CASE REPORT

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Fatal Intoxications with Chloral Hydrate

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ABSTRACT: An alcoholic man, treated with chloral hydrate (CH) syrup to which he was dependent, was discovered comatose and in respiratory arrest. Death occurred on the ninth day of hospitalization following cerebral oedema. A woman, alcohol addicted, depressed, and epileptic was admitted in the Intensive Care Unit with heart and respiratory failure following CH absorption. She died three days later after a deep coma.

In these two cases, CH intoxication was confirmed by toxicological analysis: CH and its major metabolite, trichloroethanol (TCE), were identified and determined in serum and urine using headspace-capillary gas chromatography-mass spectrometry. The concentrations measured were compared with those found in previously published fatalities. The analytical method used can be proposed for both clinical and forensic cases.

KEYWORDS: forensic science, chloral hydrate, trichloroethanol, HS-GC/MS

Chloral hydrate (CH) (2,2,2,-trichloroethane-1,1-diol) is a sedative hypnotic drug with a long history. Synthesized in 1832, CH has been used widely since the end of the 19th century.

Its mechanism of action still remains unknown even if central depression could be related to the high affinity of its metabolite, 2.2.2-trichloroethanol (TCE), for the nervous cells (1). Today, in France, several specialities containing CH are still marketed. Some are gargles, lotions, or solutions used as mouth bath owing to CH analgesic and disinfectant properties. CH is also used in syrup forms prescribed as sedatives in the elderly population, for short-term sedation in children (during NMR imaging for example), as well as in the treatment of alcoholism or strychnine poisoning (2–4). A CH oral dose in adults ranges from 0.5 to 2.0 g and in children from 25 to 50 mg/kg/day (maximum: 0.5 g) (1,5).

However, CH exhibits a significant risk of mutagenesis and carcinogenicity, which has already limited its therapeutic use (6). Today, French experts recommend that CH use should be banned. Furthermore, the literature is fraught with voluntary or accidental CH overdose reports owing to severe CNS depression, including depression of respiratory and vasomotor centers (3,5,7–16). However, few cases illustrated by the results of toxicological analyses have been reported (8,14–16).

This paper reports two fatalities after voluntary CH ingestion documented by concentration data and underlines the interest of a headspace (HS) technique coupled with gas chromatography-mass spectrometry (GC/MS) for the determination of CH and TCE.

Case Histories

Case 1

A 30-year-old man, known for chronic alcoholism, was treated with an antidepressant (paroxetine), a neuroleptic agent (amisulpride), and chloral hydrate syrup as a sedative. He presented dependence symptoms to the last one. Following absorption of approximately 10 g of chloral hydrate (a 250 mL bottle, which was five-fold the usual advised dosage), he was found comatose and in respiratory arrest. On admission, he was in deep coma with myosis and fetid diarrhea. Then he had fits, with an electroencephalogram showing alternately paroxystic and depressed periods. Brain tomography showed diffuse cerebral oedema and ischaemic areas. His state worsened within a few days. He died on Day 9.

Case 2

A 29-year-old, alcohol- and tobacco-addicted, depressed and epileptic woman was treated with chloral hydrate syrup, antipsychotic (alimemazine, mianserine), anxiolytic (meprobamate), and antiepileptic (valproic acid) drugs. She was found in cardiac and respiratory arrest following a seemingly voluntary massive absorption of chloral (unknown amount). After cardiac massage, she was hospitalized in the Intensive Care Unit in a comatose state associated with myosis, metabolic acidosis, and depressed electroencephalogram. Any nontoxicological cause could be eliminated by physical, biological, and radiological examination. She died three days later.

Serum and urine samples taken on admission of Cases 1 and 2 were sent to the toxicological laboratory for analysis.

Material and Methods

A large screening of drugs and toxicants in serum and urine was performed using both high-performance liquid chromatography

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coupled to a diode array detector (HPLC-DAD) and gas chromatography-mass spectrometry (GC-MS). More selective analyses for several classes of therapeutic drugs, drugs of abuse, alkaloid poisons, mineral toxicants . . . were carried out with various ad-hoc methods using HPLC-DAD, liquid chromatography-electrospray-mass spectrometry (LC-ES-MS), and GC with various detection modes. In particular, serum concentration of alimemazine and mianserine was determined using gas chromatography with thermoionic detection, that of meprobamate using gas chromatography-flame ionization detection, while serum valproic acid was measured using a fluorescence polarization immunoassay on AxSYM™ (Abbott Diagnostic).

Chloral hydrate (CH) and its major metabolite, trichloroethanol (TCE), were identified and quantitated in serum and urine using HS-GC/MS. Briefly, samples were prepared as follows: 500 μL of standard solution or biological material (urine or serum sample), 1 mL of satured ammonium sulfate aqueous solution, 1 mL of sulfuric acid, and 100 μL of hydrochlorofluoromethan (internal standard) were successively introduced in a 20 mL vial, which was rapidly sealed with a silicone septum and aluminum cap.

Then, the vials were introduced in the head-space system (Perkin-Elmer HS40XL) to undergo a step of volatilization of the compounds of interest (90°C for 20 min) and a step of pressurization (120°C for 1 min). The headspace gas was transferred (temperature of the needle: 100°C) to a 5890 series II gas chromatographic system (Hewlett-Packard) with helium as carrier gas at 1 kg/cm^2. A 1/5 dilution was carried out in the split-splitless injector heated at 120°C. Separation was performed on a 30 m by 0.32 mm ID SPB1 column (SUPELCO, Saint Quentin Fallavier, France). The column temperature was set at 70°C for 30 s and was then programmed up to 200°C at 25°C/min with a plateau at this final temperature for 10 min. Identification of CH and TCE was performed in the scan mode using a 5972 mass spectrometer (Hewlett-Packard), by comparison with mass spectra and relative retention times obtained with reference compounds. Retention times were 5.8, 8.3, and 10.3 min for internal standard, CH, and TCE, respectively. Then, quantitation was performed in the selected ion monitoring mode using *m/z* 82 as quantitation and *m/z* 87 as confirmation ions for CH, *m/z* 31 and 49 for TCE, and *m/z* 101 and 103 for trichlorofluoromethane, respectively.

Results and Discussion

The analytical method reported herein yielded quantitation limits (LOQ) of 100 and 500 μg/L for CH and TCE, respectively, and was linear up to 50 mg/L for both.

The analytical techniques generally used for the diagnosis and followup of such intoxications are the Fujiwara reaction and gas chromatography. The Fujiwara method, generally used for qualitative CH determination in emergency, is based on a nonspecific chemical reaction that reveals the presence of chlorinated carbohydrates in high concentration (16). It is sometimes used associated with a spectrophotometric detection for their quantitation (17). Gas chromatography was preferably used for determining CH and its metabolites in various biological matrices. The previously published methods generally involved direct sample injection or headspace injection and either flame ionization (18) or electron capture detection (15,16,18). Some gas chromatographic methods with direct sample injection and mass spectrometric detection were also reported (8,20).

With the present method, CH and TCE were simultaneously determined using headspace-capillary gas chromatography-mass spectrometry, which is much more specific than the Fujiwara reaction and makes it possible to formally identify the chlorinated carbohydrates detected. Headspace injection simplifies sample preparation and even allows the use of this GC/MS method in emergency (the run-over time between sample reception and results being approximately 3 h).

The analytical findings in the two fatalities are presented in Table 1. Although interpretation of the cause of death was based mainly on TCE concentration, several other elements were considered. Readily absorbed from the gastrointestinal tract following oral administration and distributed to all tissues, chloral is widely metabolized in the liver by ADH (alcohol deshydrogenase) (5,19,21). Thus, since blood ethanol was lower than 0.10 g/L in both cases, there was no competition between the two substrates (ethanol and chloral) and chloral was quickly converted into TCE (its major active metabolite) in as much as both subjects were alcoholic, i.e., likely to have enhanced ADH activity. In these conditions, chloral is know to have a very short plasma half-life of 4 min (1), which represents a worsening factor of intoxication since TCE is considered responsible for the respiratory depression. Consistently, chloral was found in urines at very weak concentrations but was at concentration lower than the LOQ in serum.

In addition, various associated drugs were found in Case 2. Valproic acid, alimemazine, mianserine, and meprobamate were at therapeutic serum concentrations. Nevertheless, all of them are CNS depressants and may have CNS effects additive to those of chloral hydrate (21). Moreover, Case 2 concerned an epileptic woman and, as chloral hydrate and meprobamate are potential convulsivants (21,22), they may have induced fits prior to other toxic effects.

It is also interesting to note the concept of dependency to chloral (according to the family) in Case 1. In fact, CH is a sedative and hypnotic drug whose properties are comparable to those of barbiturates. It was shown (*in vitro*) that TCE presented a mode of action close to that to barbiturates on $GABA_A$ receptors (2). In this way, dependency and tolerance (or even withdrawal) can occur with CH treatment and were previously reported as being a risk factor for overdosing (23).

Interpretation of TCE serum concentration is difficult as analytical data illustrating fatal or not fatal intoxications with chloral hydrate are sparse. Commonly, intoxication is quoted as "severe" if TCE serum concentration exceeds 50 mg/L. A fatal intoxication

TABLE 1—*Analytical findings in two cases of fatal intoxication with chloral hydrate.*

	Chloral, mg/L	TCE, mg/L	Ethanol, g/L	Other Compounds
Case 1	0.3 (urine) <0.1 (serum)	450 (urine) 57 (serum)	<0.1*	none
Case 2	0.5 (urine) <0.1 (serum)	119 (urine) 29 (serum)	<0.1*	valproic acid: 17.9 μg/L* alimemazine: 52.2 μg/L* mianserine: 77 μg/L* meprobamate: 10.3 μg/L*

* Serum concentration.

was previously reported with a TCE concentration of 127 mg/L in blood and 128 mg/L in urine (8), whereas a low postmortem concentration of TCE in blood (33 mg/L) was reported in another case (16). The death of a two-year-old male child was attributed to a combination of lidocaine, nitrous oxide and CH, with TCE concentration of 79 and 31 mg/L in plasma and urine, respectively (14). Finally, an extraordinarily high blood TCE concentration (1700 mg/L) was measured subsequently to a fatal overdose following absorption of CH as pure chemical (15).

The TCE serum concentration levels measured in Cases 1 and 2 (57 and 29 mg/L, respectively) appear to belong to the lowest lethal range. However, the associated factors seen above (especially the polymedication in Case 2) as well as the apparent pharmacokinetic and pharmacodynamic variability of CH in humans advocate for the responsibility of CH in these fatalities (1,3,5).

This large interindividual variability has also been previously observed with respect to the lethal quantity of CH when orally ingested. It seems to be about 10 g on average, but this is dependent on the rapidity and efficacy of medical support, as illustrated by a recent case of voluntary ingestion of 70 g chloral hydrate by a 29-year-old man that had a favorable issue (7).

In conclusion, these two fatal intoxication cases further point out the danger of this drug still "naively" used as a sedative. The HS-GC/MS method used is simple and reliable and can be proposed for the diagnosis and followup of clinical intoxications, as well as to document forensic cases. The concentrations reported herein can help increase forensic interpretation databases.

References

1. Baselt RC. Disposition of toxic drugs and chemicals in man. 5th ed. Foster City, 2000.
2. Vade A, Sukhani R, Dolenga M, Habisohn-Schuck C. Chloral hydrate sedation of children undergoing CT and MR imaging: safety as judged by American Academy of Pediatrics guidelines. Am J Roentegenol 1995;165:905–9.
3. Graham SR, Day RO, Lee R, Fulde GW. Overdose with chloral hydrate: a pharmacological and therapeutic review. Med J Aust 1988;149: 686–8.
4. Chung T, Hoffer FA, Connor L, Zurakowski D, Burrows PE. The use of oral pentobarbital sodium (Nembutal) versus oral chloral hydrate in infants undergoing CT and MR imaging: a pilot study. Pediatr Radiol 2000;30:332–5.
5. Pershad J, Palmisano P, Nichols M. Chloral hydrate: the good and the bad. Pediatr Emerg Care 1999;15:432–5.
6. George MH, Moore T, Kilburn S, Olson GR, De Angelo AB. Carcinogenicity of chloral hydrate administered in drinking water to the male F344/N rat and male B6C3F1 mouse. Toxicol Pathol 2000;28:610–8.
7. Ludwigs U, Divino Filho JC, Magnusson A, Berg A. Suicidal chloral hydrate poisoning. J Toxicol Clin Toxicol 1996;34:97–9.
8. Heller PF, Goldberger BA, Caplan YH. Chloral hydrate overdose: trichloroethanol detection by gas chromatography/mass spectrometry. Forensic Sci Int 1992;52:231–4.
9. Jastak JT, Pallasch T. Death after chloral hydrate sedation: report of case. J Am Dent Assoc 1988;116:345–8.
10. Buur T, Larsson R, Norlander B. Pharmacokinetics of chloral hydrate poisonning treated with hemodialysis and hemoperfusion. Acta Med Scan 1988;223:269–74.
11. Sing K, Erickson T, Amitai Y, Hryhorczuk D. Chloral hydrate toxicity from oral and intravenous administration. J Toxicol Clin Toxicol 1996; 34:101–6.
12. Ludwigs U, Divino Filho JC, Magnusson A, Berg A. Suicidal chloral hydrate poisoning. J Toxicol Clin Toxicol 1996;34:97–9.
13. Zahedi A, Grant MH, Wong DT. Successful treatment of chloral hydrate cardiac toxicity with propanolol. Am J Emerg Med 1999;17:490–1.
14. Engelhart DA, Lavins ES, Hazenstab CB, Sutheimer CA. Unusual death attributed to the combined effects of chloral hydrate, lidocaine, and nitrous oxide. J Anal Toxicol 1998;22:246–7.
15. Levine B, Park J, Smith TD, Caplan YH. Chloral hydrate: unusually high concentrations in a fatal overdose. J Anal Toxicol 1985;9:232–3.
16. Meyer E, Van Bocxlaer JF, Lambert WE, Piette M, De Leenheer AP. Determination of chloral hydrate and metabolites in a fatal intoxication. J Anal Toxicol 1995;19:124–6.
17. McBay AJ, Boling VR, Reynolds PC. Spectrophotometric determination of trichloroethanol in chloral hydrate poisoning. J Anal Tox 1980;4: 99–101.
18. Flanagan RJ, Lee TD, Rutherford DM. Analysis of chlormethiazole, ethchlorvynol and trichloroethanol in biological fluids by gas-liquid chromatography as an aid to the diagnosis of acute poisoning. J Chromatogr 1978;153:473–9.
19. Mayers DJ, Hindmarsh KW, Sankaran K, Gorecki DK, Kasian GF. Chloral hydrate disposition following single-dose administration to critically ill neonates and children. Dev Pharmacol Ther 1991;16:71–7.
20. Yan Z, Henderson GN, James MO, Stacpoole PW. Determination of chloral hydrate metabolites in human plasma by gas chromatography-mass spectrometry. J Pharm Biomed Anal 1999;19:309–18.
21. Goodman and Gilman's The pharmacological basis of therapeutics. 9th ed., McGraw-Hill, New York, 1996.
22. Munoz M, Gomez A, Soult JA, Marquez C, Lopez-Castilla JD, Cervera A, Cano M. Seizures caused by chloral hydrate sedatives doses. J Pediatr 1997;131:787–8.
23. Stone CB, Okun R. Chloral hydrate dependence: report of a case. Clin Toxicol 1978;12:377–80.

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