K32 Coexistence and Concentration of Ethanol and Diazepam in Postmortem Blood Specimens

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The objective of this presentation is to present toxicological results from the analysis of postmortem blood specimens and to discuss the potential for toxic interactions between two of the most commonly used psychoactive drugs, namely ethanol and diazepam.

Serious drug interactions involving alcohol are not uncommon and these have accounted for many fatal poisonings. The combined effect of alcohol and barbiturates was notorious and these two central nervous system (CNS) depressants caused countless deaths by accidental overdose and by suicide. Another dangerous drug-alcohol combination arises with the pain-killer propoxyphene. Even drugs from the benzodiazepine group, such as diazepam and flunitrazepam, despite their reputation of low toxicity in overdose have been implicated in many deaths, especially when used together with a large dose of ethanol.

Notwithstanding the difficulties in interpreting the results of postmortem drug concentrations, owing to the many factors that must be considered, the authors evaluated the coexistence and concentrations of ethanol and diazepam in postmortem femoral venous blood samples. The toxicological results are discussed in relation to the pharmacology of ethanol and diazepam and the risk for toxic response when these CNS agents are taken together.

We located 234 autopsy cases when ethanol and diazepam with or without its primary metabolite nordiazepam were the only drugs present. All blood specimens were taken from a femoral vein and 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 by headspace gas chromatography on two different stationary phases and the mean concentration was reported with a limit of quantitation (LOQ) of 0.01 g% in routine casework. Diazepam and its metabolite nordiazepam were determined simultaneously in whole blood by capillary column gas chromatography after solvent extraction without derivatization. The GC instrument was fitted with a N-P detector and the method LOQ was 0.03 mg/L for both diazepam and nordiazepam.

The distributions of diazepam and nordiazepam concentrations in blood were markedly skewed to the right and in the vast majority of cases diazepam concentrations were within the therapeutic range of 0.07-0.42 mg/L for whole blood, according to the TIAFT listing. In this material, only 10 cases (2.5%) contained a diazepam concentration above 0.8 mg/L, which is considered the lower point of the toxic range. The highest concentration of diazepam was 2.6 mg/L. The concentrations of diazepam and its primary metabolite nordiazepam were highly correlated ($r = 0.73$, $p<0.001$). By contrast, the concentrations of ethanol and diazepam were not at all correlated ($r = -0.15$, $p >0.05$). The mean blood-ethanol concentration was 0.23 g% (median 0.25 g%), which confirms a high proportion of heavy drinkers in this forensic material. Indeed, 90 individuals (38%) had a BAC over 0.3 g%, which is approaching a dangerously high concentration even without the coexistence of another CNS depressant drug. Cases with blood-diazepam >0.8 mg/L were investigated in detail by checking the cause of death according to the pathologists report. Several instances of traumatic deaths were observed so the drug-alcohol combination cannot be considered as the cause but night have contributed to the death. There were other instances of nothing remarkable at autopsy except the presence of the two depressant drugs.

Many studies have demonstrated that small doses of ethanol and diazepam impair psychomotor skills more so than either drug alone. Ethanol and diazepam both cause sedation and their pharmacodynamic interaction involves activation of the inhibitory $GABA_A$ receptor, opening of the chloride channel to elicit a tranquilizing effect on the individual. There is no strong evidence for pharmacokinetic interaction between ethanol and diazepam. Autopsy blood-specimens submitted for analysis are always hemolyzed and often contain clots. For drugs like diazepam, which are predominantly bound (>96%) to plasma proteins, the concentration in serum or plasma will be appreciably higher than in whole blood or erythrocytes. Postmortem toxicology results should not be compared directly with clinical pharmacology reports based on the analysis of plasma or serum. The plasma/whole-blood distribution ratio for diazepam is 1.8:1 (Clarke 1982). The blood-ethanol concentration required to cause death is generally considered to be 0.4-0.5 g% but this figure can vary widely depending on different circumstances such as age of the individual, development of chronic tolerance, inhalation of vomit, positional asphyxia, hypothermia and not least the combined use of other psychoactive drugs. When trauma can be excluded and no other complicating factors exist it seems reasonable to accept a high bloodethanol concentration and a blood-diazepam concentration within the toxic range as the cause of death. The sedative effect of these two CNS depressant drugs is additive.

Ethanol, Diazepam, Interaction

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