping), anxiolytic (anxiety relief) and muscle relaxant effects by binding to the receptor called gamma-aminobutyric acid (GABA) in the central nervous system (brain). Benzodiazepines are classified as short-acting, intermediate-acting and long-acting types.

Diazepam is a type of long-acting benzodiazepine. It is converted to nordiazepam after its metabolism in the body. Diazepam and its metabolite, which are highly lipophilic, can rapidly cross the blood-brain barrier and exert their effects. While the drug takes effect within 1-3 minutes of intravenous (intravenous) ingestion, the initiation of oral dose varies between 15-60 minutes (31). Nordazepam

is a type of benzodiazepam that is a 1,4-benzoazepine derivative. Nordazepam, nordiazepam, deoxydemoxepam or desmethyldiazepam are different names for the same molecule. The nordezapam molecule is formed as a result of the metabolism of diazepam, chlordiazepoxide, clorazepate, prezepam, pinazepam and medazepam. It acts by binding to GABA-A receptors. The half-life of nordazepam can vary between 36-200 hours due to age and gender, and it continues to interact with GABA-A receptors (32).

Chlorazepate, prezepam and pinazepam are not included in the list of benzodiazepines routinely examined in the annex of the chemical examination report. The nordiazepam detected in the blood of the concrete case, any of these 3 molecules or the result of the use of diazepam may have been positive in the body. However, nordiazepam detected in our report may have been due to the use of both diazepam and 3 other benzodiazepam derivatives. Since the level of these 3 benzodiazepine derivatives is not included in the list attached to the report, it cannot be said clearly which benzodiazepine derivative was used in this case.

γ-Aminobutyric acid-A (GABA-A) is an important inhibitory intermediate molecule in the central nervous system of humans. This molecular pathway is an area where benzodiazepines and barbiturate-derived drugs are effective. In behavioral studies, it has been determined that the use of a drug called GABA mimetic (stimulating this pathway) may adversely affect motor (voluntary movement) behaviors on the body muscles.

It is known that the inhibition of benzodiazepine metabolism by ethyl alcohol results from the inhibition of the formation of a benzodiazepine-enzyme complex with P450 (33). Because both ADH and CYP2E1 are involved in ethanol metabolism at high ethanol concentrations, the metabolism of benzodiazepines is competitively inhibited following a significant alcohol intake. On the other hand, in case of low ethanol concentrations in alcohol in social drinkers, CYP2E1 is minimally involved in ethanol metabolism and induction is not a factor. However, the mechanism governing the interaction involving both is complex (34).

Benzodiazepines, which have various clinical uses, are often used in the treatment of convulsions (episodic seizures), anxiety disorder (anxiety disorder) and muscle spasms (muscle spasms). In other words, diazepam and therefore its active ingredient nordiazepam have muscle relaxant effects. The recommended dose of the companies producing this drug, which can relax the muscle, is 5-15 mg/day. This is possible even if the dose of nordiazepam detected in the blood of the concrete case is 14 ng/ml, it is unlikely to interact with alcohol and develop a suppressive effect on the central nervous system (brain) tissue.

3. Conclusion

As a result, a narcotic drug was detected in the blood of this case, and it cannot be understood according to the content of the present report whether the body tissues have taken another narcotic-stimulant drug that is not on the routine chemical examination list. At current doses, benzodiazepine overdose poisoning cannot be mentioned as the cause of death of the case. However, if the amount of alcohol detected in the blood of the person was taken orally, the person may have lost his voluntary movements due to a temporary

suppression in brain functions due to the additive (combined) effect of alcohol and benzodiazepines. This situation is open to interpretation and due to ethical issues; human studies on interactions at these doses in the medical field are not available in the literature.

4. Conflict of Interest

There is no conflict of interest.

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