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Coexistence and Concentrations of Ethanol and Diazepam in Postmortem Blood Specimens: Risk for Enhanced Toxicity?*

ABSTRACT: Both ethanol and diazepam are classified as depressants of the central nervous system and exert their effects via the $GABA_A$ receptor complex. We report the coexistence and concentrations of ethanol, diazepam, and its primary metabolite nordiazepam in a case series of 234 forensic autopsies collected over a ten-year period. Diazepam, nordiazepam, and ethanol were determined in femoral venous blood by highly selective gas chromatographic methods. The mean (median) femoral blood concentrations were ethanol 0.24 g/100 mL (0.25 g/100 mL), diazepam (D) 0.23 μg/g (0.10 μg/g), nordiazepam (ND) 0.24 μg/g (0.20 μg/g), sum (D + ND) 0.43 μg/g (0.30 μg/g), and the ratio D/ND was 1.19 (1.0). When cause of death was attributed to alcohol and/or drug intoxication ($N = 50$), the mean and median blood-ethanol concentration was higher, being 0.36 g/100 mL and 0.38 g/100 mL, respectively, whereas the mean (median) and range of blood-diazepam concentrations were about the same, 0.23 μg/g (0.10 μg/g) and 0.05 to 1.2 μg/g. The femoral-blood concentrations of diazepam and nordiazepam were highly correlated ($r = 0.73$), but there was no correlation between the concentrations of ethanol and diazepam ($r = -0.15$). In another 114 fatalities (all causes of death) with diazepam and/or nordiazepam as the only drugs present, the mean (median) and range of blood-diazepam concentrations were 0.22 μg/g (0.10 μg/g) and 0.03 to 3.5 μg/g. The pathologists report showed that none of these deaths were classed as drug intoxications. The impression gleaned from this study of ethanol-diazepam deaths is that high blood-ethanol concentration is the major causative factor. We found no evidence that concurrent use of diazepam enhanced the acute toxicity of ethanol, although interpretation is complicated by the high blood-ethanol concentration (median 0.38 g/100 mL), making it difficult to discern an added effect of diazepam.

KEYWORDS: forensic science, alcohol, autopsy, drug-toxicity, ethanol, diazepam, drug interaction, postmortem, toxicology

Adverse drug reactions involving ethanol are not uncommon, and many fatal poisonings have been documented (1–3). The combined effects of alcohol and barbiturates were notorious, and these central nervous system (CNS) depressants have been responsible for many deaths, both accidental and with suicidal intent (4,5). Another serious drug-alcohol interaction arises when the painkiller propoxyphene is taken together with a large dose of ethanol (6,7). Benzodiazepines, such as diazepam, temazepam, and flunitrazepam, despite their reputation for low toxicity in overdose, are commonly encountered along with other drugs in postmortem toxicology reports (8–12).

A number of epidemiological surveys of drug overdose leading to emergency hospital treatment showed a high prevalence of drugs from the benzodiazepine group, e.g., diazepam, triazolam, and flunitrazepam (13,14). A study from the United Kingdom based on mortality statistics and prescription rates for benzodiazepines estimated that ~6 deaths occurred per million prescriptions either alone or together with alcohol (14). This probably reflects the wide prescribing of sedative-hypnotic drugs in society rather than the direct toxic effects of the substances themselves (15).

Finkle et al. (16) investigated diazepam and drug-associated deaths in North America and Canada with the main focus on cause-of-death statements issued by the certifying pathologist. From an initial sample of 1239 deaths, after trauma and disease were excluded, there remained 914 drug-related deaths, which were subjected to a detailed evaluation with the main focus on drug overdose and toxicity. Diazepam was the only drug present in just two drug-related deaths (0.2%), and the concentrations reported were 5 and 19 μg/mL, which compares with 51 deaths (5.6%) involving co-ingestion of ethanol. The BAC was skewed to higher concentrations of ethanol, with a clustering of deaths between 0.24 and 0.32 g/100 mL. The corresponding blood-diazepam concentrations covered a wide range and were similar to those found in the entire sample of drug-combination deaths. There were at least eight deaths attributed to diazepam-alcohol toxicity in which the blood-diazepam concentration was within the therapeutic range and the BAC was below 0.10 g/100 mL. The authors cautioned about the concurrent use of these two CNS depressants (16).

Benzodiazepines, including diazepam, have potential for abuse, particularly in people addicted to alcohol and/or opiates (17–20). In this connection, flunitrazepam, which is registered in Sweden, is a hypnotic drug commonly encountered in postmortem blood specimens (21,22). Scores of investigations have reported the negative influence of benzodiazepines both alone and in combination with alcohol on psychomotor skills related to driving (23,24). The detrimental effects of ethanol and diazepam on psychomotor performance and sedation are probably additive considering that both substances activate GABAnergic neurotransmission by facilitating opening of the chloride ion-channel (24,25).

Notwithstanding difficulties in interpreting postmortem drug concentrations in relation to drug-related toxicity and cause of

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death, we report here the coexistence and concentrations of ethanol and diazepam in postmortem femoral venous blood samples. The toxicological results are discussed in relation to the potential toxicity of this particular drug-alcohol combination.

Material and Methods

All blood specimens for this study were taken from a femoral vein during routine forensic postmortem examinations. The analytical toxicology was done at one central laboratory, the National Laboratory of Forensic Toxicology (Linköping, Sweden). The concentration of ethanol in blood was determined in duplicate by headspace gas chromatography on two different stationary phases, and the mean concentration was reported (26). The limit of quantitation (LOQ) in routine postmortem casework was 0.01 g/100 mL. When the BAC was 0.10 g/100 mL or more, the results were truncated to two decimal places so that 0.159 g/100 mL was reported as 0.15 g/100 mL, etc.

Diazepam and its metabolite nordiazepam were determined in whole blood by capillary column gas chromatography after solvent extraction with butyl acetate and direct injection without derivatization. The Hewlett Packard GC 4890, series II instrument was fitted with a nitrogen-phosphorous detector, and a DB-5 capillary column was used for chromatographic separations. The method LOQ was 0.03 μg/g for both diazepam and its primary metabolite nordiazepam. For postmortem blood samples, it is the custom in our laboratory to measure the aliquots needed for analysis (~1 g) by weight so the final result has concentration units in mass/mass (μg/g). These values are similar to concentrations expressed as μg/mL, but, considering the varying composition of postmortem blood, it is a lot easier to dispense aliquots by weight rather than by volume. Details of the analytical methods are reported elsewhere (21,27).

Diazepam is a drug that binds to plasma proteins (~98%), and, according to Osselton et al. (28), the plasma/whole blood distribution ratio is 1.8:1. The widely used TIAFT list of therapeutic and toxic concentrations of drugs gives 0.125 to 0.75 mg/L as a therapeutic range for diazepam in plasma, which therefore corresponds to 0.07 to 0.42 mg/L in whole blood. The toxic concentration range for diazepam, according to TIAFT, is 1.5 to 5 mg/L in plasma (0.83 to 2.8 mg/L) in whole blood, assuming a plasma/blood ratio of 1.8:1. In this study, we have arbitrarily assumed a whole-blood diazepam concentration of 0.2 μg/g as the midpoint of the therapeutic range and 0.8 μg/g as the start of the toxic range.

We searched the databases (ToxBase and RättsBase) belonging to the National Board of Forensic Medicine for all instances of ethanol and diazepam with or without its metabolite nordiazepam as the only drugs present in femoral blood regardless of the actual cause of death. Between 1992 and 2002 we found 234 instances when the investigating pathologists gave an opinion about the cause and circumstances of the death, and in 50 cases this was reported as drug/alcohol intoxication. Over the same time period, we located 144 cases with diazepam and/or nordiazepam as the only drugs present, but none were regarded as drug intoxications.

Results

Table 1 presents descriptive statistics showing the concentrations of ethanol, diazepam, and nordiazepam in postmortem femoral blood. The frequency distributions of diazepam and nordiazepam concentrations and the D/NA ratio are markedly skewed to the right (Fig. 1), and for diazepam most are within the therapeutic range, being 0.07 to 0.42 μg/g for whole blood. In ten cases (2.5%) the concentration of diazepam was above 0.8 μg/g, which is considered the start of the toxic range, and the highest concentration found was 2.6 μg/g. Adding together the concentration of diazepam and its metabolite nordiazepam, which is also pharmacologically active, gave 0.43 μg/g with a median of 0.30 μg/g. The concentrations of diazepam and nordiazepam were highly correlated ($r = 0.73$, $p < 0.001$), although no such correlation was found between the concentrations of ethanol and diazepam ($r = -0.15$, $p > 0.05$). The mean ratio of D/ND was 1.19 (range 0.16 to 15.0), indicating that most people were regularly taking their medication because the concentration of metabolite (ND) with longer half-life had accumulated in the blood.

TABLE 1—*Descriptive statistics for concentrations of ethanol, diazepam, nordiazepam, and the diazepam/nordiazepam ratio in femoral venous blood representing all causes of death.*

Substance	*N*	Mean	Median	Min and Max
Ethanol	234	0.24 g/100 mL	0.25	0.01 and 0.61
Diazepam	234	0.23 μg/g	0.10	0.03 and 2.6
Nordiazepam	187	0.24 μg/g	0.20	0.04 and 2.1
Diazepam + Nordiazepam	234	0.43 μg/g	0.30	0.05 and 4.7
Diazepam/ Nordiazepam	187	1.19	1.0	0.16 and 15.0

In a case series of 144 fatalities (all causes of death) with diazepam and/or nordiazepam as the only drugs present, the mean (median) and range of diazepam concentrations were 0.23 μg/g (0.10 μg/g) and 0.03 to 3.4 μg/g, respectively (Table 2). None of these deaths were considered drug-intoxication according to the pathologists' report.

A histogram of blood-ethanol concentrations is presented in Fig. 2 and includes all causes of death ($N = 234$). The mean concentration was 0.24 g/100 mL, median 0.25 g/100 mL, and range 0.01 to 0.61 g/100 mL, indicating a high proportion of heavy drinkers in this forensic material. Indeed, there were 90 individuals (38%) having a BAC exceeding 0.30 g/100 mL, which is approaching a dangerously high concentration even without the presence of other CNS depressant drugs.

Those cases when blood-diazepam concentration was considered in the toxic range (>0.8 μg/g) were investigated in more detail by looking at the circumstances surrounding the death by reading the pathologist's report (Table 3). Most causes of death were trauma (suicide, falls, etc.) or disease or other complicating factors, so alcohol and/or diazepam toxicity cannot be considered directly responsible. However, it should be noted that although a gunshot to the head (Cases 5 and 10) or other means of suicide (Case 7) kills the person, a high concentration of alcohol and/or diazepam might have led to the circumstances that proved fatal (e.g., drowning, traffic crash, etc.).

Table 4 compares blood-ethanol concentrations at autopsy (median 0.38 g/100 mL) when the forensic pathologist ascribed the cause of death to alcohol and/or drug poisoning ($N = 50$) with acute alcohol poisoning deaths without other drugs present: median 0.36 g/100 mL (29). Note that the mean and median blood-diazepam concentration in acute alcohol and/or drug poisonings (0.23 μg/g and 0.1 μg/g) was about the same as those observed when all causes of death were considered (see Table 1) and also when diazepam and/or nordiazepam were the only substances present (see Table 2).

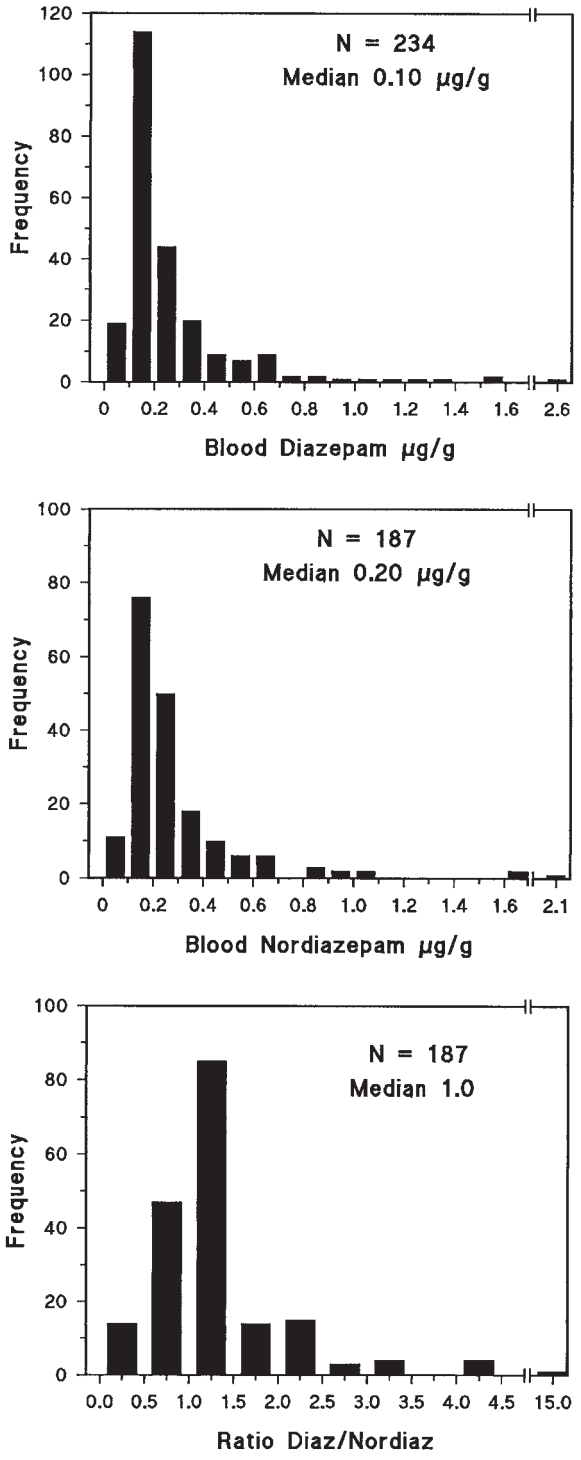

FIG. 1—*Frequency distributions of the concentrations of diazepam (upper plot), nordiazepam (middle plot), and the concentration ratios of diazepam/nordiazepam (lower plot) in femoral venous blood from fatalities (all causes of death) in which ethanol and diazepam were the only drugs present.*

Discussion

In terms of toxicity, diazepam is a relatively safe medication even when taken in overdose, and this is supported by our failure to find any drug-related fatalities with diazepam as the only psychoactive substance present (21,31,32). However, many reports of fatal poisonings exist that include diazepam in combination with other depressant drugs such as alcohol and opiates (13–15). In these situations, it seems that the other drugs are probably more important determinants for a fatal outcome than the diazepam (16).

The common finding of diazepam and/or nordiazepam in autopsy blood specimens along with other more dangerous drugs can be explained, at least in part, by the wide prescribing of this anxiolytic in society (33,34). Furthermore, the long elimination half-life of diazepam (30 to 50 h) compared with many other drugs makes it likely that some of these other substances had decreased to concentrations below LOQ by the time of death (35,36). The absence of nordiazepam or finding a high ratio of parent drug to metabolite probably suggests that death occurred shortly after taking the medication. By contrast, finding a low ratio of diazepam to nordiazepam suggests that the last dose of diazepam was taken long before death owing to the longer half-life of the nordiazepam metabolite (35,36). Neither nordiazepam nor clorazepate, which is metabolized to nordiazepm, are registered in Sweden.

Interpreting the concentrations of drugs determined at autopsy is not easy, and making an unequivocal statement about the number of tablets or dose of a drug taken before death is very difficult if not impossible (37). For some drugs, the phenomenon of postmortem redistribution needs consideration, especially when cardiac blood is the specimen used for toxicological analysis (37,38). The distribution ratio for diazepam between cardiac and femoral blood was reported as 1.6:1 (range 0.2 to 12) in 46 cases (39). The risk of redistribution artifacts is much less when drugs are analyzed in femoral venous blood as in the present study (40).

The concentrations of drugs measured in postmortem blood are difficult to compare with so called “therapeutic ranges” derived from clinical pharmacology studies because the latter almost always involves measuring drug concentrations in plasma or serum and not whole blood, which is the specimen available in postmortem toxicology (35,36,40). The many compilations of therapeutic, toxic, and lethal concentrations of drugs have limited value for forensic toxicologists for the simple reason that the threshold concentrations listed refer to serum or plasma and furthermore the number of cases is not always specified (41–45). In one large study into the pharmacokinetics of diazepam, 48 healthy men each received a 10-mg dose (35). The mean peak concentration in plasma was 0.406 mg/L (range 0.253 to 0.586 mg/L), which corresponds to a mean of 0.220 mg/L (range 0.141 to 0.325 mg/L) in whole blood assuming a plasma/whole blood distribution ratio of 1.8:1 (28). During continuous dosing with diazepam, owing to the long elimination half-life, the steady state concentration is probably higher than that observed after a single dose.

Many of the older compilations of therapeutic and toxic concentrations of licit and illicit drugs have only limited usefulness today because the analytical methods now in use in forensic toxicology laboratories are much improved in terms of the selectivity and LOQ. Accordingly, there is an urgent need for forensic toxicologists to reach an agreement about what constitutes the toxic concentration range for various psychoactive substances. This will help to avoid differences of opinion when expert witnesses are called to testify in court about whether a certain concentration of alcohol and/or drug combination might have accounted for the person’s death.

Regarding ethanol toxicity, some toxicologists consider that a concentration of 0.35 to 0.40 g/100 mL is sufficient to cause death (46,47), but one should also consider that many drunk drivers

TABLE 2—*Comparison of blood-diazepam concentrations in femoral blood (all causes of death) without other drugs present with concurrent use of ethanol and diazepam (all causes of death) and ethanol-diazepam–related deaths that were attributed to alcohol/drug intoxication.*

Drugs Present	*N*	Mean and (Median) Blood-Diazepam Conc., μg/g	Min and Max Blood-Diazepam Conc., μg/g
Diazepam/nordiazepam alone (all causes of death)	144	0.22 (0.1)	0.03–3.4
Diazepam/nordiazepam + ethanol (all causes of death)	234	0.23 (0.1)	0.03–2.6
Diazepam/nordiazepam + ethanol (alcohol/drug intoxication)	50	0.23 (0.1)	0.05–1.2

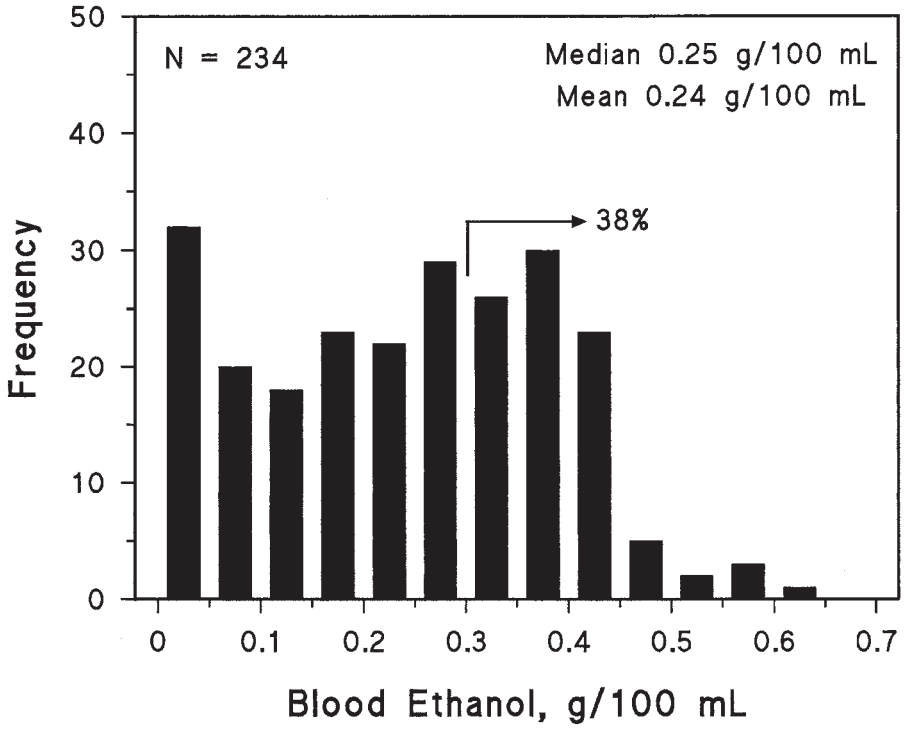

FIG. 2—*Frequency distribution of the concentrations of ethanol in femoral venous blood in fatalities (all causes of death) in which ethanol and diazepam were the only drugs present. Note that 38% of cases had blood-ethanol concentration exceeding 0.3 g/100 mL.*

surpass this level and survive (48). However, the amount of alcohol required to reach a BAC of 0.35 to 40 g/100 mL requires forced drinking over many hours or days, which leads to the development of tolerance (29). Acute alcohol poisoning deaths are usually the result of respiratory or cardiac failure owing to depression of the vital centers in the mid-brain and medulla, leading to fatal cardiorespiratory failure (46,47). However, other factors also need to be considered, such as compromised breathing if a comatose or unconscious person is placed face down (positional asphyxia) or inhales vomit when the gag reflex is inhibited (46).

Identifying a psychoactive substance in postmortem blood at a concentration exceeding the therapeutic range proves exposure but not necessarily that the drug was a causative factor in the person's death. However, an unusually high concentration of the drug compared with the recognized therapeutic concentration might indicate an overdose or abuse of the substance in question. In this connection, diazepam is known to have a wide safety margin, and the LD_{50}/ED_{50} ratio is high. However, studies with a single drug cannot be compared with real world situations when several different medications are combined, sometimes along with a high blood-ethanol concentration. The safety margin for ethanol is only about 8:1 because a blood-concentration of 0.05 g/100 mL causes mild euphoria, whereas 0.40 g/100 mL might result in death owing to direct depressive effects on the brainstem, causing respiratory failure.

Drummer and Odell (31) recently suggested that a blood-diazepam concentration of 5 μg/mL might be a threshold value for drug toxicity and could result in a fatal outcome. This compares with 5 μg/mL and 19 μg/mL found in two diazepam-associated deaths without other drugs present reported by Finkle et al. (16). In Baselt and Cravey's widely used book, a mean blood-diazepam concentration of 4.8 μg/mL was reported for three deaths involving sole use of this drug (49). It should not be overlooked that diazepam has pharmacologically active metabolites (nordiazepam,

TABLE 3—*Age, gender, and concentrations of ethanol, diazepam, and nordiazepam in femoral venous blood in ten fatalities (all causes of death) containing the highest concentrations of diazepam.*

Case	Age and Gender	Ethanol, g/100mL	Diazepam,* μg/g	Nordiazepam, μg/g†	Cause/Circumstances of the Death According to the Forensic Pathologists Report
1	59 M	0.38	0.9	. . .	Poisoning with alcohol and diazepam, found besides tablets (Valium) and a bottle of vodka.
2	57 F	0.24	0.8	. . .	Poisoning with alcohol and diazepam, found dead at home in the cellar.
3	48 M	0.19	0.8	1.6	Undetermined owing to putrefied corpse, know to be a chronic alcoholic.
4	45 M	0.13	1.0	. . .	Poisoning with alcohol and diazepam, known substance abuser found dead at home.
5	67 M	0.025	1.1	0.9	Suicide with a gunshot in the head—suffered from depression.
6	56 F	0.021	1.2	0.6	Poisoning with alcohol and diazepam, chronic alcoholic found in empty bath tub.
7	62 F	0.017	1.3	. . .	Suffocation in a plastic bag, mentioned intent to commit suicide.
8	56 M	0.012	1.5	0.1	Suicide by gunshot to the chest.
9	46 M	0.072	1.5	1.6	Poisoning with alcohol and diazepam, decomposed body.
10	44 M	0.14	2.6	2.1	Suicide by gunshot to the stomach.

*Diazepam > 0.8 μg/g marks the lower end of the toxic range.
†Missing values indicate that the concentration of nordiazepam was below LOQ of the method.

TABLE 4—*Mean and median blood-ethanol concentrations in deaths attributed to alcohol/drug intoxication with or without coingestion of diazepam.*

Conditions (Reference)	*N*	Mean (Median) Blood Ethanol Concentration, g/100 mL	Min and Max Blood-Ethanol, g/100 mL
Ethanol alone (29)	693	0.36 (0.36)	0.07–0.68
Ethanol alone (30)	615	0.35 (0.35)*	0.10–0.65[1]
Ethanol and diazepam (present study)	50†	0.36 (0.38)	0.02–0.61
Ethanol and diazepam (30)	161‡	0.36 (0.35)*	0.12–0.62[1]

*BAC was reported as w/w units and was converted here to w/v units.
†Mean (median) and range of blood-diazepam concentration 0.23 μg/g (0.10 μg/g) and 0.05 to 1.2 μg/g.
‡Median and range of diazepam + nordiazepam + chlordiazepoxide concentration 0.4 (0.1 to 12.5) mg/L.

temazepam, and oxazepam), and these are also CNS depressants leading to more pronounced sedation and possibly additive effects (30,31). For this reason, a toxicological analysis for diazepam should always include its primary metabolite nordiazepam.

When Koski et al. (30) investigated the combined toxicity of ethanol and diazepam, they added the concentration of diazepam, nordiazepam, and even chlordiazepoxide if this benzodiazepin was present, with the motivation that these drugs had a similar pharmacological profile. Our results regarding coexistence of ethanol and diazepam in postmortem blood support the findings of Koski et al. (30), namely that the blood-ethanol concentration in fatal poisonings was about the same (0.36 to 0.38 g/100 mL) with or without the presence of diazepam (see Table 4). Many studies have dealt with the combined effects of diazepam and ethanol on psychomotor function and skills resembling driving, but acute effects of drugs on performance and behavior has little relevance to assessing toxicity of various drug-drug or drug-alcohol combinations. Untoward effects on psychomotor performance are more severe in first-time users of diazepam, and the effect is worsened after coingestion of alcohol (50–52).

The mechanism of interaction between ethanol and diazepam involves the inhibitory neurotransmitter GABA, which is widely distributed in the mammalian brain (31,32). Diazepam is a GABAnergic agonist, with binding sites on the $GABA_A$ receptor remote from GABA itself. This benzodiazepine facilitates opening of an ion channel to allow chloride ions to flow into the cell and elicit a pharmacological effect. Diazepam, therefore, enhances the effect of GABA and brings about a tranquilizing or sedative effect on the individual. The $GABA_A$ receptor also includes an alcohol-sensitive site, and one of the actions of ethanol is to promote the binding of GABA to its receptor. Accordingly, diazepam and alcohol can exert an additive effect leading to a reduction in nerve activity and an overall sedation of the individual (53).

The following conclusions can be drawn from this study of coexistence and concentrations of ethanol and diazepam in a forensic autopsy material:

1. The similar mechanism of action and the fact that sedative effects are likely to be additive make ethanol and diazepam a potentially dangerous drug combination in overdose.
2. Although we found no evidence that concurrent use of diazepam enhanced the toxicity of ethanol, it is important to note that blood-ethanol concentrations were always very high (median 0.38 g/100 mL), making it hard to discern any additive effect of diazepam.
3. Because both ethanol and diazepam are CNS depressants, it seems prudent not to prescribe diazepam to heavy drinkers.
4. It seems reasonable to accept that a high concentration of diazepam in blood (>0.8 μg/g) along with a high blood-ethanol concentration (>0.2 g/100 mL) raises the potential for toxic drug interactions.

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