Unusual Death Attributed to the Combined Effects of Chloral Hydrate, Lidocaine, and Nitrous Oxide

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Abstract

A case in which the death of a 2-year-old male child was the result of an acute intoxication with chloral hydrate, lidocaine, and nitrous oxide is presented. Trichloroethanol (TCE), the primary metabolite of chloral hydrate, was qualitatively detected by the Fujiwara reaction. Quantitation of TCE was carried out by gas chromatography-mass spectrometry (GC-MS) with the following results: plasma, 79.0 mg/L; urine, 31.8 mg/L; gastric contents, 454.0 mg/L; bile, 111.0 mg/L; vitreous, 40.2 mg/L; cerebrospinal fluid (CSF), 68.3 mg/L; and liver, 164 mg/kg. Lidocaine was quantitated by GC analysis using nitrogen-phosphorus detection with the following results: plasma, 11.9 mg/L; urine, 3.7 mg/L; gastric contents, 15.3 mg/L; bile, 19.0 mg/L; vitreous, 17.8 mg/L; CSF, 9.4 mg/L; and liver, 19.0 mg/kg. Nitrous oxide was quantitated in the blood with a value of 4.4 mL/L.

Introduction

Chloral hydrate is a sedative hypnotic that is readily absorbed following oral administration. It is rapidly metabolized by alcohol dehydrogenase to its active metabolite, trichloroethanol (TCE), with a half life of 4 min (1). TCE is further metabolized by oxidation to trichloroacetic acid and by conjugation with glucuronic acid. Lidocaine may be used as a local anesthetic or as an antiarrhythmic drug. Metabolic reactions include N-deethylation, hydrolysis, and ring oxidation with a plasma half life of 1-2 h (2). Both N-deethylation products, monoethylglycinexylidide and glycinexylidide, are also active antiarrhythmic agents.

Case History

A 2-year-old male was administered a prescribed medication of chloral hydrate at approximately 8:30 a.m. and was then transported to a dental center for an appointment. At this time, nitrous oxide and lidocaine were administered, and dental procedures were performed. Following the surgical procedure, attempts to awaken the child were made with negative results. A fire rescue squad was called, and they administered treatment upon arrival. The child, who was in full arrest, was then transported to an emergency room at 10:40 a.m. Advanced cardiac life support protocol and drug therapy were instituted; however, the child failed to respond and was pronounced dead at 11:00 a.m.

Experimental

Specimens

Postmortem blood, urine, bile, vitreous, liver, and gastric contents were obtained during autopsy, which was performed approximately 21 h after the time of death. Blood samples were stored in 50-mL glass screw-capped tubes containing approximately 0.6 g of sodium fluoride/potassium oxalate (5:1, w/w) and sealed with Teflon-lined caps. Urine was placed in a 50-mL glass screw-capped tube and sealed with a Teflon-lined cap. Vitreous specimens were placed in 7-mL red topped vacutainers. Bile and gastric contents were collected in Nalgene™ polypropylene wide-mouth bottles. Liver samples were prepared by homogenizing 6.0 g of liver in 30 mL of deionized water. The samples were placed in 50-mL glass screw-capped tubes containing sodium fluoride/potassium oxalate that were sealed with a Teflon-lined cap. Cerebrospinal fluid (CSF) was placed in a 15-mL grey-topped vacutainer and stored at -20°C. All other specimens were stored 4°C.

Extraction

Aqueous TCE working standards of 1.0, 5.0, 10.0, 50.0, and 100.0 mg/L were prepared by making serial dilutions of a 1000-mg/L stock solution. The extraction procedure was adopted from the literature (3). A standard curve of drug concentration versus the peak-area ratio of drug and internal standard was used for quantitation. Specimens were diluted with deionized water when necessary to bring the concentration within the linear range of the standard curve.

Lidocaine, using promazine as the internal standard, was extracted as previously described (4). Briefly, 3 mL of standards and specimens, 2 mL of a saturated aqueous NaCl solution, 2 mL of a saturated aqueous NH₄Cl solution (pH 9.2), and 0.1 mL of 6N NaOH were extracted with 10 mL of ethyl acetate. The drugs were then back extracted from the ethyl acetate with 2 mL of 0.5N H₂SO₄. Tris buffer (3 mL, 1.2M, pH 9.2) was added to the acid and then extracted with 5 mL of hexane/isopropanol (9:1). The organic
layer was evaporated to dryness and reconstituted in 50 μL of MeOH, and 2 μL was injected into the GC. A standard curve of drug concentration versus the peak-area ratio of drug and internal standard was used for quantitation. Specimens were diluted with deionized water when necessary to bring the concentration within the linear range of the standard curve.

Instrumentation
TCE was qualitatively detected colorimetrically according to the Fujjwara reaction using a Perkin-Elmer Lambda 3B UV-vis spectrophotometer (5). Quantitation of TCE was performed by gas chromatography–mass spectrometry (GC–MS) with a Hewlett-Packard model 5890 GC and a Hewlett-Packard 7673A liquid autosampler interfaced into a model 5970 mass selective detector. The column was a J&W Scientific DB-5 (30 m x 0.25 mm, 0.25-μm film thickness) with helium at a flow rate of 1.0 mL/min as the carrier gas. The injection port and ion source temperatures were 125 and 280°C, respectively. The injection port was operated in the splitless mode with a purge delay of 1.0 min. The oven was operated isothermally at 50°C. The ions collected in the selective ion monitoring mode were as follows: TCE, m/z 77, 82, and 113 and tetrachloroethylene, m/z 166 and 129.

Lidocaine was quantitated by GC analysis using a Hewlett-Packard model 6890 GC equipped with a nitrogen-phosphorus detector and a Hewlett-Packard 7673A liquid autosampler. The column was a Restek RTX-50 (30.0 m x 0.32 mm, 0.25-μm film thickness) with helium at a flow rate of 1.5 mL/min as the carrier gas. The inlet and detector temperatures were 250 and 300°C, respectively. The oven temperature was programmed to hold at 130°C for 3 min, rise to 270°C at 10°C/min, and then hold for 1.0 min. The injector was in the splitless mode with a purge delay of 0.75 min.

Nitrous oxide quantitation in the blood was performed by National Medical Services (Willow Grove, PA).

Results and Discussion
Quantitative TCE and lidocaine results are given in Table I. TCE was linear over the concentration range tested (1.0–100.0 mg/L, r = 0.999). The total ion chromatogram of the extracted specimens and the mass spectrum of TCE were similar to those previously reported (3) and are not shown here. The retention times for tetrachloroethylene and TCE were 4.50 and 6.84 min, respectively. Lidocaine was also linear over the concentration range tested (0.1–10.0 mg/L, r = 0.998). The retention times for lidocaine and promazine were 10.01 and 14.58 min, respectively.

The continued use of chloral hydrate as a prescribed sedative is controversial because of its low therapeutic ratio. A typical therapeutic dose is 50 mg/kg, whereas doses slightly higher, in the range of 100–150 mg/kg, have resulted in cardiac arrhythmia or death or both (6). Following investigation, it was determined that this child was accidentally given a dosage of 95 mg/kg, which resulted in a TCE plasma concentration of 79.0 mg/L, which is three times the normal level of 27.0 mg/L that is produced from usual oral sedative doses (7). Toxic blood TCE concentrations have been reported from 9 to 1700 mg/L (8).

Lidocaine was also present in this case at a plasma level of 11.9 mg/L. It should be noted that lidocaine was only administered before the dental procedures and not at the emergency room. Postmortem blood concentrations of lidocaine that have resulted in death have ranged from 5.0 to 92.0 mg/L; however, people have survived peak blood concentrations as high as 19.0 mg/L (9). In postmortem cases in which nitrous oxide was detected, expected blood concentrations were greater than 46 mL/L (10). The blood level of 4.4 mL/L, determined in this case, was considerably lower.

The Coroner's final ruling was that the death resulted from the combined effects of all three drugs, chloral hydrate, lidocaine, and nitrous oxide.

References

Table 1. Toxicological Findings

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Trichloroethanol (mg/L)</th>
<th>Lidocaine (mg/L)</th>
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<tbody>
<tr>
<td>Plasma</td>
<td>79.0</td>
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<td>Urine</td>
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