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ELECTROCARDIOGRAPHIC CHANGES WITH SEGMENTAL AKINESIA AFTER CHLORAL HYDRATE OVERDOSE

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□ **Abstract—We report a case of deliberate ingestion of 12.5 g chloral hydrate in a 25-year-old psychiatric patient. Coma and life-threatening ventricular dysrhythmias were observed soon after ingestion. Repeated electrocardiographic examination was consistent with ischemic changes appearing on day 3. They were associated with segmental abnormal left ventricular wall motion by echocardiography. A coronary angiogram was performed and was normal. Toxic metabolites of chloral hydrate, trichloroethanol and trichloroacetic acid were found in the urine until day 7. This case illustrates that with halogenated aliphatic hydrocarbons, sustained changes in cardiac contractility may occur in addition to early life-threatening ventricular dysrhythmias.** © 2006 Elsevier Inc.

□ **Keywords—chloral hydrate; metabolites; poisoning; ventricular dysrhythmias; cardiac contractility**

INTRODUCTION

Chloral hydrate is a hypnotic drug that was introduced in 1869 into clinical practice. Chloral hydrate is also a metabolite of trichlorethylene and tetrachlorethylene. Concerns exist regarding genotoxic effect of prolonged use of this drug (1). Chloral hydrate induces aneuploidy in several organisms, including eukaryotic organisms, mammalian cells in culture, and mammalian germ cells in vivo. Moreover, cardiotoxicity is a frequent side effect of chloral hydrate overdose (2). As there are numerous alternative sedative or hypnotic agents, chloral hydrate has been almost abandoned with the exception of pediatric critical care units, where it is used in a single dose for premedication before painful examinations or procedures.

Chloral hydrate has some common metabolites (trichloroethanol, trichloroacetic acid) with trichlorethylene, which is still widely used as a solvent. It seems likely that chloral hydrate-related cardiotoxicity could be at least mediated by these metabolites. The interest of this case is that ischemic changes on the electrocardiogram (EKG) were associated with abnormal cardiac wall motion without any lesion of the coronary arteries. Coronary vasospasm is a possible mechanism of toxicity and this complication is seen in patients exposed not only to chloral hydrate, but more frequently to chlorinated solvents.

CASE REPORT

A 25-year-old woman (50 kg weight) without risk factors for cardiovascular diseases was found comatose approximately 1 h after the deliberate ingestion of 250 mL of syrup of chloral hydrate (equivalent to 12.5 g of the substance, 250 mg/kg). At the first prehospital examina-

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tion, the Glasgow Coma Scale (GCS) score was 3/15, with dilatated and areactive pupils. Arterial blood pressure was 60/40 mm Hg, heart rate 110 beats/min, respiratory rate 16 breaths/min, SpO_2 88%, and temperature 36.1°C. The first EKG showed sinus rhythm, with multifocal premature ventricular contractions. The patient was immediately intubated and mechanically ventilated. During transfer to the hospital, episodes of ventricular tachycardia were recorded and treated by intravenous administration of lidocaine and amiodarone. Hypotension was treated by fluid infusion. Immediately after admission to the Emergency Department (ED), the patient manifested torsades de pointe, which was converted to sinus rhythm with normal QRS and QT interval after procainamide and magnesium sulfate administration.

The patient was admitted to the Intensive Care Unit (ICU), where she again manifested episodes of premature ventricular contractions and ventricular tachycardia. It was then decided to insert a temporary pacemaker device and to start propranolol infusion at the rate of 2 mg/h. No more episodes of severe cardiac dysrhythmias were noted. On day 3, while the patient was still intubated and mechanically ventilated and showing a progressive neurological recovery, negative T waves were recorded in the precordial V1–V4 and standard II-III-AVF leads (Figure 1). Progression to all precordial leads was observed on day 4. Echocardiography obtained on the same day showed a marked apical akinesia of the left ventricle. Akinesia persisted on day 5, without any changes in cardiac enzymes. There was no drop in arterial blood pressure. A coronary angiography was performed on day 6 and showed normal coronary arteries with a mild apical akinesia at ventriculography. Propranolol infusion was stopped the same day. Myocardial scintigraphy (MIBI) on day 7 was within normal range. The patient was extubated on day 8. Echocardiographic changes progressively disappeared by day 10, and EKG changes by day 12. Toxicological analysis revealed that serum trichloroethanol was 597 mg/L on admission and 97.2 mg/L 8 h later (reference value in a general population <5 mg/L) . In the urine samples obtained on admission, 8 h later and on day 7, the trichloroethanol level was, respectively, 11651.5, 3769.1 with 9.4 $mg.g^{-1}$ creatinine, and the trichloroacetic acid level was, respectively, 2010.3, 264.7 with 17.70 $mg.g^{-1}$ creatinine (the two first values being well above the reference values observed in a population exposed to chlorinated hydrocarbons).

DISCUSSION

Chloral hydrate is a halogenated aliphatic hydrocarbon and one of the oldest sedatives. This substance, however, has a low therapeutic index with toxicity occurring when doses exceed 100–150 mg/kg and its use has considerably decreased in adults. Toxicity varies greatly in different patients. In adults, deaths have been reported after ingestion of 30 mg/kg, whereas survival is possible after intake of 25 to 38 g (2,3). Interestingly, chloral hydrate is one of the metabolites of trichlorethylene. Chloral hydrate is rapidly metabolized by the liver (Figure 2). It is reduced by alcohol dehydrogenase to trichloroethanol, and to a lesser extent oxidized by aldehyde dehydrogenase to trichloroacetic acid (4). The ratio trichloroethanol/trichloroacetic acid would depend upon redox potential in the hepatocytes (ratio NADH/NAD+). Trichloroethanol is then conjugated to glucuronic acid or oxidized in trichloroacetic acid. Terminal half-life in case of overdose may be as long as 35 h for trichloroethanol and 100 h for trichloroacetic acid (4). Whereas thrichloroethanol seems responsible for the sedative effects, cardiac manifestations could be related to trichloroacetic acid (4–7). The different terminal half-life of both metabolites could explain why delayed cardiotoxicity is observed after complete neurological recovery (5). Indeed, not only has trichloroacetic acid a longer half-life, but trichloroethanol itself is secondarily transformed into trichloroacetic acid and there is also evidence that, after excretion by the kidney, trichloroacetic acid is actively reabsorbed in the bladder (8). However, as cardiac dysrhythmias are observed early after chloral hydrate exposure, the parent compound is probably also involved in cardiac toxicity (5).

Chloral hydrate in large doses has been shown to shorten the refractory period and depress the contractility of the myocardium. Cardiocirculatory disorders are responsible for most of the deaths after chloral hydrate overdose (8,9). Severe hypotension is usually the consequence of impaired myocardial contractility and decreased vascular resistances (8). Life-threatening dysrhythmias are the main complication of chloral hydrate exposure. The incidence of ventricular dysryhthmias (premature ventricular beats, ventricular tachycardia, ventricular fibrillation, torsades de pointe) is about 25% (7). Their onset may vary from 30 min to 10–12 h. They are usually precipitated by external conditions (e.g., hypoxia, hypercapnia, agitation) (10). Several mechanisms may be involved: shortening of the refractory period, increased automaticity of the pacemaker cells, delayed intraventicular conduction (3,9,11). As chloral hydrate causes catecholamine release and also sensitizes the myocardium to the effects of the catecholamines, propranolol has been the most commonly used beta adrenergic blocker for chloral hydrate-induced dysrhythmias; lidocaine is proposed in case of dysrhythmias refractory to propranolol or esmolol (12). Class Ia, Ic or III antidysrhythmics (amiodarone and procainamide were given