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Death Caused by Ethanol and Diazepam in a Patient with Liver Cirrhosis

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Abstract

We present an autopsy case of a patient with liver cirrhosis and relatively high concentrations of ethanol and diazepam and its metabolites. Quantitative toxicological analysis showed that concentrations of diazepam and its metabolites (nordiazepam, temazepam and oxazepam) in femoral blood were 0.078 μg/ml, 0.136 μg/ml, 0.011 μg/ml, 0.004 μg/ml, respectively, while the concentration of ethanol was 280 mg/dl. We concluded that the cause of death was combined intoxication by ethanol and benzodiazepines. The present case indicates that delays in metabolism and decreased protein binding may increase the sensitivity to drugs and ethanol in patients with cirrhosis.

Keywords: liver cirrhosis, diazepam, pharmacological active metabolite

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INTRODUCTION

In daily forensic practice, hepatic dysfunction such as steatosis, steatohepatitis or liver cirrhosis is sometimes encountered (1). The liver is a major organ participating in the metabolism of xenobiotics such as ethanol and various drugs. Liver cirrhosis, as a late stage of hepatic dysfunction, cause jaundice, fatigue, easy bleeding and other symptoms (1). It also impairs the metabolism of drugs and chemicals, but the precise effects are still not fully understood (2).

Ethanol is frequently detected in combination with benzodiazepines in forensic practice (3-6), and forensic toxicologists often discuss the interactions between ethanol and benzodiazepines. Ethanol is usually ingested as an alcoholic beverage and mainly metabolized in the liver (7), however, its elimination is largely unaffected by hepatic dysfunction, such as liver cirrhosis (8,9). Diazepam is a benzodiazepine that is widely prescribed as an anxiolytic or anticonvulsant (10). Diazepam is metabolized via *N*-demethylation to nordiazepam and by 3-hydroxylation to temazepam, mainly mediated by the cytochrome P450 enzymes CYP2C19 and CYP3A4, respectively (3,5,11). Both metabolites are pharmacologically active. The half-life of diazepam is prolonged 2- to 5-fold in patients with liver cirrhosis, and sensitivity to diazepam is also increased (12,13). Although many reports have described fatal cases involving drug interactions following co-administration of ethanol and diazepam (3-6), few reports have considered the effects of concomitant liver dysfunction.

Here we report a case of death due to combined use of ethanol and diazepam in a patient with severe liver cirrhosis, and discuss the interactions involved.

CASE REPORT

A female in her 40s was found dead in her house. Subsequent police investigations revealed that the deceased had been receiving therapy for decompensated cirrhosis, with symptoms of hepatic encephalopathy. Medico-legal autopsy revealed many bruises, but these were not considered contributory to the cause of death.

The deceased was 160 cm tall and weighed 62.5 kg. Slight yellowish discoloration of the skin and sclera was observed. The heart weighed 314 g and contained 320 ml of blood without coagulum. The brain weighed 1186 g without any injuries. The left and right lungs weighed 382 g and 411 g, respectively, and were congested. The liver weighed 1737 g, and showed a hard surface with multiple nodules (Fig. 1a).

Figure 1. a) The cut surface of the liver was hard with multiple nodules

Histological findings showed thick collagen bands around cirrhotic nodules (Fig. 1b).

Approximately 1200 ml of yellowish ascites had accumulated in the abdominal cavity. Negative results were obtained for hepatitis B surface antigen and hepatitis C antibody using immunochromatography kits.

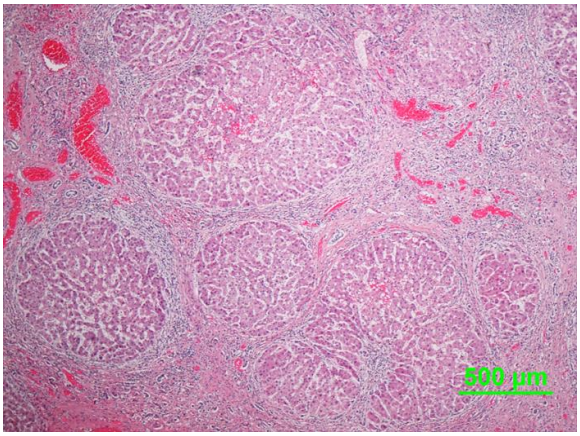

Figure 1. b) Thick collagen bands surround cirrhotic nodules (objective × 4)

A drug screening test using a Triage™ panel (Biosite Diagnostic, San Diego, CA) yielded positive results for benzodiazepines. Postmortem blood, urine and bile were collected for toxicological investigations. Toxicological analysis using liquid chromatography tandem mass spectrometry was performed in accordance with a previous report (14). Quantitation of ethanol was performed using headspace gas chromatography.

RESULTS AND DISCUSSION

Toxicological analysis identified diazepam and its metabolites (nordiazepam, oxazepam and temazepam), and ethanol. Ethanol concentrations in blood and urine were 280 mg/dl and 310 mg/dl, respectively. Table 1 shows the quantification of each drug in the victim's blood, along with the current ranges for fatal, toxic and therapeutic levels (15,16).

Analytical results indicated that concentrations of diazepam and its metabolites were at the therapeutic level or below, while ethanol was within the intoxication range. As diazepam and nordiazepam have similar pharmacological effects, the sum of their concentrations (0.214 µg/ml) was used for the purposes of interpretation (4).

High blood concentrations of ethanol have been reported as the major causative factor in ethanol-diazepam deaths (6), and a high concentration of diazepam in blood (>0.8 µg/ml) along with a high

Table 1. Concentrations found for each drug and metabolite in the post-mortem samples (µg/ml)

Specimen	Blood	Urine	Bile	Therapeuticl range *	Toxic range*	Lethal range *
diazepam	0.078	0.011	0.064	0.1-2.5	3-5	4.8-30
nordiazepam	0.136	0.037	0.156	0.02-0.8	1.5-2	5.5-15
oxazepam	0.004	0.109	B.D.L	0.2-1.5	2	3-5
temazepam	0.011	0.298	B.D.L	0.02-0.9	1	8.2-14

* Therapeutic, Toxic and lethal ranges are cited from the reference (15) and (16).
B.D.L : below the detection limit

blood ethanol level (≥200 mg/dl) raises the potential for toxic drug interactions (6). In the present case, a high blood ethanol concentration (280 mg/dl) was detected, but the sum of diazepam and nordiazepam (0.214 μg/ml) remained at a therapeutic concentration. Patients with liver disease have been reported to show increased sensitivity to diazepam, and the risk of excessive sedation should be considered (17). This may be due to a decrease in the plasma protein binding rate for diazepam against a background of liver cirrhosis, and the resulting increase in the free diazepam ratio in plasma (18).

Based on the autopsy findings and the results of toxicological examinations, we concluded that diazepam and ethanol led to her death due to their combined toxicity enhanced by severe liver dysfunction.

From the perspective of forensic toxicokinetic practice, it is interesting to note that the ratio of diazepam to nordiazepam in the present case was 0.57. This suggests that the victim may have taken the last dose of diazepam long before her death (6). Although only a small amount of data exists concerning the effects of hepatic dysfunction on drug metabolism and sensitivity to drugs, the present case suggests the need for greater attention to metabolic retardation in patients with liver cirrhosis.

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Conflict of Interest Disclosure: The authors declare that they have no conflict of interest.

REFERENCES

1. Theise ND. Liver and gallbladder. *In*; Robbins basic pathology (10th eds). Kumar V, Abbas AK, Aster JC, eds. Philadelphia: Elsevier:637-678, 2018.

2. Oates JA. The science of drug therapy. *In*; Goodman & Gilman's The pharmacological basis of therapeutics (11th eds). Brunton LL, Lazo JS, Parker KL, eds. New York, Chicago: McGraw-Hill:117-136, 2006.

3. Tanaka E, Misawa S. Pharmacokinetic interactions between acute alcohol ingestion and single doses of benzodiazepines, and tricyclic antidepressants – an update. J Clin Pharm Ther 1998; 23:331-336.

4. Koski A, Ojanpera I, Vuori E. Alcohol and benzodiazepines in fatal poisonings. Alcoholism Clin Exp Res 2002; 26:956-959.

5. Tanaka E. Toxicological interactions between alcohol and benzodiazepines. J Toxicol Clin Toxicol 2002; 40:69-75.

6. Holmgren P, Jones AW. Coexistence and concentrations of ethanol and diazepam in postmortem blood specimens: risk for enhanced toxicity? J Forensic Sci 2003; 48: 1416-1421.

7. Fleming MF, Mihic SJ, Harris A. Ethanol. *In*; Goodman & Gilman's The pharmacological basis of therapeutics (11th eds). Brunton LL, Lazo JS, Parker KL, eds. New York, Chicago: McGraw-Hill:591-606, 2006.

8. Adachi J, Mizoi Y, Fukunaga T, Ogawa Y, Imamichi H. Comparative study on ethanol elimination and blood acetaldehyde between alcoholics and control subjects. Alcoholism Clin Exp Res 1989; 13:601-604.

9. Jones AW. Ethanol metabolism in patients with liver cirrhosis. J Clin Forensic Med 2000; 7:48-51.

10. Baselt RC. Diazepam. *In;* Disposition of toxic drugs and chemicals in man, (8th ed). Foster City, CA: Biochemical Publications. 424-427, 2008.

11. Andresen H, Augustin C, Streichert T. Toxicogenetics – cytochrome P450 microarray analysis in forensic cases focusing on morphine/codeine and diazepam. Int J Leg Med 2013; 127:395-404.

12. Klotz U, Avant GR, Hoyumpa A, Schenker S, Wilkinson GR. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 1975; 55:347-359.

13. Andreasen PB, Hendel J, Greisen G, Hvidberg EF. Pharmacokinetics of diazepam in disordered liver function. Eur J Clin Pharmacol 1976; 10:115-120.

14. Kinoshita H, Tanaka N, Takakura A, Kumihashi M, Jamal M, Ito A, Tsutsui K, Kimura S, Matsubara S, Ameno K. Flunitrazepam in stomach contents may be a good indicator of its massive ingestion. Rom J Legal Med 2017; 25:193-195.

15. Schulz M, Iwersen-Bergmann S, Andresen H, Schmoldt A. Therapeutic and toxic blood concentrations of nearly 1000 drugs and other xenobiotics. Crit Care 2012; 16: R136.

16. Information index for drugs and poisons. Suzuki O, Ohno Y, Suzaki S, Hanajiri-Kikura M, eds. Tokyo: Japan Medical Journal; 2014.

17. McConnell JB, Curry SH, Davis M, Williams R. Clinical effects and metabolism of diazepam in patients with chronic liver disease. Clin Sci 1982; 63:75-80.

18. Branch RA, Morgan MH, James J, Read AE. Intravenous administration of diazepam in patients with chronic liver disease. Gut 1976; 17:975-983.