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Chlordiazepoxide and Alcohol: A Fatal Overdose

Chlordiazepoxide hydrochloride (Librium®) has been a safe and effective drug in the treatment of the acute effects of alcohol withdrawal [*1*] and has been a popular psychotropic agent in the treatment of chronic alcoholism because of its low incidence of side effects, low reported incidence of abuse leading to addiction, and wide margin of safety. Hollister [*2*] states that massive overdoses of the benzodiazepines offer little difficulty in management and concludes that the benzodiazepines are "virtually suicide-proof." Davis et al [*3,4*] note that fatalities due to overdose of chlordiazepoxide alone have not been reported. In addition, there have been, to our knowledge, no reported fatalities with a combination of chlordiazepoxide and alcohol. The purpose of this paper is to report a fatal overdose in which a combination of chlordiazepoxide and ethanol was found. A second fatal overdose is presented in which chlordiazepoxide and ethanol were probably the only drugs taken.

Case Reports

Case 1

The patient was a 31-year-old, separated, Spanish American male. He had been treated for many years at the local Veterans Administration Unit for psychiatric symptoms and had been taking major and minor tranquilizers at different times. He had a history of alcohol abuse. One evening he was found unconscious in his bed by his parents and next to the bed was a half-empty bottle of medication labeled Librium® and another half-empty bottle labeled Elavil®. When he arrived at the local hospital he was dead. An autopsy and complete toxicologic examination were performed by the Chief Medical Investigator of the State of New Mexico. The significant parts of the report were as follows: The subject was well developed and well nourished and without evidence of serious external or internal injury. There was no evidence of recent needle marks or puncture wounds. The hypopharynx, larynx, trachea, bronchi, and pulmonary vessels were normally developed and patent. The pulmonary parenchyma in the lower lobes exuded slight to moderate amounts of blood and frothy, tan fluid. The coronary arteries, aorta, and vena cava were free of thrombi. The liver weighed 1460 g

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and the hepatic capsule was smooth and intact, covering a moderately congested parenchyma with no focal lesions noted. The stomach contained 30 ml of dark purple, sanguineous, homogeneous material. Gross examinations of the brain, dura, and leptomeninges were unremarkable. Histologic examination of all organs was unremarkable.

The toxicologic examination was performed by gas-liquid chromatography (GLC), thin-layer chromatography (TLC), and ultraviolet (UV) spectrophotometry. The significant results were as follows. Gastric contents showed a total fluid content of 30 ml, 7 μg/ml of chlordiazepoxide, and no evidence of barbiturates, phenothiazine, amphetamine, or amitriptyline. Blood plasma contained 2 μg/ml of chlordiazepoxide, 350 mg/ml (0.350%) of ethanol, and no evidence of amitriptyline, barbiturates, phenothiazines, acetominophen, antihistamines, or salicylates. Urine showed 420 mg/ml (0.420%) of ethanol and no narcotics or amphetamines.

The Chief Medical Investigator of the State of New Mexico reported the cause of death as "Ethanol in combination with chlordiazepoxide."

Case 2

The patient was a 24-year-old, married, Spanish-American male. He had psychiatric symptoms since his early teens and had made many suicide gestures and attempts with overdoses of drugs and by lacerating his wrists and forearms. By the age of 17 he had been admitted ten times to psychiatric hospitals and three months before his fatal overdose he was admitted to the Bernalillo County Mental Health Center for the 25th and last time. On his last admission he was diagnosed as suffering from a severe personality disorder. He had been treated extensively by many therapists and had been supported by different agencies. His previous physician had commented that he had been an alcoholic since his late teens and that he had been treated for delirium tremens. He had taken miscellaneous drugs excessively and said that he had used heroin. One physician noted on one occasion that he had seen needle marks. He had not been observed to be under the influence of opiates during any of his contacts with physicians. His personal physician believed that the patient had not used heroin.

One hospital admission a year before his death is of particular relevance. He was admitted comatose in August 1972 after a large overdose of various medications. On admission drug blood plasma levels were as follows: Librium® 17 μg/ml, phenobarbital 25 μg/ml, Mebaral® (mephobarbital) 2 μg/ml, and ethanol 166 mg/100 ml (0.166%). No phenothiazines or other drugs were found on toxicologic examination. He remained comatose for about 30 h, recovered with supportive medical treatment, and was subsequently discharged for further outpatient treatment. His last admission was in May 1973, when he was admitted after having lacerated his arms and wrists with a razor. After this discharge he failed to keep his outpatient appointments.

Six days before his death in August 1973, he was treated in the emergency room for multiple lacerations of his right forearm. On the day of his death the patient was seen by his private physician, who subsequently described him as anxious and depressed but physically in good health. The physician prescribed 30 capsules of chlordiazepoxide 25 mg and 20 capsules of 30-mg flurazepam (Dalmane®). The physician said subsequently that the patient did not appear to be under the influence of any drugs. Approximately 24 hours later the subject was found dead under a culvert near a major highway in the city. A postmortem examination and toxicologic report were ordered and the significant results were as follows.

External examination revealed numerous healed and healing cuts over the medial and lateral aspect of both arms, each arm bearing more than 25 healed cuts measuring up to 9.5 cm in length. The right forearm had a splint which appeared to be hospital applied; underneath were recent cuts approximated by continuous black silk sutures. The recent cuts were superficial, with the exception of one cut located immediately below the right antecubital fossa which did not involve any vital vascular structures. There were no reported needle marks or puncture wounds of the upper or lower extremeties. There was no other external evidence of injury and there was no evidence of internal injury. The respiratory system revealed large amounts of a grayish-red and frothy fluid in the hypopharynx, larynx, trachea, and bronchi, which were otherwise normally developed. The pulmonary parenchyma was boggy in consistency and the cut surfaces oozed copious amounts of reddish frothy fluid. The pulmonary arteries were normally developed, patent, and without evidence of thrombus or embolus formation. The liver weighed 1900 g; the hepatic capsule was smooth, glistening, and intact; and the hepatic parenchyma was congested and dark brown. No focal lesions were noted. The stomach was distended, containing approximately 200 cm^3 of grayish, granular, viscid material. Gross examinations of the brain, dura, and leptomeninges were unremarkable. Histologic examination of the lungs and liver showed multiple granulomata. These were not considered tubercular or fungal but possibly the result of foreign body debris often seen in subjects who inject drugs. The granulomata were considered an incidental finding by the pathologist.

The toxicologic examination was performed by GLC and the results were as follows. Gastric contents showed a total fluid content of 200 ml, 239 μg/ml of chlordiazepoxide, and no evidence of flurazepam, barbiturates, phenothiazines, or amphetamines. Blood plasma contained 7.7 μg/ml of chlordiazepoxide and 190 mg/100 ml (0.190%) ethanol. Blood plasma opiate level was not performed. Urine examination revealed chlordiazepoxide 2.2 μg/ml and urine opiate level was not performed.

The Chief Medical Investigator of the State of New Mexico reported the cause of death as "overdose of chlordiazepoxide." Pathological diagnoses included (1) acute bilateral pulmonary edema (considered consistent with death by overdose); (2) multiple old, healing, and recent slash wounds of extremeties, and (3) marked passive congestion of viscera.

Discussion

The judgment that a particular drug caused death must be made with caution, particularly if there is a history of drug abuse with various drugs. In the second case the toxicologic investigations are incomplete in that opiate level examination was not carried out. Moreover, the microscopic granulomata in the lungs and liver may have been caused by intravenous drug administration. The data in both cases, however, point to the death having been caused by a combination of chlordiazepoxide and ethanol. This would suggest a synergistic effect of ethanol and chlordiazepoxide when taken in high dosage.

It is commonly believed that ethanol and all psychotropic drugs act in synergy as central nervous system depressants. Two reports [*5,6*] have recently presented data that support the *antagonistic* action of chlordiazepoxide to the effects of alcohol. Dundee et al [*5*] demonstrated the antagonistic action of chlordiazepoxide to the soporific action of intravenous alcohol in healthy women undergoing surgery. This antagonistic action was noted with large doses of chlordiazepoxide but within therapeutic range. It was also noted that diazepam (Valium®) did not affect tolerance to alcohol. Likewise,

Goldberg [7] studied the behavioral and physiological effects of alcohol on man with subjective mood and objective performance tests. He noted that chlordiazepoxide reduced the effects of alcohol both subjectively and objectively, and acted antagonistically in the acute as well as the postalcohol phase.

An interesting aspect of the second case was that the patient survived an equally large overdose of chlordiazepoxide and ethanol in addition to barbiturates one year earlier. There was no postmortem evidence of severe liver damage in this patient but it is conceivable that many years of heavy drinking and multiple drug abuse and overdoses may have gradually impaired the patient's ability to detoxify.

In other studies of overdoses, authors usually report the likely number of pills taken, but few report the blood levels of the drugs. Since there is evidence of large differences in absorption rates and plasma levels, even at normal dosage, it seems advisable to include blood plasma levels in case reports of overdoses.

Several studies suggest that chlordiazepoxide is useful in the treatment of acute alcohol withdrawal states [1,8]. Chlordiazepoxide is also frequently used in the treatment of chronic alcoholics. The safety of chlordiazepoxide would justify this. To our knowledge the present case is the only report in the literature of an apparently fatal interaction of chlordiazepoxide and ethanol. It appears that the risk of fatal interaction of chlordiazepoxide and ethanol is very small. Nevertheless, the prescribing of large amounts of even apparently safe drugs for depression-prone, impulsive alcoholics may increase the risks these patients take.

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