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A Fatal Overdose of Paraldehyde During Treatment of a Case of Delirium Tremens

Paraldehyde has been used as a hypnotic for almost one hundred years. At the present time, it is chiefly used for suppression of the symptoms of alcohol withdrawal. During its long use, paraldehyde has gained a reputation for extreme safety. Because of this reputation, it is often dispensed without due caution.

Herein is presented a case of an individual who died of an inadvertent overdose of paraldehyde while being treated for delirium tremens.

Case Report

A 35-year-old Negro male was arrested for speeding and driving while intoxicated. After three days in jail, he became agitated, tremulous, diaphoretic, and began to experience visual and auditory hallucinations. A diagnosis of delirium tremens was made. Fifteen milliliters of paraldehyde were administered orally and the patient was transferred to the county hospital. On arrival at the emergency room, the patient was given 10 mg of Valium® and 60 mg of phenobarbital intramuscularly. There were no observable effects from the medication and the patient was hospitalized.

On admission, the patient was a thin, malnourished, agitated Negro male, who was actively hallucinating. Blood pressure was 136/94 mm Hg, pulse rate was 80/min, and temperature was 98.8°F. A physical examination was essentially negative. A complete blood count, blood electrolytes, electrocardiogram, chest X-rays, and a lumbar puncture were all within normal limits. On admission, the patient had a total bilirubin of 2.2 mg percent (0.4 mg percent direct), thymol turbidity of 3.9, blood ammonia of 92 μg percent, and serum amylase of less than 320 Somogyi units. Prothrombin time and partial thromboplastin time were within normal limits. Alkaline phosphatase and serum glutamic oxaloacetic transaminase (SGOT), performed the day after admission, were 50 King-Armstrong units and 325 Karmen units, respectively. The clinical diagnosis was chronic alcholism and delirium tremens.

On admission to the ward, the following orders for medication were written in the chart: "15 cc. paraldehyde, P.O., q. 2 hours, p.r.n.; 100 mg. Librium i.m., q. 4 hours; chloral hydrate 500 mg. P.O., q.-hs. and q.-a.m. . . ."

Five hours after being seen in the emergency room, at 10 p.m. of his first day in the

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hospital, the patient was given 15 ml of paraldehyde and 500 mg of chloral hydrate. This was followed by four additional doses of paraldehyde at 2-h intervals with the last dose given at 6 a.m. the next morning (his second day of hospitalization). Total dosage of paraldehyde was 75 ml in an 8-h period. In addition to the paraldehyde and chloral hydrate, two 100-mg intramuscular injections of Librium® (chlordiazepoxide hydrochloride) were given at 2 a.m. and 6 a.m. of the second day.

At 1 p.m. on the second day of hospitalization, the patient was sent to radiology to have X-rays taken. During the procedure, the patient suffered a grand mal seizure and was given 10 mg of Valium® intravenously. On the way back to the ward, he suffered a second seizure and was felt to have aspirated. Thirty milligrams of phenobarbital, 100 mg of Dilantin® (diphenylhydantoin sodium), and 100 mg of Solu-Medrol® (methylprednisolone sodium succinate) were then administered.

Beginning at 4 p.m. of the second day and continuing at 2-h intervals up to 6 a.m. of the patient's third day in the hospital, eight 15-ml oral doses of paraldehyde were administered for a total dosage of 120 ml in a 14-h period. During the same period, 500 mg of chloral hydrate were administered at 10 p.m.; 100 mg of Librium® at 6 p.m., 10 p.m., 2 a.m., and 6 a.m.; and 30 mg of phenobarbital at 2 a.m. The patient was reported as periodically agitated and tremulous throughout the night despite this sedation. At 6:30 a.m. on the third day, the patient was observed to be asleep and breathing regularly. At 7 a.m. he was found apneic and asystolic. The patient was resuscitated and maintained on vasopressors. Antibiotics were administered. The patient was thus maintained for 9 hours and 20 minutes before being pronounced dead.

Because the deceased was a prisoner at the time of his death, the case came under the jurisdiction of the county medical examiner. The clinical impression at the time of death was that this case represented a death during alcohol withdrawal. The body was autopsied the morning of death. At autopsy, there was bilateral focal acute bronchopneumonia, a mild degree of fatty metamorphosis of the liver, and hemorrhagic gastritis. A complete toxicological analysis of blood obtained at the time of autopsy revealed a paraldehyde concentration of 80.0 mg percent, with a phenobarbital level of 0.30 mg percent and a trace amount (less than 0.010 mg percent) of diazepam. No Librium® was detected.

Comment

Paraldehyde was introduced into medicine as a hypnotic drug in 1882. It is a colorless liquid with a strong odor and a burning, disagreeable taste. The pharmacologic and toxicologic knowledge concerning paraldehyde is scanty [*1*]. On ingestion it is rapidly absorbed from the gastrointestinal tract with maximum concentrations in the brain reached in half an hour [*2*]. Sleep usually occurs 10 to 15 min after ingestion. The bulk of paraldehyde is destroyed in the liver. Up to 28 percent of a dose may be excreted by the lungs in dogs, with only about 2 percent excreted unchanged in the urine [*3*]. The minimum lethal blood concentration of paraldehyde is estimated at 50 mg percent [*4,5*]. Death is due to respiratory failure and cardiovascular depression. Paraldehyde is contraindicated in patients with hepatic insufficiency, as the impairment of normal metabolism could result in increased blood levels and hence increased toxicity.

For most of the almost 100 years paraldehyde has been in use, it has been considered an extremely safe hypnotic with a low toxicity and a wide margin of safety. Only 33 deaths due to paraldehyde poisoning were reported from 1882 to 1950. From 1950 to 1956, however, 60 deaths were counted [*5*]. The sharp increase in the number of deaths was apparently due to an increased accuracy in diagnosis and reporting of such cases. In

at least four instances, death was due to deterioration of the paraldehyde, which, on exposure to light and air, decomposes to acetaldehyde and then to acetic acid. The most extensive review of deaths due to paraldehyde is by Hayward and Boshell [5]. In their article they cite an unpublished study by Stratton, who observed a series of 19 deaths attributed to paraldehyde. Blood levels in these cases ranged from 49 to 160 mg percent. Figot et al reported four deaths due to paraldehyde [2]. The blood levels in these cases were 54.3, 84.0, 148, and 88 mg percent. In three other cases reported by Figot, paraldehyde was found as an incidental finding when death was due to physical violence. The blood levels in these latter cases were 5.5, 11.2, and 27.4 mg percent.

Paraldehyde is now used chiefly for the treatment of withdrawal reactions from alcohol. One of the reasons for its use has been its reputation as an exceptionally safe hypnotic. Any drug, however, can be toxic when given in sufficient dosage. Paraldehyde is not an exception. Therapeutic deaths with paraldehyde probably occur for two reasons. First is its reputation for safety, which leads to careless dispensation of this medication. Second, as newer hypnotics have appeared the amount of space devoted to paraldehyde in the pharmacology and therapeutic handbooks has decreased. While most of these textbooks do give information as to the correct amount of the drug for a single dose, they generally fail to give any information as to repeated dosage of a patient with paraldehyde. To obtain this information, one has to consult an older textbook. Thus, the first edition of Goodman and Gilman's textbook on pharmacology [6] in 1941 states that paraldehyde may be given orally in doses of 10 to 15 cm two or three times daily, and *The Dispensatory of the United States of America* [7] (published in 1955) states that the maximum safe dosage is 30 ml, with a total dosage in 24 h not to exceed 30 ml. Such information does not usually appear in the more recent pharmacology textbooks.

The patient in our case report was given 120 ml of paraldehyde during a 14-h period, a quantity greatly exceeding the recommended dosage for 24 h. In addition, the patient had some impairment of his liver functions on admission, as manifested by the elevated bilirubin and blood ammonia on the day of admission and the elevated SGOT and alkaline phosphatase the following day. This would make him even more susceptible to an overdosage of paraldehyde. Even though the patient lived 10 hours and 20 minutes after his last dose, his blood level of paraldehyde at autopsy was 80 mg percent. Complicating this situation was the fact that not only was he administered an overdose of paraldehyde, but also three other central nervous system depressant drugs (Librium®, chloral hydrate, and phenobarbital) during this same period. In fact, even the amount of Librium® given during this time (400 mg) exceeds the recommended 24-h dosage (300 mg) suggested by the manufacturer. Whatever the effects of the other central nervous system depressants, however, there is no escaping the fact that the patient received a toxic quantity of paraldehyde resulting in oversedation and death.

Summary

A 35-year-old man was hospitalized for delirium tremens. During a 14-h period of his hospitalization, he was given 120 ml of paraldehyde, a quantity far in excess of that recommended for a 24-h period. The patient became asystolic and apneic, was resuscitated, but finally died 10 hours and 20 minutes after his last dose. At autopsy, he had a blood paraldehyde concentration of 80 mg percent. Therapeutic deaths from an overdose of paraldehyde can be the result of its reputation for safety, leading to careless dispensation of this medication or a lack of information in the current medical literature concerning proper dosage.

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